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¹ Effect of crystal habits on the surface energy and cohesion of crystalline ² powders

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A R T I C L E I N F O

8 **Q2**

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A B S T R A C T

The role of surface properties, influenced by particle processing, in particle–particle interactions (powder cohesion) is investigated in this study. Wetting behaviour of mefenamic acid was found to be anisotropic by sessile drop contact angle measurements on macroscopic (>1 cm) single crystals, with variations in contact angle of water from 56.3 $^{\circ}$ to 92.0 $^{\circ}$. This is attributed to variations in surface chemical functionality at specific facets, and confirmed using X-ray photoelectron spectroscopy (XPS). Using a finite dilution inverse gas chromatography (FD-IGC) approach, the surface energy heterogeneity of powders was determined. The surface energy profile of different mefenamic acid crystal habits was directly related to the relative exposure of different crystal facets. Cohesion, determined by a uniaxial compression test, was also found to relate to surface energy of the powders. By employing a surface modification (silanisation) approach, the contribution from crystal shape from surface area and surface energy was decoupled. By "normalising" contribution from surface energy and surface area, needle shaped crystals were found to be \sim 2.5 \times more cohesive compared to elongated plates or hexagonal cuboid shapes crystals.

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⁹ 1. Introduction

10 The role of the physicochemical properties of particulate ¹¹ pharmaceutical materials on their cohesion and powder flow
¹² expressive heast tracted sytematic associate interest in the next four 12 properties has attracted extensive research interest in the past four
13 decedes (Fang et al. 2007: Kaerger et al. 2004: Lam and Nakagawa 13 decades (Feng et al., 2007; Kaerger et al., 2004; Lam and [Nakagawa,](#page--1-0)
14 1004: Redszeck, and Mia 1006; Redszeck, and Pávész, 1003; ¹⁴ 1994; [Podczeck](#page--1-0) and Mia, 1996; Podczeck and Révész, 1993; 15 Ridgway and [Morland,](#page--1-0) 1977). Understanding the role of physico-
 16 chemical properties on cohesion and the development of strategies 16 chemical properties on cohesion and the development of strategies
 17 to control cohesion by tailoring the properties of pharmaceutical 17 to control cohesion by tailoring the properties of pharmaceutical
 18 materials may be critically important for efficient and cost effective ¹⁸ materials may be critically important for efficient and cost effective
¹⁹ processing (Hou and Sun. 2008). The effect of particle shape and 19 processing (Hou and Sun, [2008](#page--1-0)). The effect of particle shape and 20 size on powder flow and cohesion is referred extensively in the ²⁰ size on powder flow and cohesion is referred extensively in the ²¹ literature [\(Jones](#page--1-0) et al., 2003). Moreland and Ridgway were the first $\frac{22}{100}$ to report the effect of particle change on bulk density (Bidgway and to report the effect of particle shape on bulk density ([Ridgway](#page--1-0) and

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[Morland,](#page--1-0) 1977). Podczeck and Mia reported the effect of particle $\frac{23}{24}$ size and shape on the Hausner ratio and angle of internal friction 24
(Bedracehemd Min 4006). Therefore description is interesting as 25 ([Podczeck](#page--1-0) and Mia, 1996). They found particles with higher aspect 25
notic (needle shaped smutal), showed a higher angle of internal 26 ratio (needle shaped crystal), showed a higher angle of internal 26
fristion Kasuzes at al investigated the effect of partials shape and 27 friction. Kaerger et al. investigated the effect of particle shape and 27
size on flow and compaction behaviour of blonds, reporting that 28 size on flow and compaction behaviour of blends, reporting that 28
blonds containing spherical paracetamel particles (propared using 29 29

