iGC SEA Case Study 613

Surface Energy Distributions and the Dissolution Rate of Aspirin

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Surface properties of crystalline solids have been shown to be anisotropic. Milling of crystals may lead to formation of amorphous state and/or exposure of new crystalline planes, resulting in particles with different surface energetics. This study uses Inverse Gas Chromatography (IGC) to relate the dissolution rates of milled and unmilled aspirin crystals as a function of surface energetics.

Introduction

Most real-world materials are energetically heterogeneous. Recent advances in IGC methodology have allowed for the determination of surface energy heterogeneity profiles [1,2]. A heterogeneity profile constitutes an energy "map" of the material surface and also allows prediction of the product properties.

It is well understood that primary particle properties dramatically affect the dissolution behaviour. In particular, particle size, particle shape, surface area and porosity were shown to have major impact on the dissolution rates [3,4,5,6]. However, since surface wetting can be significantly influenced by particle surface energy [7], initial wetting behaviour is also expected to be another important factor in dissolution behaviour.

This paper describes how the surface energy heterogeneity measured by IGC-SEA can be correlated to dissolution properties of unmilled and milled aspirin.

Theory

The state-of-the-art injection technology of the iGC SEA allows the precise control of the injection size, therefore different amount (mole, n) of probe vapour can be chosen to pass through the sample column to achieve different surface coverages, n/n_m. If a series of probe vapours is injected at the same surface coverage, the surface energy and free energy can be determined. Consequently, the injections of probe vapours at different surface coverages will result in a distribution of surface energy as a function of surface coverage, which is referred as a surface energy profile. The determination of surface energy heterogeneity by iGC SEA can, therefore, be described as a mapping technique. Detailed methodology has been described elsewhere [1,2].

Method

Material – Aspirin

Aspirin powders (Aldrich) were used as received and then ball-milled for 16 hours. Both the unmilled (as received) and milled samples were

sieved and two different particle size fractions were collected for further analysis: 75-106µm and 150-250µm.

Tablet Compaction

50mg of each sieve fraction was compacted using a 5mm diameter evacuable pellet die (Specac Ltd, UK) and a manual press (Specac Ltd, UK) at a compression force of 10kN (509MPa).

Dissolution Testing

USP apparatus II method described in BP2012 was adapted for dissolution testing. The prepared compact(s) were placed in 500ml of pH 4.5 buffer (29.9g of sodium acetate tri-hydrate – analytical grade, 16.6ml of glacial acetic acid – analytical grade, purified water up to 10L) and stirred using a 40mm x 8mm magnetic stirrer bar in a 1 litre glass beaker. The solution was kept at room temperature and pressure (298K and 760mmHg) using plate stirrer for 90 minutes at approximately 50rpm. 20ml aliquots were taken at set intervals, and replaced with equal volume of medium using 20ml plastic syringes. The sample will be filtered using a 0.22µm Millipore filter and UV absorbance of the filtrate immediately measured at 265nm, with appropriate dilution when required. Concentration at each interval can be determined using Beer-Lambert law with path length of the quartz cuvette being 1cm and final concentration being 100mgL^{-1}.

Particle Size Analysis

Particle size analysis (Malvern Mastersizer 2000) was performed on the sieved fractions of unmilled and milled aspirin. Water was used as the dispersant.

Surface Energy Heterogeneity

All analyses were carried out using iGC Surface Energy Analyzer (SMS, Alperton, UK) and the data were analysed using both standard and advanced SEA Analysis Software. For all experiments, about 2g of samples were packed into individual silanised glass column (300mm long by 4mm inner diameter) using the SMS Column Packing Accessory.

Samples were run at a series of surface coverages with alkanes and polar probe molecules to determine the dispersive surface energy distribution. For the analysis, method of Dorris and Gray was employed for dispersive component [8].Each column was pre-conditioned for 2 hours at 30°C and 0%RH with helium carrier gas to remove any physisorbed water. All experiments were carried out at 30°C with 10sccm total flow rate of helium, using methane for dead volume corrections.

