MONASH University

Investigating the Nature of Surface Coatings on Fine Drug Powders and the Potential in Producing Novel Oral Solid Dosage Forms

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Abstract

The objective of this thesis was to investigate a mechanical dry powder coating approach to improve flow and fluidization of cohesive powder for producing direct compaction tablets. A fine cohesive ibuprofen powder (D_{50}=25 μm) with a low-melting point (~76°C) was coated with varying coating materials (magnesium stearate (MgSt), l-leucine, sodium stearyl fumarate (SSF) and silica-R972) in order to examine the effects on flow and tabletability of the processed powders.

Firstly, ibuprofen powder was dry coated via mechanofusion with between 0.1 to 5% (w/w) MgSt. ToF-SIMS demonstrated high degrees of coating coverage of MgSt on the particle surfaces. Robust tablets could be produced from the mechanofused powders and surprisingly the release rate of drug was not retarded. This is the first study to demonstrate such a single-step dry coating of ibuprofen with MgSt, with promising flow improvement and non-inhibited dissolution rate.

Secondly, ibuprofen powder was dry coated with 1% (w/w) of several materials including MgSt, l-leucine, SSF and silica-R972 to screen potential coating materials and develop directly-compacted tablets of high-dose drug. FT4 powder characterisation indicated coating of MgSt, l-leucine and silica-R972 produced improvement in powder flow. ToF-SIMS demonstrated a near-complete layer on the drug particle surface after coating with MgSt and silica-R972. The dissolution rates of all mechanofused powders were enhanced even with a hydrophobic material such as MgSt and silica. Such enhanced dissolution rate was attributed to the lesser

agglomeration resulting from the reduced cohesion between the drug particles after mechanofusion.

Thirdly, ibuprofen powders with various coating materials (MgSt, l-leucine and silica-R972), PVP and superdisintegrant were co-processed using mechanofusion and then directly compacted into tablets to achieve a single-step tablet production. FT4 indicated substantial improvement in powder flow. Robust tablets were produced from the co-processed ibuprofen and all excipient powders and the dissolution rates of these tablets were enhanced compared to control batch. However, the tablets made with silica-R972-mechanofused powders could not dinsitegrate and release under the same conditions.

Finally, l-leucine has been found to have promising capacity of improving flowability of ibuprofen powder via mechanofusion. Such processed powder was able to be compacted into tablets directly. Therefore, a study was proposed to evaluate the influence of particle size of l-leucine (D_{50} of 10 – 260 μm) on the flowability and tabletability of mechanofused ibuprofen powder. ToF-SIMS demonstrated an increasing trend of coverage level of l-leucine on the drug particle surface with reducing l-leucine particle size. Dissolution data of processed powders were fitted with multi-exponential equation models, representing dissolution from dispersed and agglomerated particle distributions.

In conclusion, improvements in ibuprofen powder flowability via mechanofusion can result in a promising trend allowing tablets to be formed by direct compaction and enhanced dissolution rate of both powders and tablets. Surprisingly, coating of hydrophobic guest particles did promote dissolution of powders or corresponding

tablets rather than retardance of dissolution rates. Multi-exponential modelling indicated that such improvements in the dissolution performance were attributed to the reduction in agglomerate strength caused by decreasing powder intrinsic cohesion after surface modification.

Declaration

In accordance with Monash University Doctorate Regulation 17.2 Doctor of Philosophy regulations the following declarations are made:

This thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

General Declaration

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes three original papers published in peer reviewed journals and two unpublished publications. The core theme of the thesis is 'Investigating the Nature of Surface Coatings on Fine Drug Powders and their Potential in Producing Novel Oral Solid Dosage Forms'. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the candidate, working within the Drug Delivery, Disposition and Dynamics, Monash University under the supervision of A/Prof. David AV Morton, Prof. Karen P Hapgood and Prof. Peter J Stewart.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

In the case of 2-6 chapters, my contribution to the work involved the following:

Thesis chapter	Publication title	Publication status*	Nature and extent (%) of students contribution
2	Particle engineering via mechanical dry coating in the design of pharmaceutical solid dosage forms	published	70%
3	Investigation of the potential for direct compaction of a fine ibuprofen powder dry-coated with magnesium stearate	published	65%
4	Influence of coating material on the flowability and dissolution of dry-coated fine ibuprofen powders	published	75%
5	Single-step co-processing of cohesive powder via mechanofusion for direct compression	submitted	70%

6	Effects of particle size of coating material L-leucine on flow, tableting and dissolution behaviour of dry-coated ibuprofen powders	submitted	65%

** e.g. 'published'/ 'in press'/ 'accepted'/ 'returned for revision'*

I have renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Student signature: [redacted] **Date: 08/03/2016**

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the student and co-authors' contributions to this work.

Main Supervisor signature: [redacted] **Date: 08/03/2016**

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Publications and communications

Peer reviewed journal papers

Qu, L., John A Denman, Peter J Stewart, Karen P Hapgood, Qi (Tony) Zhou, David A V Morton. Effect of l-leucine particle size on flow, tableting and dissolution behaviour of dry-coated ibuprofen powders. **Submitted**.

Qu, L., Peter J Stewart, Karen P Hapgood, Qi (Tony) Zhou, David A V Morton. Single-step co-processing of cohesive ibuprofen powder with excipients via mechanofusion for direct-tableting. **Submitted.**

Qu, L., Morton, D., Zhou, QT. Particle engineering via mechanical dry coating in the design of pharmaceutical solid dosage forms. Current Pharmaceutical Design 21.40 (2015): 5802-5814.

Qu, L., Qi (Tony) Zhou, John A Denman, Peter J Stewart, Karen P Hapgood, David A V Morton. Influence of coating material on the flowability and dissolution of dry-coated fine ibuprofen powders. European Journal of Pharmaceutical Sciences 78 (2015): 264-272.

Qu, L., Zhou, Q., Gengenbach, T., Denman, J.A., Stewart, P.J., Hapgood, K.P., Gamlen, M., Morton, D.A. Investigation of the potential for direct compaction of a fine ibuprofen powder dry-coated with magnesium stearate. Drug development and industrial pharmacy 41.5 (2015): 825-837.

Peer-reviewed conference papers

Qu, L., Zhou, Q.T., Stewart, P.J., Hapgood, K.P., Morton, D.A.V., 2015. Effect of coating materials on the surface coating quality, flowability and dissolution of dry-coated cohesive ibuprofen powders. AAPS Annual Meeting and Exposition 2015, Orlando, USA, October 25-29, 2015.

