ABSTRACT

The rational design of drug crystals to facilitate particle size reduction

Mohammad Hossain SHARIARE B.Pharm (Hons.)

Keywords: Crystallisation, micronisation, particle size and morphology, mechanical properties, crystallinity, surface free energy, dissolution, aerodynamic characteristics, molecular modelling.

Micronisation of active pharmaceutical ingredients (APIs) to achieve desirable quality attributes for formulation preparation and drug delivery remains a major challenge in the pharmaceutical sciences. It is therefore important that the relationships between crystal structure, the mechanical properties of powders and their subsequent influence on processing behaviour are well understood. The aim of this project was therefore to determine the relative importance of particle attributes including size, crystal quality and morphology on processing behaviour and the characteristics of micronised materials. It was then subsequently intended to link this behaviour back to crystal structure and the nature of molecular packing and intermolecular interactions within the crystal lattice enabling the identification of some generic rules which govern the quality of size reduced powders. In this regard, different sieve fractions of lactose monohydrate and crystal variants of ibuprofen and salbutamol sulphate (size, morphology and crystal quality) were investigated in order to determine those factors with greatest impact on post-micronisation measures of particle quality including particle size, degree of crystallinity and surface energy.

The results showed that smaller sized feedstock should typically be used to achieve ultrafine powders with high crystallinity. This finding is attributed to the reduced number of fracture events necessary to reduce the size of the particles leading to decreases in milling residence time. However the frequency of crystal cracks is also important, with these imperfections being implicated in crack propagation and brittle fracture. Ibuprofen crystals with a greater number of cracks showed a greater propensity for comminution. Salbutamol sulphate with a high degree of crystal dislocations however gave highly energetic powders, with reduced degree of crystallinity owing to the role dislocations play in facilitating plastic deformation, minimising fragmentation and extending the residence of particles in the micronizer. Throughout these studies, morphology was also shown to be critical, with needle like morphology giving increased propensity for size reduction for both ibuprofen and salbutamol sulphate, which is related to the small crack propagation length of these crystals. This behaviour is also attributed to differences in the relative facet areas for the different morphologies of particles, with associated alternative deformation behaviour and slip direction influencing the size reduction process. Molecular modelling demonstrated a general relationship between low energy slip planes, d-spacing and brittleness for a range of materials, with finer particle size distributions achieved for APIs with low value of highest d-spacings for identified slip planes. The highest d-spacing for any material can be readily determined by PXRD (powder x-ray diffraction) which can potentially be used to rank the milling behaviour of pharmaceutical materials and provides a rapid assessment tool to aid process and formulation design.

These studies have shown that a range of crystal properties of feedstock can be controlled in order to provide micronised powders with desirable attributes. These include the size, morphology and the density of defects and dislocations in the crystals of the feedstock. Further studies are however required to identify strategies to ensure inter-batch consistency in these attributes following crystallisation of organic molecules.

Published Work

Sections of the work in this thesis have previously been published or presented in the following form –

Publications as Research Papers

- Shariare, M.H., De Matas, M., York, P. & Shao, Q. (2011) **"The impact of material attributes and process parameters on micronisation of lactose monohydrate"**. *Int. J. Pharm*. 408, pp. 58-66.

- Shariare, M.H., De Matas, M. & York, P. (2011) **"Effect of crystallisation conditions and feedstock morphology on the aerosolization performance of micronised salbutamol sulphate"**. *Int. J. Pharm. 2011, 415: 62-72.*

- Shariare, M.H., Leusen, F.J.J., De Matas, M., Anwar, J. & York, P. (2011) **"Prediction of the mechanical behaviour of active pharmaceutical ingredients"**. *Pharm. Res*. 2011.

- Shariare, M.H., Blagden, N., De Matas, M. & York, P. (2011) **"Influence of solvent properties on the morphology of ibuprofen crystals and its impact on particle size reduction"**. *J. Pharm Sci.* (In Press).

Oral Presentation

- **"A rapid method for predicting the mechanical behaviour of active pharmaceutical ingredients",** Presented at CMP seminar, University of Bradford, UK, March, 2011.

- **"Towards a rapid method for predicting the mechanical behaviour of active pharmaceutical ingredients",** Presented at ***APS Materials by design***, University of Nottingham, UK, June 22-23, 2011.

- **"Milling to achieve the appropriate particle properties for inhalation, how can we rank or predict?"** Presented at '*APS Inhalation'* University of Bath, UK, July 4-6, 2011.
  "Best poster presentation award from the selected abstract "

Poster Presentation

- Shariare, M.H., De Matas, M., York, P. & Shao, Q. (2009) **"Particle optimisation for enhanced respiratory drug delivery"**. Presented at British Pharmaceutical Conference (BPC) 2009 and Published in *J. Pharm. Pharmacol*., special issue: BPC conference, 2009.