blends containing spherical paracetamol particles (prepared using 29

cryptallication by conjection) with microcryptalling collulose had 30 crystallisation by sonication) with microcrystalline cellulose had³⁰
improved flow properties compared to micropised particles $\frac{31}{2}$ improved flow properties compared to micronised particles $\frac{31}{12004}$ Camble at al investigated the effect of $\frac{32}{12004}$ ([Kaerger](#page--1-0) et al., 2004). Gamble et al. investigated the effect of 32
different sub-populations e.g. agglomerates and primary particles 33 different sub-populations *e.g.* agglomerates and primary particles, $\frac{33}{12}$ highlighting the effect of the presence of agglomerates in 34
enhancing the flow properties of bulk primary particles (Camble 35 enhancing the flow properties of bulk primary particles [\(Gamble](#page--1-0) 35
et al. 2011). Di Martino et al. studied the effect of different crystal 36 et al., [2011](#page--1-0)). Di Martino et al. studied the effect of different crystal 36
shapes of ibungers on compression and flow proportion 37 shapes of ibuprofen on compression and flow properties, 37
bighlighting improved dependenties of the emost coin tupe 38 highlighting improved densification of the smooth coin type 38
crystal habit compared to other crystals habits, which were 39 crystal habit compared to other crystals habits, which were 39
attributed to the increase in powder hed porosity 40 attributed to the increase in powder bed porosity.
Crystals of the same polymorphic form with different crystal 41

Crystals of the same polymorphic form with different crystal $\frac{41}{42}$
apper (babits) can be obtained by varying the relative growth $\frac{42}{42}$ shapes (habits) can be obtained by varying the relative growth 42
rates of the different crystals facets. This in turn can be dependent 43 rates of the different crystals facets. This in turn can be dependent

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44 on material intrinsic properties or be affected by properties of the crystallisation solvent crystal growth inhibitors or additives ⁴⁵ crystallisation solvent, crystal growth inhibitors or additives
⁴⁶ (Barkovitch Vellin 1985: Bourne and Davey 1976; Lovette et al. 46 ([Berkovitch-Yellin,](#page--1-0) 1985; Bourne and Davey, 1976; Lovette et al., 47 2008) Crystal babits not only determine the main bulk properties 47 [2008](#page--1-0)). Crystal habits not only determine the main bulk properties
 48 ef the crystalline material (e.g. bulk density, flowshility, and ⁴⁸ of the crystalline material (*e.g.* bulk density, flowability and mechanical strength) but also alter the surface energy (Ho et al. $\frac{49}{2012}$ mechanical strength) but also alter the surface energy [\(Ho](#page--1-0) et al., $\frac{50}{51}$ [2012](#page--1-0)).

⁵¹ Surface energy of crystalline pharmaceutical materials has been
 $\frac{52}{2}$ chown to be anisotropic (Hope at al. 2006a, 2007; He at al. 2008 $\frac{52}{53}$ shown to be anisotropic (Heng et al., [2006a,](#page--1-0) 2007; Ho et al., 2008, $\frac{53}{2010}$ $\frac{53}{2010}$ $\frac{53}{2010}$. Facet specific surface energy of organic crystalline material $\frac{54}{20100}$ and $\frac{1}{201000}$ and $\frac{1}{201000}$ and $\frac{1}{201000}$ and $\frac{1}{201000}$ and $\frac{1}{201000}$ and $\frac{1}{201000}$ and $\frac{1}{20100$ 55 was directly correlated with the chemical functional groups
 55 supposed on the gruttel foot surfaces using sontast angle and Y 55 exposed on the crystal facet surfaces using contact angle and X-⁵⁶ ray photoelectron spectroscopy (XPS) measurements. Considering $\frac{57}{2}$ the feast specific surface aparty of a smutalling material it is 57 the facet specific surface energy of a crystalline material, it is 58 existalling a surface 58 postulated that surface energetics of the crystalline powders
 59 depend on the relative surface energy contributions of the 59 depend on the relative surface energy contributions of the
 60 different crystal facets Using D manuitel as a model system Ho 60 different crystal facets. Using D-mannitol as a model system, Ho
 61 et al. demonstrated that decreasing the aspect ratio of peodle ⁶¹ et al. demonstrated that decreasing the aspect ratio of needle
⁶² ebanged crystals resulted in a decreasing shift in the overall 62 shaped crystals resulted in a decreasing shift in the overall contribution of the dispersive component of the surface energy 63 contribution of the dispersive component of the surface energy.
 64 This was attributed to the increasing contribution of the facet ⁶⁴ This was attributed to the increasing contribution of the facet
⁶⁵ showing lowest dispersive component of surface energy (facet (0) ⁶⁵ showing lowest dispersive component of surface energy (facet (0
 66 11)) (Ho et al. 2012). The ability to tailor crystal babits will result in 66 11)) (Ho et al., [2012\)](#page--1-0). The ability to tailor crystal habits will result in the change in the relative contribution of different crystal facets ⁶⁷ the change in the relative contribution of different crystal facets.
⁶⁸ This change will result in a dissimilar surface energy of the 68 This change will result in a dissimilar surface energy of the crystalline powders, which may have an impact on powder 69 crystalline powders, which may have an impact on powder 70 cobesion 70 cohesion.