Qu, L., Zhou, Q.T., Stewart, P.J., Hapgood, K.P., Morton, D.A.V., 2014. Improving the Flow and Dissolution of a Fine Drug Powder Dry Coated with Magnesium Stearate. Respiratory Drug Delivery 2014, Fajardo, Puerto Rico, May 4-8, 2014.

Qu, L., Zhou, Q.T., Stewart, P.J., Hapgood, K.P., Morton, D.A.V., 2013. Investigation of the potential for direct compaction of a fine surface modified ibuprofen powder. Australasian Pharmaceutical Science Association Conference 2013, Dunedin, New Zealand, December 8-11, 2013.

Scholarship and awards

Postgraduate Research Scholarship, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, 2011.

Monash Graduate Scholaship, Monash University Institute of Graduate Research (MIGR), Monash University, 2012.

Australian Postgraduate Award, Monash University Institute of Graduate Research, Monash University, 2013.

Excipient Graduate Student Award, International Pharmaceutical Excipients Council (IPEC), 2015.

Graduate Student Research Award in Formulation Design and Development, American Association of Pharmaceutical Sciences (AAPS), 2015.

Abbreviations

AIC	Akaike Information Criterion
API	Active pharmaceutical ingredient
ANOVA	Analysis of variance
C_a	concentration of agglomerates
C_d	concentration of dispersed particles
CI	Carr index
D	Dependency values
D_{10}	diameter at 10% undersize
D_{50}	Diameter at 50% undersize
D_{90}	Diameter at 90% undersize
ES	Ejection Stress
ffc	Flow function co-efficient
k_a	dissolution rate constants for agglomerated particles
k_d	dissolution rate constants for dispersed particles
Leu	L-leucine
MAIC	Magnetically Assisted Impaction Coater
MgSt	magnesium stearate
PVP	Polyvinylpyrrolidone
SDU	Sample Dispersion Unit
SEM	Scanning electron microscopy
SSF	sodium stearate fumarate

ToF-SIMS	Time-of-flight secondary ion mass spectrometry
UV	Ultraviolet
XPS	X-ray photoelectron

Table of Contents

Chapter 1

Introduction and Rational for Study

1 Introduction

1.1 Background

1.1.1 Oral dosage forms

Oral solid dosage forms such as tablets (and to a lesser extent capsules) are considered the most patient-acceptable dosage forms available today. Not only do tablets offer convenience and ease of handling, but also as solids they are inherently more stable than liquids (chemically and physically), have a high production and are relatively cost-effective to produce [1]. Many fine active pharmaceutical ingredients (APIs) tend to exhibit either or both poor compactability and poor flowability[2]. These factors are considered key in affecting the quality of tablets made, and especially so if the formulation calls for a large proportion of APIs[3]. Therefore, together with compaction properties, the flowability of powder mixture is one of the most important factors in creating tablets. This is because a free flowing powder mixture is required to ensure a uniform tablet weight such that drug content can be maintained[4]. In addition, uneven powder flow could lead to variable and excess entrapped air within powders, which in some high-speed tableting conditions may promote capping or lamination[5] (Fig.1.1).

The flowability of the API powder is affected by its particle size, surface properties and particle shape and other factors[6,7]. In wet granulation and preliminary compression the API is combined with excipients and granulated to provide flow and compaction properties to the granulation. In direct compression, the API is added to a direct compression vehicle (with or without excipients) in order to achieve flow and compaction. Optimising these powder properties is critical for achieving robust manufacturing processes in pharmaceutical industries.

1.1.2 Tablet preparation

Traditionally, the problems for tableting arising from particle properties, including particle size distribution, particle shape and particle surface properties have been dealt with by a number of

methods of size enlargement and morphological modification. These transformations also have the advantage of improving compaction. Dry or wet granulation has been traditionally applied as the most common forms of such transformation/modification. In the pharmaceutical industry, most tablets are produced through the wet granulation process. Granulation methods combine all particles (API and excipients) into a distribution of granules, which has an effect in minimising segregation. However, the particle size of the powders in the granules do not change which eliminates the risk of segregation as a problem[8]. Also this process should improve the flowability and compactability of the bulk powders. Therefore, good quality of tablets will be ensured. Therefore, the physicochemical and bulk properties of the API will dictate the type of tablet processing. For example, an API which had good flow properties could be processed by wet granulation since the quantities of disintegrant and lubricant will be small. Wet granulation is often the first choice for low dose drugs. Typically a wet granulated formulation will contain one or more diluents for bulk or to aid processing, a binder to facilitate granule growth and to aid compaction, a disintegrant to increase dissolution rate and a lubricant to facilitate ejection of tablets. Additionally, wetting agents, stabilizing agents and colorants are used as required. However for high-dose drug products, it is important to minimise the amounts of various formula excipients to keep the tablet size small enough to swallow[9]. For example, There are some very high dose tablets in which the drug content is near 1000mg, such as anti-HIV drugs and multi-vitamin supplements which are not suitable to be processed by wet granulation[10]. Also wet granulation is a more time-consuming technique compared with direct compression and there is also a risk of product cross-contamination and product loss during the different processing steps (granulation, drying, sieving)[3]. All of these factors can increase costs compared with direct compaction.

