Effect of Processing Route on the Physical Properties of Amorphous Indomethacin

Jiyi Khoo1, Daniel J. Burnett1, Majid Naderi1, George D. Wang2 and Jerry Y.Y. Heng2

Surface Measurement Systems Ltd. | Department of Chemical Engineering, Imperial College London,

The aim of this case study was to investigate the effect of processing routes on material surface properties as a function of surface energetics. Inverse Gas Chromatography (IGC) was employed for determination of surface energy distributions and surface acid-base properties of crystalline, milled and amorphous Indomethacin samples.

Introduction

Crystalline active pharmaceutical ingredients can become amorphous either intentionally (i.e. spray-drying, freeze-drying, extrusion etc.) or unintentionally during different manufacturing processes (e.g. blending and micronization).

Even though they may be produced via all above processing routes, these amorphous regions can be manifested throughout the entire crystal, or affect only the surface of crystal, or even at localised points of the surface. Hence, the physical properties and ultimate behaviour of these materials may vary dramatically [1]. The changes in behaviour subsequently can relate to difficulties in product formulation and even the final product attributes, such as wet granulation of micronised drugs and performance variability in inhalation products.

Finite concentration Inverse Gas Chromatography (IGC) experiments allow for the determination of surface energy distributions which more accurately describe the anisotropic surface energy for real materials. In this case study, the surface energy heterogeneity and surface acid-base properties of Indomethacin were measured to investigate the effects of different processing routes on material surface properties.

Indomethacin was used as model compound for this work. It is an anti-pyretic and anti-inflammatory drug used in many pharmaceutical preparations [2, 3]. It has been proposed to have up to four polymorphic forms, though α- and γ- forms are the most commonly studied [4].

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 [5].

Method

Material – Indomethacin

Indomethacin (>98% purity, γ-form) was provided by Novartis Pharmaceuticals Ltd. (Basel, Switzerland). Crystalline Indomethacin was used as received (Figure 1).
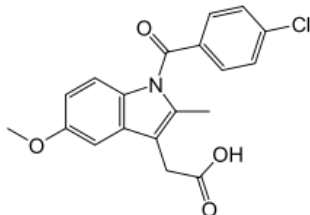

Figure 1. Molecular structure of Indomethacin

Preparative Techniques

Amorphous Indomethacin was prepared by quench cooling. About 150mg of as-received crystalline Indomethacin was weighted into a circular aluminium weighing boat and was heated on a hotplate at a temperature above its melting point: 175°C. The sample was heated for about 5 minutes and until it was fully vitrified – with no apparent crystallinity, bubbles or signs of decomposition. The glassy Indomethacin was then grinded gently into powder form using pestle and mortar.

Another sample of crystalline Indomethacin was subjected to milling using a ceramic ball mill apparatus. About 7g of crystalline Indomethacin and 20 ceramic balls (approximate 13.5mm in diameter) were placed in a sealed 1L ceramic jar (mass ratio 1:40). The ball mill apparatus was rotated on a Pascall Engineering 1600-VS-A roller mixer at a setting of 10 for a period of two hours.

All samples were sieved to a particle size fraction of 90-106μm to minimize any dependence on particle size and focus on differences in surface properties. Quench cooled and milled samples were kept in dessicator prior to any IGC measurements.

Characterisation of Samples

Powder X-ray diffraction (PXRD) and differential scanning calorimetry (DSC) were performed to confirm the presence of amorphous form and/or any disordered forms. Measurements were performed immediately after quench cooling and milling as disordered Indomethacin is known to be highly unstable, with a relatively low glass transition temperature (T_g between 42~45°C) [6, 7].

PXRD diffractograms of all samples were obtained by using a X'Pert Pro diffractometer (PANalytical B.V., Almelo, The Netherlands). Samples were gently consolidated in a flat aluminium sample holder and scanned from 5° to 60° 2θ with a Cu Kα radiation generated at 40kV and 40mA. About 8mg of sample was crimped in an aluminium DSC pan. Samples were heated from 25°C to 180°C at a ramping rate of 20°C/min, under a nitrogen gas flow of 50mL/min. The calorimeter was calibrated with indium.