⁷¹ Although it is well known that particle–particle interactions,
⁷² e g cohesion/adhesion are governed by the surface the effect of 72 e.g. cohesion/adhesion, are governed by the surface, the effect of 73 crystal shapes on powder flow properties have not considered the 73 crystal shapes on powder flow properties have not considered the 74 impact of the anisotropic surface properties of the crystals 74 impact of the anisotropic surface properties of the crystals.
 75 Considering that particle shape surface energy and surface area 75 Considering that particle shape, surface energy and surface area
 76 can influence flow properties it is essential to understand the 76 can influence flow properties, it is essential to understand the 77 contribution of each of these factors $\frac{77}{78}$ contribution of each of these factors.

 78 This study aims to firstly study the effect of crystal habit on 79 surface operay and cohering of crystalline pharmaceutical 79 surface energy and cohesion of crystalline pharmaceutical 80 pougless Secondly an approach to decouple the contributions $\frac{80}{100}$ powders. Secondly, an approach to decouple the contributions $\frac{81}{1000}$ of surface aperay and particle shape is presented Mefenamic Acid. ⁸¹ of surface energy and particle shape is presented. Mefenamic Acid, $\frac{82}{2}$, a pop steroidal, anti-inflammatory drug is used as a model $\frac{82}{3}$ a non-steroidal, anti-inflammatory drug, is used as a model
 $\frac{83}{3}$ compound Macroscopic single crystals of mefenamic acid are compound. Macroscopic single crystals of mefenamic acid are 84 grown and used for determining facet specific surface energies.
 85 This is then correlated to the surface energy betergeonaity. $\frac{85}{100}$ This is then correlated to the surface energy heterogeneity $\frac{86}{100}$ measurements of gratalling pourders of metaphysics and gratal $\frac{86}{2}$ measurements of crystalline powders of mefenamic acid crystal-
 $\frac{87}{2}$ lised in different crystal babits. Cohesian values of different shape $\frac{87}{100}$ lised in different crystal habits. Cohesion values of different shape ⁸⁸ mefenamic crystal were measured using a uniaxial compression
 $\frac{89}{100}$ to the Desults uses correlated with surface operational crystal shape ⁸⁹ test. Results were correlated with surface energy and crystal shape
 $\frac{90}{20}$ to elucidate their respective effect on sebesian Eurther the effect ⁹⁰ to elucidate their respective effect on cohesion. Further, the effect $\frac{91}{100}$ of surface onergy on cohesion was "normalised" with silapication 91 of surface energy on cohesion was "normalised" with silanisation
 92 of metapomic acid, allowing do coupling the contribution of $\frac{92}{23}$ of mefenamic acid, allowing de-coupling the contribution of $\frac{93}{23}$ cructal shape on sobosion from that of surface operation and surface 93 crystal shape on cohesion from that of surface energy and surface 94 area.