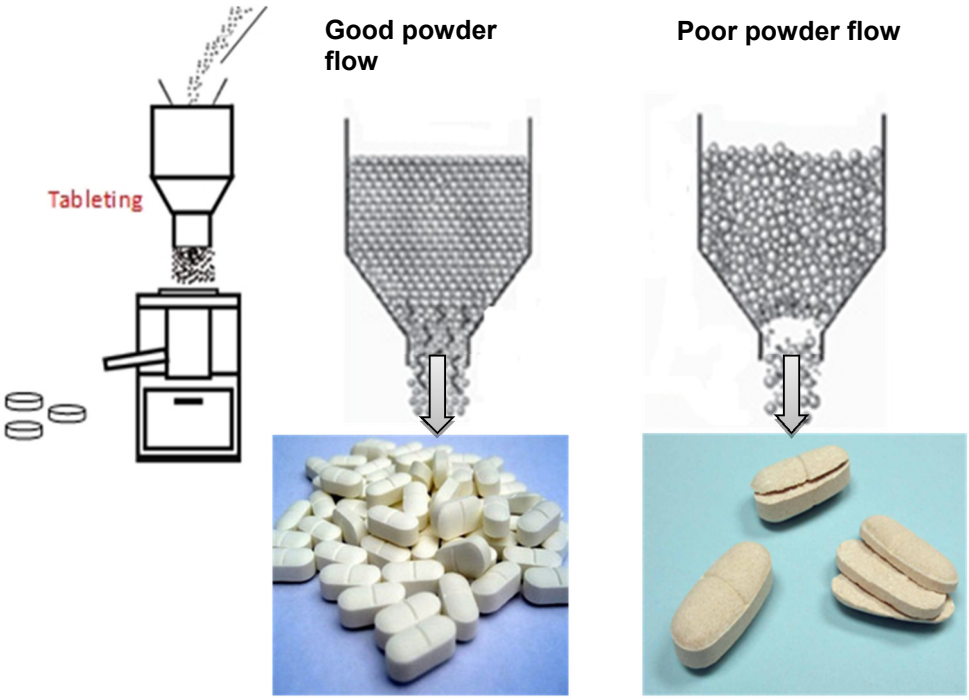

Figure 1.1 Tableting processing with good flowing and poor flowing powders

As an alternative to wet granulation, a dry granulation process can be introduced to generate granules without using a liquid solution. This may be advantageous if the product to be processed is sensitive to moisture and heat. However, the equipment used for dry granulation may be noisy and dusty due to the high pressure provided to densify the bulk powders[11]. Furthermore, if the fines in the bulk powders failed to be removed during the dry granulation processing, capping, laminating and hardness problems may occur during the tableting process[12].

More recently, a direct compression strategy is a popular choice for the pharmaceutical industry because this provides a potentially more efficient, more effective and less complex (hence potentially less costly) way to produce tablets. However, this process does require a critical selection of excipients in comparison to the granulation processes, because the raw materials must demonstrate good flowability and compressibility for successful operation[7]. As a result, direct compression in general requires a relatively high percentage of excipients, and these specialty excipients can be expensive. In Fig.1.2, flow charts are presented to represent tableting process via wet granulation, dry granulation and direct compression, respectively.

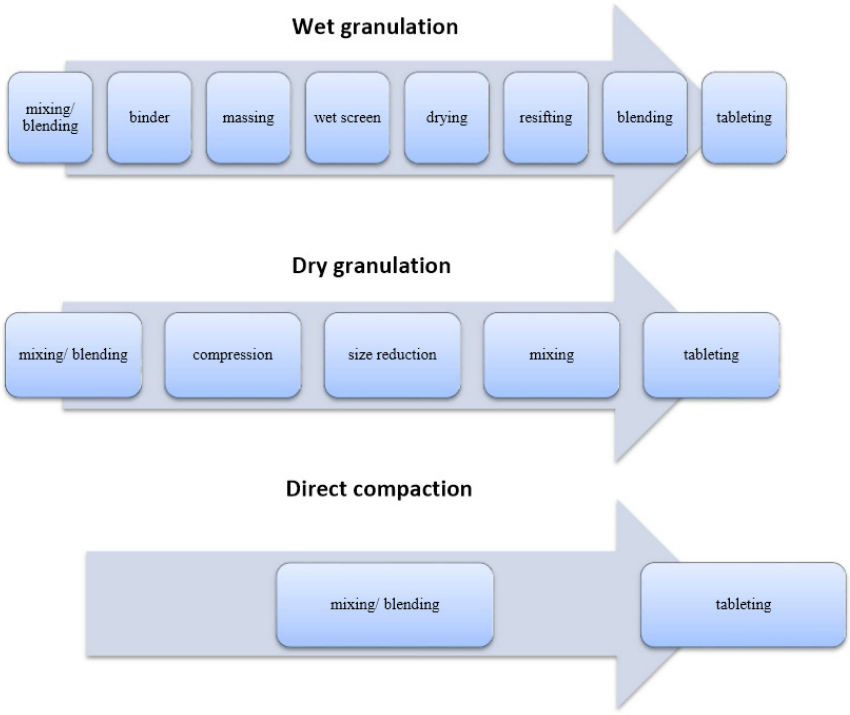

Figure 1.2 Flow chart of tableting processes.

1.1.3 Particle engineering

Advanced particle engineering technologies have been prevalent to formulate improved and next generation inhaled medicines[13]. However, despite such recent activity, it can be argued that oral solid dosage forms have not received a similar level of attention. Technological development in tablets (and capsules) appears to have been relatively static, in terms of the numbers of journal publications and patent applications. Perhaps the particle engineering techniques (e.g. super critical fluid precipitation) are more suited to scale up of smaller batches for inhalation and cannot be saled up to produce large batches for solid dose production.

Only a very limited number of publications have considered the possibility of directly compacting API particles into tablets. These have indicated applying a very low level of additive or morphology modification. For example, particle thin-coating in a fluidized bed system has been performed to improve the flow properties of ibuprofen powder[14]. However, this technique is a complex system that requires comprehensive knowledge about the properties of materials used to

predict an influence of process variables on the potency of coating[15]. Spray drying has been also applied to modify particle properties and enhance their manufacturing performance[16]. But this technique has limitations, for example:

- In many cases, organic solvents are acquired which has both cost, environmental and safety implications
- During biopharm processing because the atomization requires high shear rates during the spray drying processing, which can denature proteins[17]
- It may not be suitable to process some small organic molecules due to the formation of meta-stable amorphous structures using the spray drying route[18]
- Spray drying is highly energy intensive, requiring hot and dry airstreams to dry a wide range of products, which is energy intensive and may cause stability issues. Exhaust air from a dryer is usually vented to the atmosphere with little or no heat recovery

In contrast, mechanical dry coating techniques, such as mechanofusion, have acquired increasing interest for improving the flowability of the API powders because they can be more efficient, relatively cheaper, more environmental-friendly and safer in comparison with those conventional solvent-based coating approaches[19]. For example, the flow characteristic of a very fine and poor flowing lactose powder was improved dramatically to a free flowing powder after dry coating with magnesium stearate using a mechanofusion approach, and without altering particle size or shape. For pulmonary drug delivery, mechanofusion has been applied to modify a lactose carrier's surface in order to improve its flow, fluidization and aerosolisation behavior for dry powder inhalers. Therefore it is known that the crystalline sugar lactose alpha monohydrate can be successfully tailored in this way.

However, there is currently no specific report on the application of particle surface modification of other materials, such as API particles via mechanofusion, in order to improve bulk properties

for oral solid dosage forms. Also, no further investigation has been done on the tableting behaviours for tablets directly compacted with such dry coated powders.