Results

Characterisation of Indomethacin Samples

Figure 2 shows the PXRD diffractograms of the as-received crystalline Indomethacin and processed Indomethacin samples. Complete absence of diffraction peaks in the diffractograms (amorphous halo) of quench cooled Indomethacin revealed that the sample was completely amorphous. Milled Indomethacin, on the other

hand, shows merely a small reduction in crystallinity, in particular over the range of angle 15° to 25° 2θ, presumably due to formation of disordered regions on the milled surfaces.

DSC thermograms of all samples are depicted in Figure 3. Crystalline Indomethacin (γ-form) shows a distinct endotherm as its melting peak, at temperature onset 160°C. However, for milled Indomethacin, there are two endotherms with onsets at 154°C and 160°C, which were reported as the melting peaks of metastable α- and γ-form of Indomethacin polymorphs. It is therefore assumed that a small fraction of the disorder regions may have transformed into the α-Indomethacin.

For quench cooled Indomethacin, the DSC thermograms exhibited an additional endotherm at 45°C ±5°C, and an exothermic event in the range of 100 – 140°C. These thermal events can be associated with the glass transition (T_g) of the sample, and recrystallization of amorphous Indomethacin. Only one melting peak was observed at 152°C onset, implying that quenched cooled sample crystallised entirely into the α-Indomethacin.

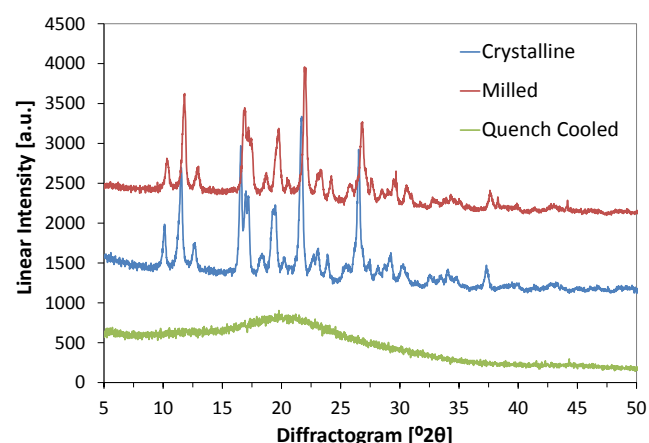*Figure 3. Thermograms of crystalline form, ball-milled and quench cooled Indomethacin samples.*
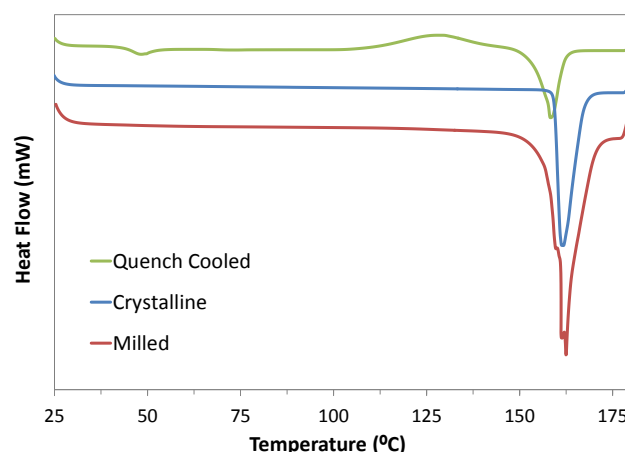

Figure 2. PXRD diffractograms of crystalline form, ball-milled and quench cooled Indomethacin samples.

Dispersive Surface Energy Heterogeneity

Dispersive (γ_s^D) surface energy profiles for the crystalline, milled and quench cooled Indomethacins are displayed in Figure 4.

Dispersive surface energy profiles show similar shapes for the crystalline and quench cooled Indomethacin, with the quench cooled form having marginally higher dispersive surface energy values across the surface coverage range measured. Even crystalline sample shows some degree of heterogeneity. This could be due to different crystal facets having different surface

energies. This phenomena has been observed previously for several different materials [9, 10].