- Shariare, M.H., Blagden, N., De Matas, M., Leusen, F.J.J. & York, P. (2010). **"Influence of crystallisation conditions on the morphology of Ibuprofen crystals"**. Presented at UKPharmSci conference 2010 and published in *J. Pharm. Pharmacol*., 62 (10), 1337.

- Shariare, M.H., De Matas, M., York, P. & Shao, Q. (2009) **"Particle process optimisation for enhanced respiratory drug delivery"**. Presented at American Association of Pharmaceutical scientists (AAPS), 2009.

- Shariare, M.H., Blagden, N., De Matas, M., Leusen, F.J.J. & York, P. (2010). **"Influence of solvent properties on the morphology of Ibuprofen crystals and its impact on particle size reduction"**. Presented at FIP Pharmaceutical Sciences world congress in association with American Association of Pharmaceutical scientists (AAPS) 2010.

- Shariare, M.H., Blagden, N., De Matas, M. & York, P. (2010) **"The Effect of crystallisation conditions and feedstock morphology on the aerosolization performance of micronized salbutamol sulphate delivered by DPI".** Presented at "Drug deliver to the lung 21" organised by The Aerosol Society, December, 2010. *J. Aerosol Med.* (In press).

- Shariare, M.H., Blagden, N., De Matas, M. & York, P. (2010) **"The impact of morphology and process parameters on micronisation of salbutamol sulphate"** Presented at EuPAT 4 conference, Kuopio, Finland, 2010.

Acknowledgement

I would like to express my gratitude and special thanks to my supervisors Prof. Peter York, Dr. Marcel de Matas, Dr. Nick Blagden and Dr. F.J.J. Leusen for their inspiration, support and guidance throughout the period of this research. I would also like to thank Prof. Jamshed Anwar for his helpful comments and guidance.

I would like to acknowledge the lactose samples supplied by DMV –Fonterra, Netherlands and salbutamol sulphate sample supplied by Cipla, India. I am indebted to the technical and secretarial staff within the School of Life Sciences. I would like to thank Dr. Wendy Hulse for her support during this study. I would also like to thank the school of life sciences purchasing department for their help, in particular A.K. Tucny for her support throughout the research work.

Finally I must appreciate the help of all my friends in IPI, University of Bradford for their encouragement and help.

I dedicate this thesis
to my Mum, Dad and Wife (Shimu)
with thanks
for their unfailing love,
support and encouragement

TABLE OF CONTENTS

List of Tables

List of Figures

Units, symbols and abbreviations

SI Units

C	Centigrade
cal	Calorie
g	Gram
J	Joule
l	Litre
m	Metre
mol	Mole
Pa	Pascale
s	Second
T	Temperature

Prefix used with SI units

k	kilo
m	milli
m	milli
M	mega
µ	micro

Symbols

$CHCl_3$	chloroform
d_{hkl}	Spacing between crystal planes
E^{att}	Attachment energy
H	Hardness
K_{ICO}	critical stress intensity factor
min	minutes
R_{hkl}	Relative growth rate
THF	Tetrahydrofuran
Å	Angstrom
Θ	angle of X-ray beam diffraction
σ_{ym}	Modified yield stress
γ_{hkl}	specific surface energy

Abbreviations

API	Active pharmaceutical ingredients
BCF	Barton, Cabrera and Frank crystal growth model
BFDH	Bravais-Friedel-Donney-Harker
CCDC	Cambridge Crystallographic Data Centre
CSD	Cambridge structural database
DSC	Differential scanning calorimetry
DPI	Dry powder inhaler
DVS	Dynamic vapour sorption
D50	Median particle size

Et-Ibu	Ibuprofen crystallised from ethanol
ED	Emitted dose
FID	Flame ionization detector
FPF	Fine particle fraction
FPD	Fine particle dose
FR	Feed rate
GP	Grinding pressure
HPLC	High-performance liquid chromatography
Hx-Ibu	Ibuprofen crystallised from hexane
IGC	Inverse gas chromatography
IP	Injector pressure
IPA	Iso-propyl alcohol
Mag	Magnification
PDI	Polydispersity index
PXRD	Powder X-ray diffractometry
RD	Recovered dose
rpm	Rotation per minute
RH	Relative humidity
SS	Salbutamol sulphate
SEM	Scanning electron microscopy
TSLI	Twin stage liquid impinge
UV	Ultraviolet
VMD	Volume mean diameter
d_{crit}	Critical particle size (diameter)
0D	Absence of hydrogen bonding
1D	One dimension hydrogen bonding
2D	Two dimension hydrogen bonding
3D	Three dimension hydrogen bonding