1.2 Research questions

Therefore, there are two main research questions to be addressed in this project, which are as follows:

1. Can the key particle characteristics of surface structure of API particles (ibuprofen) be modified in order to sufficiently improve bulk powder flow behaviors, in such a way that this is then suitable for flowing from a hopper into a die during the manufacturing of tablets?

Although a recent study has indicated the surface chemical modification via intensive mechanical dry coating has ability to enhance powder flowability of some materials[20], it is unknown if this is applicable to differnt fine API powders (ibuprofen), for example with different physical properties such as shape, size and tensile strength.

2. Secondly, will such a surface modification, designed to reduce cohesion, then allow the formation of robust tablets via compression?

It is well known that if tablet lubricants such as magnesium stearate are applied to granules at above a certain concentration, or are mixed too well such that granule coating occurs, tablets cannot be produced with sufficient hardness[21-23]. Additionally, some studies demonstrated that the use of lubricants with a hydrophobic character such as magnesium stearate had some negative effects on the *in vitro* dissolution of immediate release tablets. A number of experimental studies had found that the deleterious effect of lubricants on dissolution is due to their hydrophobicity which, in combination with their large surface area, hinder water penetration[24,25]. However, this aspect has only been shown to apply in traditional systems, where enlarged composite granules are formed. In this case, robust tablet formation is dependent on the compression process where the granules are fractured or plastically deform to form some increased surface contacts.

The recent research on the MgSt-coated lactose powders[26] has revealed a dramatic and previously unseen shift in powder compressibility behavior. This shift is highly sensitive to particle size distribution and hence powder surface area. The powder surface area and hence potential particle-particle contact area is far higher for these materials than that has been considered previously for tableting. Consequently, it is not known how these much finer materials, upon which novel surface modifications are made, will behave under compression.

It is also not known how such novel surface modifications may alter other properties such as disintegration or dissolution kinetics. If the coatings are highly hydrophobic, such as using a magnesium stearate, will the dissolution behaviour be affected? Conventional approaches suggest materials such as magnesium stearate will reduce dissolution[25,27], however the coatings provided by mechanofusion have been shown to be much thinner and effectively spread than those previously studied from conventional blending[28]. Very recently, a study revealed that dissolution rate has been surprisingly enhanced in such circumstances due to the improvement in fine particle dispersion[29]. Furthermore, it would be hypothesized that the *in vitro* and bulk performances of the coated materials using alternative coating agents, such as the less hydrophobic material of sodium stearyl fumarate or colloidal silica may be different?

It would also be possible to consider that if tablets cannot be created, an alternative strategy may be possible to examine if flow and dissolution behaviour is suitable for the administration as powders filled into hard capsules?

1.3 Hypotheses

From the context of these two challenging research questions, based on the perception that an alternative to a direct compression for the formation of solid oral dosage forms is possible, a set of 3 specific hypotheses have been derived to form the foundation of this programme of research. These are as follows:

1) The bulk flow behaviour of cohesive fine pharmaceutical drug powders (ibuprofen) can be improved to give better flow from a hopper into a tablet die by modifying particle surface characteristics using an intensive mechanical dry coating approach.

2) Such dry coated drug powders may then be directly compacted into tablets with a basic tensile strength suitable for commercial product.

3) The disintegration and dissolution behaviour of the direct compacted tablets is influenced by varying the coating materials with a hydrophobic or hydrophilic character.

1.4 Research Aims

Following these 3 hypotheses, a set of specific research aims have been developed, which are designed, in turn, to test each hypothesis in the context of this study of potentially novel solid oral dosage forms:

1) To investigate the effect of coating concentration and varying coating materials on the improvement of the powder flow behaviors for selected model poor-flowing drug powders with different properties. This aim is directed to test Hypothesis 1. This aim will be addressed in primarily in Chapter 3 and 4.

2) To optimize the tablet compression conditions by investigating its tensile strength of such tablets formed by dry coated fine drug powders with varying coating materials as a function of compaction pressure. This aim is directed to test Hypothesis 2. This aim will be addressed in primarily in Chapter 3, 4, 5 and 6.

3) To investigate the effect of different coating concentration and varying coating materials on the rate of the drug release from such directly compressed tablets into the dissolution medium and their disintegration time. This aim is directed to test Hypothesis 3. This aim will be addressed in primarily in Chapter 4, 5, and 6.

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Chapter 2

Literature Review*

This chapter have been published as:

Review

Qu, L., Morton, D., Zhou, QT. Particle engineering via mechanical dry coating in the design of pharmaceutical solid dosage forms. Current pharmaceutical design 21.40 (2015): 5802-5814.

Declaration for Thesis Chapter 2

Declaration by candidate

In the case of Chapter 2, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Writing the manuscript	70%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
David A V Morton	Manuscript revision	15
Qi (Tony) Zhou	Manuscript revision	15

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

Candidate's Signature	[redacted]	**Date08/03/2016**
Main Supervisor's Signature	[redacted]	**Date08/03/2016**

*Note: Where the responsible author is not the candidate's main supervisor, the main supervisor should consult with the responsible author to agree on the respective contributions of the authors.

2 Particle engineering via mechanical dry coating in the design of pharmaceutical solid dosage forms

2.1 Abstract

Cohesive powders are problematic in the manufacturing of pharmaceutical solid dosage forms because they exhibit poor flowability, fluidization and aerosolization. These undesirable bulk properties of cohesive powders represent a fundamental challenge in the design of efficient pharmaceutical manufacturing processes. Recently, mechanical dry coating has attracted increasing attention as it can improve the bulk properties of cohesive powders in a cheaper, simpler, safer and more environment-friendly way than the existing solvent-based counterparts. In this review, mechanical dry coating techniques are outlined and their potential applications in formulation and manufacturing of pharmaceutical solid dosage forms are discussed. Reported data from the literature have shown that mechanical dry coating holds promise for the design of superior pharmaceutical solid formulations or manufacturing processes by engineering the interfaces of cohesive powders in an efficient and economical way.

2.2 Introduction

Solid formulations comprise the most popular forms of pharmaceutical products. During the manufacturing of solid dosage forms, the "particulate state" is the most basic unit and particulate handling is largely inevitable in most manufacturing processes [1]. Fine and ultra-fine particles are often present and handling the resulting cohesive powders is a generic industrial problem because these powders may exhibit poor bulk properties such as flow, fluidization and dispersion due to strong inter-particulate forces [2].