Between the three samples, milled Indomethacin has much higher dispersive surface energy values across the entire range of surface coverages measured. In addition, the milled sample exhibited a fairly homogenous dispersive surface energy profile.

Data in Figure 4 is fitted to a an empirical function and converted into a normalized distribution to display the surface energy results in a more clear manner in Figure 5. Milled Indomethacin has a higher average value, but a narrower distribution. The difference in surface energy between the minimum and maximum values determined is only ~2.5 mJ/m^2 ($\gamma_s^D{}_{min}$ 41.26 mJ/m^2, $\gamma_s^D{}_{max}$ 43.77 mJ/m^2).

It is clearly shown that the quench cooled Indomethacin does have a slightly higher average dispersive surface energy value and wider variation of surface sites ~8.8 mJ/m^2 ($\gamma_s^D{}_{min}$ 34.81 mJ/m^2, $\gamma_s^D{}_{max}$ 43.62 mJ/m^2), compared to the crystalline Indomethacin with a variation of ~7.6 mJ/m^2.

As mentioned earlier, there was no evidence of any bulk amorphisation in milled Indomethacin from PXRD and DSC results. Therefore, the higher surface energy values on milled surfaces could be due to formation of defect sites, kinks, steps etc. or exposure of higher energy crystal facets during the milling process.

It has been demonstrated that dispersive surface energy profiles can be used to detect subtle changes on the surface properties, and to differentiate materials prepared from different processing routes, i.e. quench cooling and milling.
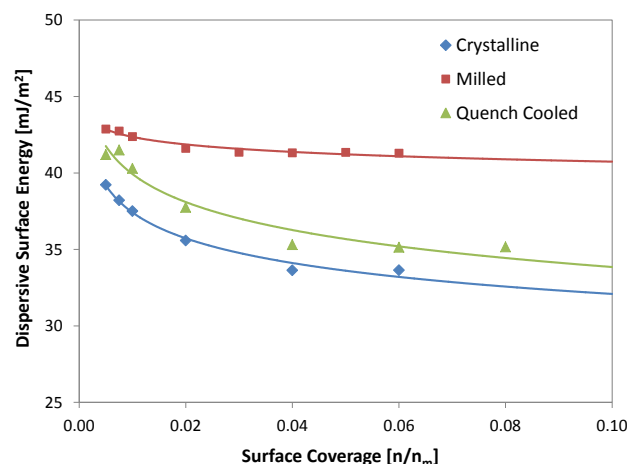

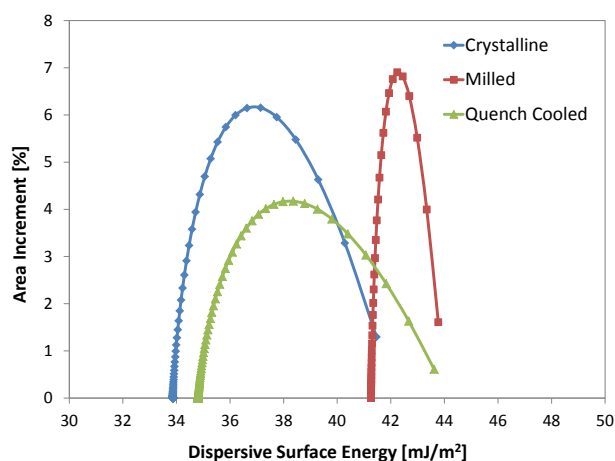*Figure 4. Dispersive surface energy profiles of Indomethacin samples.*

Figure 5. Dispersive surface energy distributions of Indomethacin samples.