⁹⁵ 2. Materials

96 Mefenamic acid (2-(2, 3-dimethylphenyl) amino benzoic acid)
97 (99.0% Sigma-Aldrich Dorset IIK) acetone (>99.5%) and methanol 97 (99.0% Sigma–Aldrich, Dorset, UK), acetone (>99.5%) and methanol
98 (>99.5%) were obtained from VMR BDH Prolabo, Lutterworth, LIK 98 (>99.5%) were obtained from VWR BDH Prolabo, Lutterworth, UK
99 and used for growth of a macroscopic single crystal of mefenamic ⁹⁹ and used for growth of a macroscopic single crystal of mefenamic
¹⁰⁰ acid Toluene (>99.5%) diethyl ether (>99.5%) ethyl acetate 100 acid. Toluene (>99.5%), diethyl ether (>99.5%), ethyl acetate $(>99.5\%)$, dichloromethane (>99.0%) acetone (>99.5%) isopropyl ¹⁰¹ (>99.5%), dichloromethane (>99.0%), acetone (>99.5%), isopropyl
¹⁰² alcohol (>99.5%) and methanol (>99.5%) were all received from 102 alcohol (>99.5%) and methanol (>99.5%) were all received from 103 VWR BDH Prolabo Tutterworth TIK and used without further 103 VWR BDH Prolabo, Lutterworth, UK and used without further 104 purification for crystallisation of different crystal habits of ¹⁰⁴ purification for crystallisation of different crystal habits of 105 mefenamic acid Dejonised water ethylene glycol (>99.0% Sigma ¹⁰⁵ mefenamic acid. Deionised water, ethylene glycol (>99.0%, Sigma
¹⁰⁶ Aldrich Dorset UK) formamide (>99.5% Acros Organics Tough-¹⁰⁶ Aldrich, Dorset, UK), formamide (>99.5%, Acros Organics, Lough-
¹⁰⁷ harvesh UK), and dijedemathane (>99.9%, Agree Organics, borough, UK) and diiodomethane (>99.0%, Acros Organics, Loughborough, UK) were used as probe liquids for contact angle 108
measurements in beyang (500.0%) othul acetate (500.5%) and 109 measurements. *n*-hexane (>99.0%), ethyl acetate (>99.5%) and 109
dishloromethane (>99.5%) were obtained from VA/P BDH Brolabo ¹¹⁰ dichloromethane (>99.5%) were obtained from VWR BDH Prolabo, Lutterworth, UK), whereas *n*-heptane (\geq 99.0), *n*-octane (\geq 99.0%), ¹¹¹
n nonane (\geq 00.0%) and *n* decane (\geq 00.0%) were obtained from ¹¹² *n*-nonane (\geq 99.0%) and *n*-decane (\geq 99.0%) were obtained from 112
Sigma Aldrich Dorset UK and used without further purification as 113 Sigma–Aldrich, Dorset, UK and used without further purification as probe liquids in inverse phase gas chromatography. 114

3. Methods 115

¹¹⁶ 3.1. Growth of mefenamic acid macroscopic single crystal

Mefenamic acid seed crystals of a few millimetres in size were 117
tained from along approaching of a supergeturated solution of 118 obtained from slow evaporation of a supersaturated solution of ¹¹⁸
materials as a setting an mathemal at game temperature. ¹¹⁹ mefenamic acid in acetone or methanol at room temperature. ¹¹⁹
Macroscopic cingle gratals were obtained by claw solvent. ¹²⁰ Macroscopic single crystals were obtained by slow solvent 120
synocration from seturated mothanol solution at room tempora 121 evaporation from saturated methanol solution at room tempera-
ture A saturated solution of methanol in methanol was a 122 ture. A saturated solution of mefenamic acid in methanol was 122
prepared under constant stirring A single seed of mefenamic acid prepared under constant stirring. A single seed of mefenamic acid and the state of method in the state of 124 crystal was tied with an aramid fibre and suspended in the 124
seturated solution which is kent without stirring Slow evapora 125 saturated solution, which is kept without stirring. Slow evapora- 125
tion of the solvent was maintained resulting in the crystal growth 126 tion of the solvent was maintained resulting in the crystal growth. 126
The saturated solution of meteoromic acid in methanol was 127 The saturated solution of mefenamic acid in methanol was 127
periodically changed Macroscopic single crystals of mefenamic periodically changed. Macroscopic single crystals of mefenamic 128
asid obtained were dried under ambient conditions and weed for 129 acid obtained were dried under ambient conditions and used for 129
further abaracterisation and contact angle measurements 130 further characterisation and contact angle measurements.