The bulk behaviors of cohesive powders are highly complex phenomenon and they have a major impact on the manufacturing performance. The cohesion is primarily associated with particle size, but also density, shape and surface properties [3]. Pharmaceutical scientists and engineers have

exploited numerous elegant particle engineering strategies such as supercritical fluid technology [4], plasma-enhanced chemical vapor deposition [5], and aerosol flow reactor methods [6] to modify particle shape and/or density in order to resolve the problems caused by cohesion. However, such strategies are relatively complex, expensive and also can provide challenges to scale up [7].

In contrast, modifying particle surface *via* a dry, single-step mechanical method has been recognized as a potentially simpler, cheaper, faster, safer and more environment-friendly approach compared to those conventional solvent-based coating techniques [8]. Surface modification can be achieved by coating particle surfaces with appropriate additives, where the additives reduce surface cohesive forces between particles or between particles and equipment [9]. In this review, recent developments and applications of dry coating techniques for solid dosage forms in the pharmaceutical sector are outlined and discussed.

2.3 Dry coating techniques

2.3.1 Mechanical dry coating devices

Mechanical dry coating techniques were pioneered by Japanese scientists in 1970s to 1980s. As a result of this development foundation, a number of specialized mechanical dry coating devices are now commercially available. These include the Hybridizer®, the Magnetically Assisted Impaction Coater (MAIC)®, the Mechanofusion® and the Theta-composer® [8] (Fig 1). Other equipment such as the Cyclomix® high shear mixer [10,11] and the Comil® [12,13] have also been employed in coating cohesive powders, although they are not specifically designed for just dry powder coating. The configurations of different mechanical dry coating devices may vary, but the principles of operation are similar: high-shear and high-energy interactions between particle-particle or particle-device are generated as directed to coat the surface of host particles with a guest material.

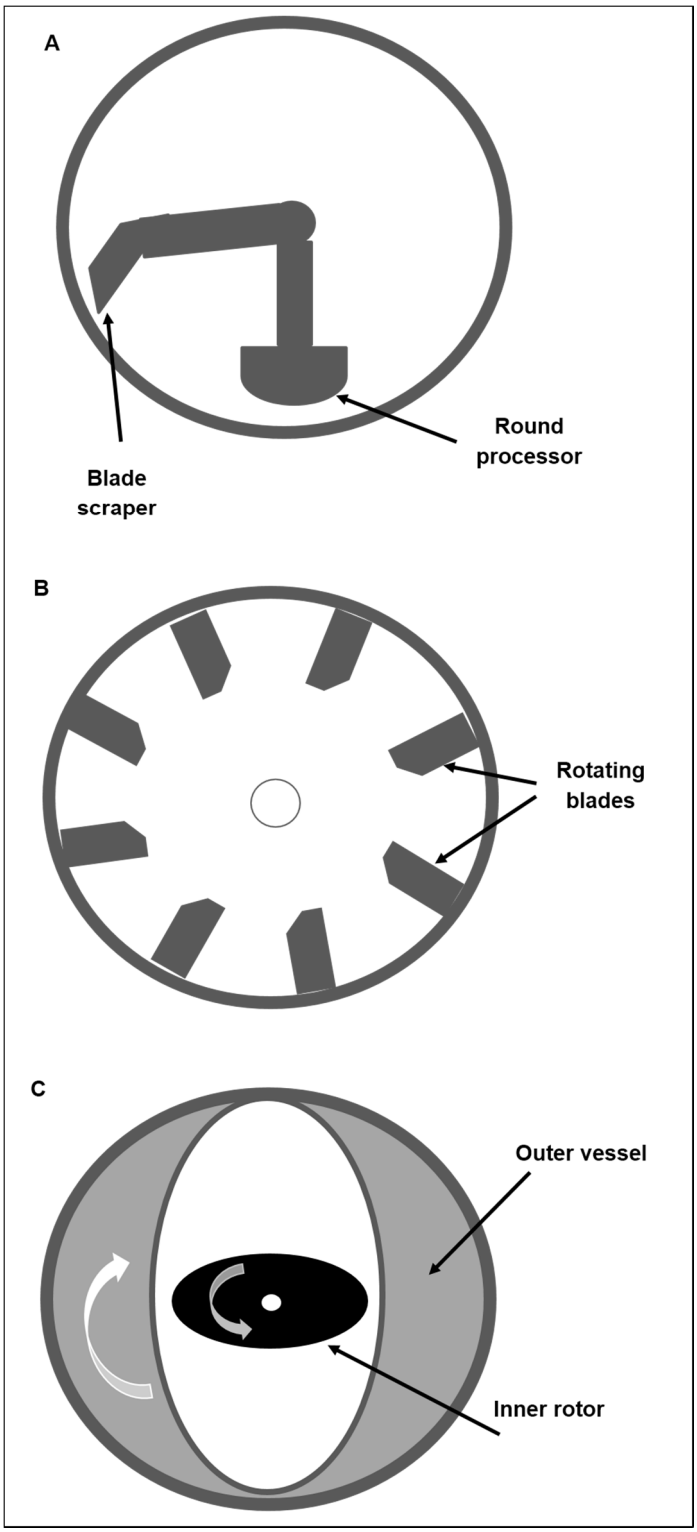

Figure 1 Schematic diagram of dry coating devices: (A) Mechanofusion; (B) Hybridizer; (C) Theta-composer.

Such dry coaters may be considered as a special type of high-shear mixers which provide maximum surface interaction but with minimized attrition effect. The true mechanisms of dry coating have not been fully understood because the processes involve complex interactions

between host and guest particles, guest and guest particles as well as particles and devices. The binding mechanisms between guest and host particles can be material and process dependent; physical and/or chemical binding may contribute to the adhesion of guest material on the host particles. For example, a mechano-chemical reaction mechanism between the host cornstarch and the guest silicon dioxide particles was proposed after dry coating by MAIC, based on a reduction in hydrophilicity of cornstarch powder and decreased FT-IR absorption caused by O–H stretching vibrations [14].

The operation of dry coating equipment is mostly a straightforward single-step process: i.e. load the powder mixture (guest and host powders), turn on the machine for a set time/speed, turn off the machine and unload the powder. The process can also be designed for continuous manufacturing. Once the process is optimized and validated, the manufacturing process should be robust with minimal concern of process inconsistency due to the operators' skill. Moreover, most dry coating processes have the apparent potential to be scaled up. For example, the bulk properties (including densities, cohesion and flow function) of milled lactose powders coated with a lab-scale (Nobilta-AMS Mini, powder load up to 0.1 L) mechanofusion system (Hosokawa Micron Corporation, Osaka, Japan) were comparable to those coated with the equivalent pilot-scaled (Nobilta-130, powder load up to 0.5 L) system (Table 1). The scalability of dry coating processes to a larger manufacturing scale for pharmaceutical applications requires a more robust investigation.