Acid-Base Surface Energy and Electron Donor-Acceptor Properties

The acid-base (γ_s^{AB}) component of the surface energy was determined using the Good-Van Oss-Chadury approach and applying the Della Volpe scale [11]. Figure 6 depicts that the crystalline Indomethacin has the lowest specific (acid-base) surface energy values, meanwhile the milled and quench cooled samples have measurably higher surface energy values. Specific (acid-base) surface energy values indicate a more uniform distribution on the quench cooled sample, whereas the milled sample is more heterogeneous (Figure 7).
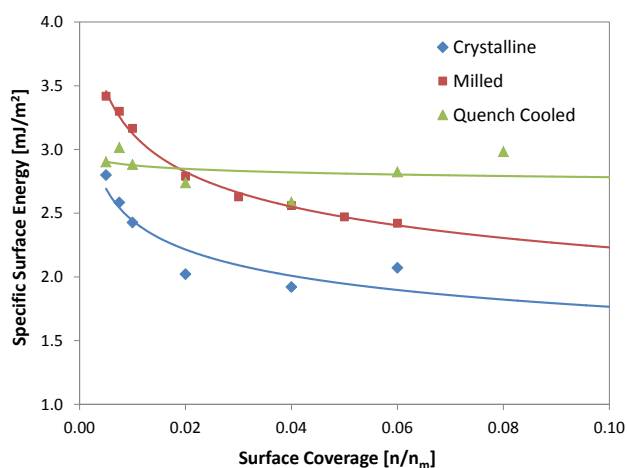
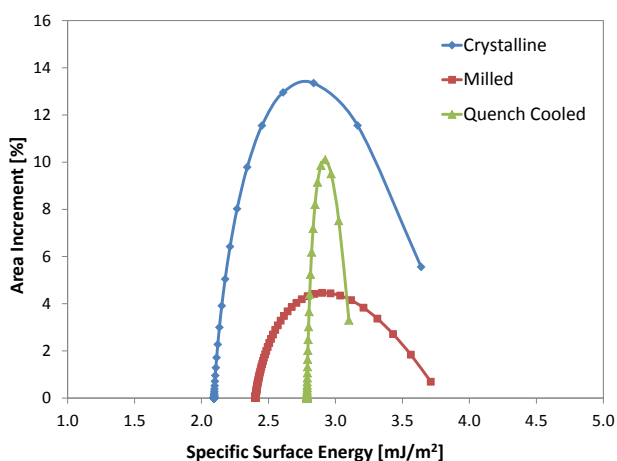Figure 6. Specific (acid-base) surface energy profiles of Indomethacin samples.

Figure 7. Specific (acid-base) surface energy distributions of indomethacin samples.

The Gutmann acid-base theory was applied to determine the electron donor-acceptor properties of the material surfaces. Figure 8 shows that all samples have higher base number (K_b), than acid number (K_a) across the entire surface coverage range measured, implying Indomethacin surfaces are more basic in nature. This also shows that all surfaces possess higher concentration of electron-donating functional groups.

K_a/K_b ratio profiles in Figure 9 clearly depicts that crystalline Indomethacin has the lowest electron donor values, followed by quench cooled sample which has marginally higher electron donor

values. The milled Indomethacin has the higest electron donor values. Although both processed Indomethacins have disordered/amorphous regions, their surface properties are notably different, as detected by iGC SEA.
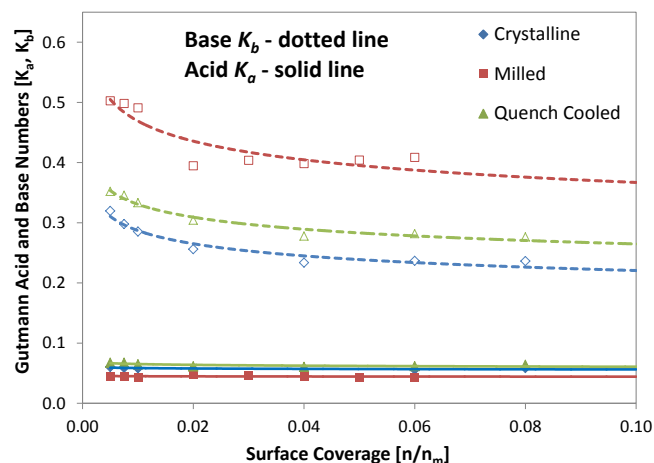