¹³¹ 3.2. Crystallisation of mefenamic acid from different solvent systems

Saturated solutions of mefenamic acid in seven different 132
sanic solvents with varying polarity were propaged at $50\degree C$ Λ 133 organic solvents with varying polarity were prepared at 50° C. A 133°
single stap cooling profile was adopted. Saturated solutions of 134 single step cooling profile was adopted. Saturated solutions of 134
motonamic acid at 50 °C wore transformed to an incubator (Surface 135 mefenamic acid at 50 °C were transferred to an incubator (Surface 135
Measurement, Sustams, Ltd., London, LIK), maintained, at $4\degree$ C 136 Measurement Systems Ltd. London, UK) maintained at 4° C. ¹³⁶ Measurement scid crustals obtained after 24 b were filtered through 137 Mefenamic acid crystals obtained after 24 h were filtered through $\frac{137}{2}$ general-purpose laboratory filter paper (Whatman, UK) and dried
under ambient conditions. Dried crystals were stared in the glass and the under ambient conditions. Dried crystals were stored in the glass 139
container and used for further characterisation container and used for further characterisation.

¹⁴¹ 3.3. Silanisation of mefenamic acid powders

¹⁴² Recrystallised mefenamic acid powders were silanised using a ¹⁴³ protocol reported in the literature [\(Al-Chalabi](#page--1-0) et al., 1990). In a ¹⁴⁴ typical process, 500 mg of mefenamic acid powder was added to a 50 mL 5% (v/v) solution of dichlorodimethylsilane in cyclohexane. 145
The mixture was refluxed at 80 % for 24 b. Then the reastion 146 The mixture was refluxed at 80° C for 24 h. Then, the reaction 146
mixture is allowed to seel down to ream temperature and filtered 147 mixture is allowed to cool down to room temperature and filtered 147
using general nurpose, laboratory filter paper (Whatman, $1W$) 148 using general-purpose laboratory filter paper (Whatman, UK) 148
followed by drying in a vacuum over at 80% for 4b, Bost 149 followed by drying in a vacuum oven at 80° C for 4 h. Post 149
silapisation the silapised metapamic asid poughers were stared in 150 silanisation, the silanised mefenamic acid powders were stored in $\frac{150}{151}$ a glass vial at ambient conditions.

¹⁵² 3.4. Single crystal X-ray diffraction for crystal facet indexing

The indexing of the crystal faces was performed using an Oxford
fraction Xcalibur, 3, E. diffractometer, (Agilent, Technologies, 154 Diffraction Xcalibur 3 E diffractometer (Agilent Technologies, 154
Oxford UK) equipped with ceramic XPD C tech tube and Oxford 155 Oxford, UK) equipped with ceramic XRD C-tech tube and Oxford 155
Diffraction Sapphire detector, Single crystal Y ray diffraction data 156 Diffraction Sapphire detector. Single crystal X-ray diffraction data was obtained at 50 kV and 40 mA. Based on the single crystal X-ray 157 diffraction data crystal facets were indexed using Agilent $Q4$ 158 ¹⁵⁹ CrysAlisPro (Agilent Technologies, Oxford, UK) software system.

3.5. Contact angle measurements of a macroscopic single crystal 160

A Krüss Drop Shape Analyser DSA 10 (Krüss GmbH, Hamburg, 161 Germany) was used for the static sessile drop contact angle

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