Table 1. Shear cell data of coated lactose powders with 1% w/w magnesium stearate by the pilot and lab scale mechanofusion systems. Data are adopted from ref [15] and [16].

	Nobilta-130 (pilot scale)	Nobilta-AMS Mini (lab scale)
Cohesion (kPa)	0.47	0.36
Flow function	10.7	11.7

Of the available techniques, the mechanofusion system has arguably received the most attention in pharmaceutical applications [9]. An early version of the mechanofusion concept consists of a

processing vessel, a round processor and a blade scraper (Fig. 1A). Driven by a motor, the vessel rotates at a controlled speed (up to 2000 rpm) while the processor and scraper are stationary. A water jacket can be used to cool the processing chamber wall, if the process-induced heat is a concern. In the later lab-scale version (AMS-Mini), the design is simplified: the processor and scraper are replaced by an exchangeable processor module. The processor rotates at a speed up to 6000 rpm and the vessel is stationary. Two types processors are available for the AMS Mini: the Nobilta model has a propeller processor with four blades (Fig. 2a); and the Nanocular model has a rounded processor (Fig. 2b). The Nobilta model allows higher powder load because of the higher voidage space. Zhou *et al.* [15] has shown the coating quality of the two modules is apparently equivalent when a lab-scale mechanofusion system was employed to engineer micronized salbutamol sulphate particles (volume median diameter (VMD) < 5 μm).

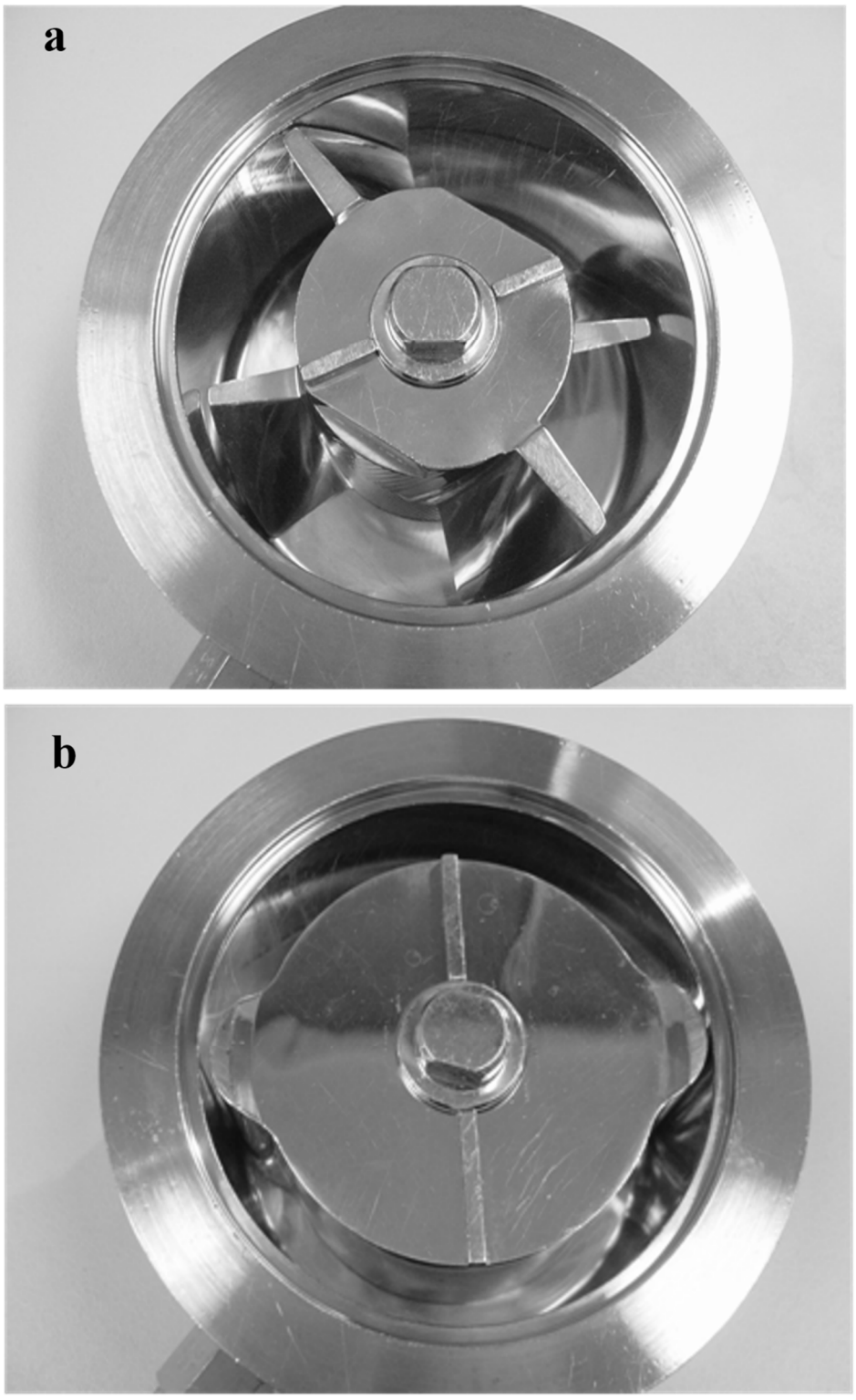

Figure 2 Lab-scale mechanofusion AMS Mini system with the exchangeable processor of (a) Nobilta or (b) Nanocular. Reprint from [15] with permission from Elsevier.

One concern is that due to the high-shear interactions between particles surfaces, local heat may be generated which may lead to the damage or degradation of heat-sensitive particles and surface damage may occur due to attrition. This was observed when lactose monohydrate particles were

mechanofused with or without 1% w/w colloidal silica, but it was not found for those mechanofused with 1% magnesium stearate [17]. In principle, the process should be optimized for each case with appropriate processing parameters (i.e. speed and time) or with addition of protective excipients (such as lubricants to reduce friction) to avoid damage. For example, a significant improvement in powder flow was achieved without any observed particle damage for a low melting-point drug, ibuprofen when powders were mechanofused with 1% w/w magnesium stearate at a speed of 900 rpm [18].