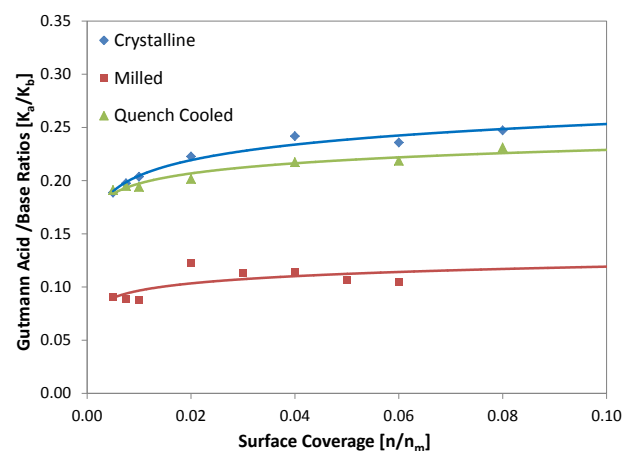Figure 8. Gutmann acid and base number profiles of Indomethacin samples.

Figure 9. Gutmann acid and base ratio profiles of Indomethacin samples

Conclusion

Surface properties of Indomethacin with different processing routes were investigated. Although quench cooling and milling both produced disorder and amorphous regions, their surface properties were measurably different as determined by IGC. The milled Indomethacin sample had a relatively higher dispersive surface energy and higher surface basicity (electron donor capability). These properties could cause the sample to interact differently with other surfaces (i.e. excipients, devices, and processing equipment). Therefore, both final product state (crystalline or amorphous) and processing route must be controlled to maintain the final product's desired physical properties.

References

[1] Thielmann, F., Burnett, D.J. and Heng, J.Y.Y. (2007) Determination of the surface energy distributions of different processed lactose. Drug Dev. & Ind. Pharm. 33, p1240-1253.

[2] Shen, T.Y., Lucas, S., Sarett, L.H. et. al (1963) Non-steroid anti-inflammatory agents. J. Am. Chem. Soc. 85, p488–489.

[3] Winter, C.A., Risley, E.A. and Nuss, G.W. (1963) Anti-inflammatory and antipyretic activities of indo-methacin, 1-(p-chlorobenzoyl)-5-methoxy-2-methyl-indole-3-acetic acid. J. Pharmacol. Exp. Ther. 141, p369–376.

[4] Borka, L. (1974) Polymorphism of indomethacin – new modifications, their melting behavior and solubility. Acta Pharm. Suec. 11, p295–303.

[5] Yla-Maihaniemi, P.P., Heng, J.Y.Y., Thielmann, F., and Williams, D.R. (2008) Inverse gas chromatographic method for measuring the dispersive surface energy distribution for particulates. Langmuir 24, p9551-9557.

[6] Planinsek, O., Zadnik, J., Kunaver, M. et. al (2010) Structural evolution of indomethacin particles upon milling: time-resolved quantification and localization of disordered structure studied by IGC and DSC. J. Pharm. Sci. 99, p1968–1980.

[7] Karmwar, P., Graeser, K., Gordon, K.C. et. al (2011) Investigation of properties and recrystallisation behaviour of amorphous indomethacin samples prepared by different methods. Int. J. Pharm. 417, p94–100.

[8] Dorris, G.M. and Gray, D.G. (1980) Adsorption of n-alkanes at zero surface coverage on cellulose paper and wood fibers. J. Colloid & Interface Sci. 77, p353-362.

[9] Heng, J.Y.Y., Bismark, A. and Williams, D.R. (2006) Anisotropic surface chemistry of crystalline pharmaceutical solids. AAPS Pharm. Sci. Tech. 7, Article 84.

[10] Ho, R., Hinder, S.J., Watts, J.F. et. al (2010) Determination of surface heterogeneity of D-mannitol by sessile drop contact angle and finite concentration inverse gas chromatography. Int. J. Pharm. 387, p79-86.

[11] Della Volpe, C. and Siboni, S. (1997) Some reflections on acid-base solid surface free energy theories. J. Colloid Interface Sci. 195, p121-136.