Results

Particle Size

Particle size distributions for the unmilled and milled aspirin powders at 75-106 µm and 150-250 µm particle size fractions are shown in Figure 1. Also, the d_{10}, d_{50}, and d_{90} values are listed in Table 1. As Figure 1 and Table 1 show, there are only minimal differences in the particle size distributions between the unmilled and milled aspirin samples at the same sieve fractions. For the 75-106 µm sieve fraction, the milled powders have a slightly larger average particle size value (73.1 compared to 61.8 µm). For the 150-250 µm particle size fraction, the milled aspirin powder has a slightly lower average particle diameter (93.6 compared to 95.6 µm). These differences are considered minor. Also, DSC and XRD experiments (data not shown) confirm that there is neither change in polymorphic forms nor amorphization of the samples post milling.

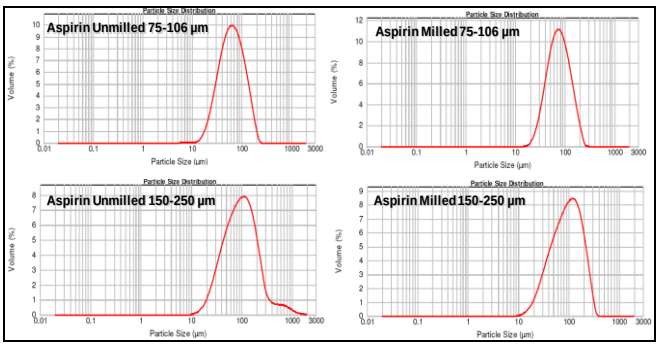


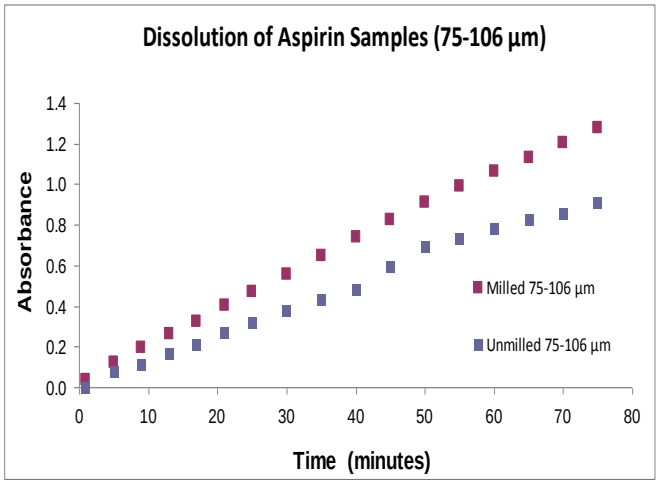
Figure 1. Particle size distribution plots for the sieved-milled samples and sieved-unmilled samples.

Table 1. Particle size results for the sieved-milled samples and sieved-unmilled samples.

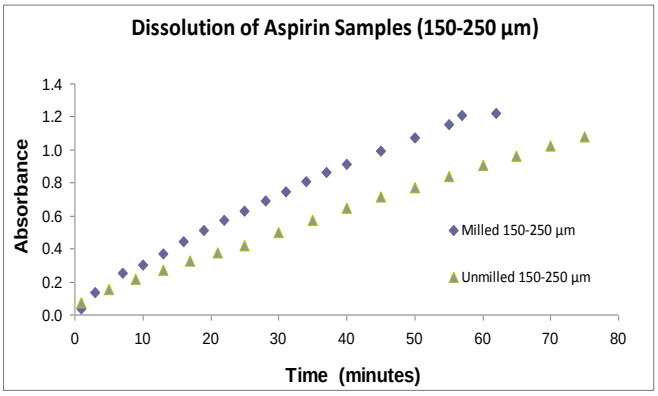
Sample	d_{10} [µm]	d_{50} [µm]	d_{90} [µm]
Unmilled 75-106 µm	29.0	61.8	127.2
Unmilled 150-250 µm	35.2	95.6	241.3
Milled 75-106 µm	37.3	73.1	142.2
Milled 150-250 µm	34.2	93.6	205.3

Dissolution Behaviour

Figure 2 displays the dissolution results for the unmilled and milled compacted aspirin samples at 75-106 µm (2a.) and 150-250 µm (2b.) particle size fractions. Clearly, dissolution behaviour is influenced by both particle size and milling. Smaller particles (75-106 µm) dissolved faster than the larger particles (150-250 µm). Additionally, for both particle size fractions, the milled samples dissolved faster than the unmilled samples. As stated previously, there was no evidence of amorphous regions or polymorphic changes in the milled samples. The equilibrium solubility of all samples was found to be similar. Therefore, it is expected that the differences in dissolution behaviour is driven by surface phenomena.