The design of the Hybridizer is similar to that of mechanofusion systems. Basically, the Hybridizer consists of a processing chamber with a few motor-driven blades (Fig. 1B). During the operation, the blades rotate at high speeds up to 16,000 rpm.

The Theta-composer has an outer elliptical vessel operating at a lower speed of approximate 30 rpm and an inner rotor operating at a faster speed of approximate 500 – 3000 rpm. As the vessel and the rotor rotate in the opposite directions, host and guest particles are pushed through the small gap between the vessel and the rotor (Fig. 1C).

The design and operation mechanism of Magnetically Assisted Impaction Coater are different to above three mechanical dry coating devices. During the coating, magnetic beads are placed in the processing vessel with the host and guest powders [8]. Oscillating magnetic fields generated surrounding the vessel agitate the magnetic particles. Collisions occur between the magnetic particles and the guest or host particles, as well as between guest and host particles. The magnetic particles may need an appropriate coating to avoid shedding contamination.

Because Cyclomix [11] and Comil [19] are not specifically designed for dry coating, the configuration of these two equipment is not detailed here and can be found in the literature.

2.3.2 Computational modeling

Numerical simulation by discrete element method has been conducted on the mechanofusion [20], Comil [19] and Cyclomix [11], aiming to provide better understanding in dry coating processes. Chen *et al.* has reported numerical simulations of mechanofusion using DEM [20]. The force on the rounded processor as a function of the rotational speed of the chamber and particle loading was calculated. Impact forces and collision velocities were also computed aiming to understand the effect of device design on the particle interactions during the coating process. The data showed the scraper has a positive influence on the impact velocities thereby is beneficial for coating. It was demonstrated that the average force on the round processor is a function of the square of the rotational speed of the chamber, which was in good agreement with experimental results [20].

Due to the computational limitations, only a limited number of host particles can be considered in the simulation and guest particles are not included because of their low concentration and the large difference in particle sizes between the host and guest particles. Future studies, which include the interactions between guest-host particles, are warranted if computational processing allows modeling the process in a more realistic way. Overall, these studies suggest that computational modeling has potential to obtain valuable information on the process interactions and help guide optimized coating devices or processes.

2.4 Coating material

Theoretically, a coating material should be either smaller or softer than the guest particles [8]. For the former condition, small guest particles can be adhered and distributed onto the larger guest particle surfaces. For the latter, soft guest particles can be laminated and/or smeared onto the harder guest particle surfaces. Currently used materials for dry coating can be categorized into two major groups: silica glidants (small guest particles) and boundary lubricants (soft guest particles). The physico-chemical properties and mechanisms of function for two groups coating materials vary largely.

2.4.1 Colloidal silica

Colloidal silica (or colloidal silicon dioxide) is widely used as a flow-aid additive for oral solid dosage forms. Particle size has a substantial influence on the powder flow and the commonly used colloidal silicas are typically in the nanometer scale (10s to 100s nm). Yang *et al.* has shown the flowability of coated cornstarch particles (15 μm) was inversely proportional to silica guest particle size [21]. For example, the powder coated with 20 nm silica exhibited superior flowability than those coated with 500 nm silica particles [21]. Due to the small particle size, colloidal silica particles exist as loose agglomerates and possess very low bulk density (0.029 – 0.042 g/cm^3) [22]. Consequently, the volume of silica powder can be high even when the mass amount used in the manufacturing is low (0.1 – 1 w/w %) [22]. For non-cohesive powders, low-shear mixing can be sufficient to distribute such fine glidant particles onto the host particle surface, with improved flowability. For example, Zhou *et al.* showed that flowability of a less-cohesive mixture powder (75% ibuprofen, 22% microcrystalline cellulose (Avicel PH102), 3% sodium croscarmellose) blended with 0.5% colloidal silica (M-5P, Cab-o-sil) was similar to that after 5 comilling cycles [23]. However, the capability of silica glidants to improve flow can be limited for more cohesive host particles. Blending colloidal silica did not improve flowability of a cohesive Avicel PH105 powder; while comilling was able to achieve efficient coating [12]. This is because when the agglomerate strength of cohesive particles is strong, much of the surface of individual host particles is hidden inside agglomerates and so unavailable for interacting with the glidant particles. So, distribution of glidant particles on the cohesive host particle surfaces is non-homogenous, which can lead to low efficiency in improving powder flow. In this case, high-shear dry coating is needed to break the agglomerates and expose the surface of individual host particles to the coating material.

2.4.2 Boundary lubricants

Lubricants have been widely used in pharmaceutical tableting, with the main purpose to reduce friction force between the tablet surface and the wall of tableting machine. Unlike a traditional

glidant, when a lubricant is conventionally mixed with a cohesive host powder using a low to medium-shear blender, only a limited flow-aid effect is often observed [17]. This is not only because the low shear forces are unable to deagglomerate host aggregates, but they fail to laminate and smear the lubricant substantially across the surface of individual particles (Fig. 3) [17,24]. Only very high-shear processing such as the mechanical dry coating systems described in this review may achieve a high coating efficiency of lubricant for cohesive powders. Furthermore, as mentioned in Section 2.1, a lubricant as a coating material may provide protection from heat/friction/corrosion/attrition-induced damage on the particle surface by reducing the friction [17].