(2a.)



(2b.)

Figure 2a & 2b: Dissolution results for the milled and unmilled aspirin compacted samples at two sieve fractions.

Dispersive Surface Energy Heterogeneity

Dispersive surface energy profiles for the unmilled and milled samples at the two sieve fractions are displayed in Figure 3. For the unmilled samples, dispersive surface energy values measured via iGC-SEA in this study range from ~37 mJ/m^2 to ~25 mJ/m^2. These are in excellent agreement with dispersive surface energies measured on the individual facets of single crystals previously determined by contact angle measurements: 32.4 mJ/m^2 for (001), 32.5 mJ/m^2 for (100) and 37.2 mJ/m^2 for (011) crystal planes [9]. For both particle size fractions, the milled samples have higher dispersive surface energy values, particularly at low fractional surface coverages (i.e. below 0.1 n/n_m). This could be due to the formation of defect sites, kinks, steps, or exposure of higher energy (011) plane during the milling process. As mentioned earlier, there was no evidence of any bulk amorphization via X-Ray Diffraction and Differential Scanning Calorimetry. Therefore, the higher surface energy values are most likely not due to amorphous regions. At high surface coverages (i.e. greater than 0.2 n/n_m) all four samples have similar dispersive surface energy values. This would lead to similar average surface energy values as measured by traditional wetting techniques (i.e. contact angle). Therefore, the full

surface energy heterogeneity profiles obtained in this study elucidate clear differences in surface properties that may not be detected using liquid based wetting techniques.

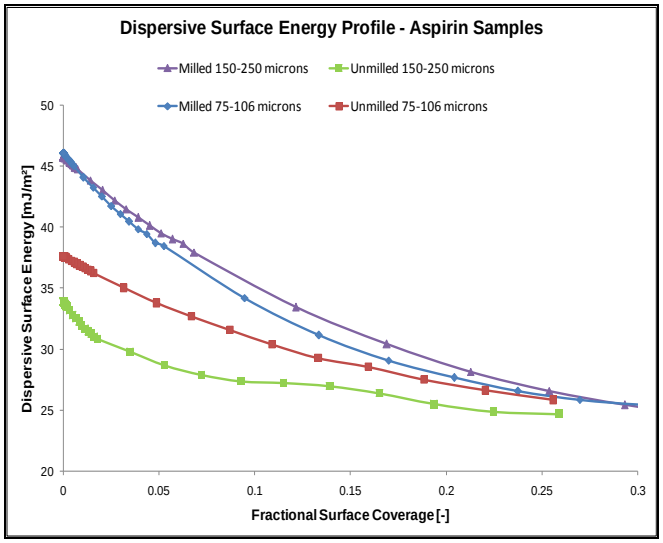


Figure 3. Dispersive surface energy heterogeneity profiles for unmilled and milled aspirin powders at two particle size fractions.

The higher dispersive surface energy values correlate to the faster dissolution rates of the milled samples at both particle size fractions. Again, bulk particle properties are similar for the milled and unmilled samples (i.e. similar surface area, particle size, XRD spectra, and DSC curves). Therefore, the differences between milled and unmilled are most likely dominated by surface properties. A higher surface energy would lead to faster initial wetting which in turn would result in faster dissolution. Another possible explanation would be milling also increases surface roughness, which was not measured in this study. This could also affect the wetting and dissolution behaviour.

Conclusions

Dispersive surface energy profiles were measured on milled and unmilled aspirin powders and compared to dissolution behaviour. Milling clearly increased the dispersive surface energy and dissolution behaviour of aspirin powders, even when normalized by particle size fraction. This study shows that surface energy differences can lead to differences in bulk powder performance properties like dissolution behaviour.

References

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