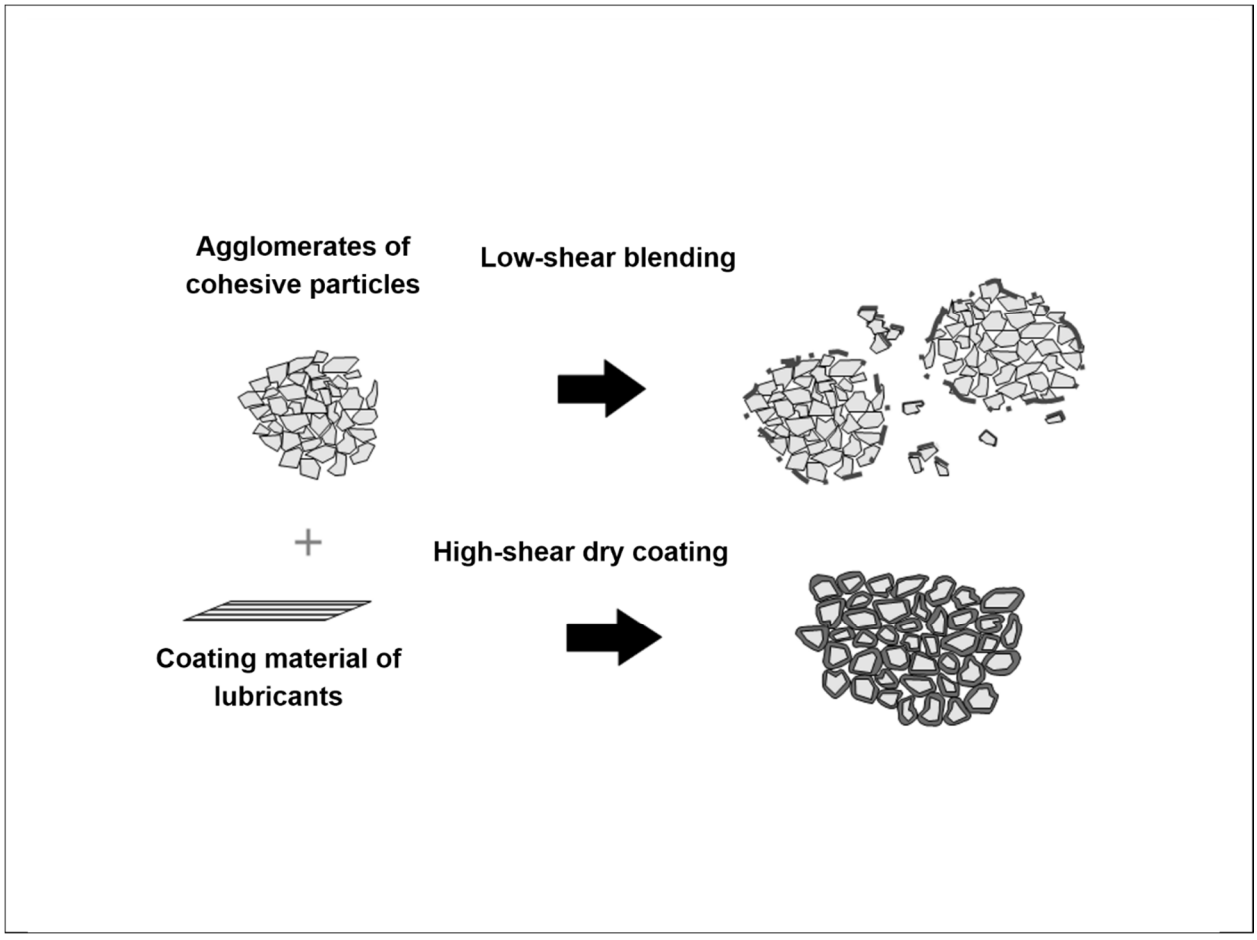

Figure 3 Low-shear blending may be unable to provide sufficient energy and forces to coat individual particles of cohesive powders, resulting in poor coating on agglomerates; while high-shear dry coating can break the agglomerates, delaminate the lubricant and coat the individual particles.

It should be noted that magnesium stearate as a coating agent (often termed a force control agent) has been extensively examined with the aim to improve the aerosolization performance of inhalation formulations [22]. Magnesium stearate has a recognized safety profile for inhalation purpose and has been approved for inhalation products of Pulmicort®, and CFC-free metered dose inhaler and Foradil® Certihaler® [25]. In contrast, inhalation of nano-sized silica raises significant safety concerns [26], even though inhalation of amorphous colloidal silica may not cause pulmonary fibrosis like its crystalline counterpart [22].

The effects of coating material on the bulk properties and formulation performance of the coated powders are discussed in detail in Section 4.

2.5 Effect of coating on powder bulk behavior and formulation performance

2.5.1 Effect of coating on powder flowability

Flowability of a pharmaceutical powder is a key property that determines the success and efficiency of modern pharmaceutical manufacturing of solid dosage forms. Satisfactory flowability is important for the handling or processing of powders in many manufacturing processes such as flowing from a hopper, filling of a tablet die or capsule, flowing into a mixer or mill and emptying of a sachet. However, many cohesive powders exhibit poor flow behavior which causes major problems in manufacturing. For example, milled fine powders generally possess high surface energy and are highly cohesive, which tend to agglomerate and are difficult to make flow or to fluidize. The past decade has seen the increasing attempts to improve the flowability of cohesive pharmaceutical powders by a mechanical dry coating approach. Substantial improvement in powder flowability has been reported for various coating devices and the key findings are listed in Table 2. As outlined in Section 3, two types of coating materials (silica glidant and boundary lubricant) have distinctive mechanisms to improve powder flow *via* dry coating.

Table 2. Key studies to improve flowability of pharmaceutical powders by dry coating.

Coating device	Coating material	Coating material concentration % w/w	Host material	Reference
Comil	Silica R972, Aerosil 200 (~10-100 nm)	1	Ibuprofen 50 (77 µm), lactose 310 (76 µm), mannitol (123 µm)	[13]
Comil	Silica M5P (20 nm), R972 (20 nm)	1	Acetaminophen (10 and 30 µm), ibuprofen 90 and 50 (102 and 61 µm), ascorbic acid (215 µm), MCC or Avicel PH101, 102 and 105 (66, 122 and 19 µm, respectively), Lactose 350 and 450 (26 and 17 µm), Pharmatose DCL11 (112 µm)	[27]
Comil	Silica M5P (~14 nm)	0.1 and 0.5	Ibuprofen	[23]
Comil	Silica M5P (~14 nm)	1	Danshen root (15.33 µm), notoginseng (131.22 µm), borneol (230.66 µm)	[28]
Comil	Silica M5P (~14 nm)	0.2-1	MCC (Avicel PH105, 20.9 µm)	[12]
Comil	Silica M5P (~14 nm)	0.1-2	MCC (Avicel PH102, 120 µm)	[29]
Cyclomix Hybridizer	Talc (14 µm)	5	Cellets 90 and 200 (100 and 305 µm, respectively)	[10]
Cyclomix	Magnesium stearate (5 µm)	5	Sugar particles (Suglets®) (250 µm)	[11,30]
Fluid energy mill	Silica M-5P (15 nm)	0.5-5	Ibuprofen (102 µm)	[31]
Fluid energy mill and Comil	Silica M-5P (16 nm)	1	Ibuprofen 50 (58 µm)	[32]
LabRAM (resonant acoustic mixer), FEM	Silica TS530 (7 nm), R972 (16 nm), M5P (20 nm), OX50 (40 nm), alumina (13 nm), titanian (21 nm)	Theoretical weight percent of guest particles in relation to the total mass of the host and guest particles in order to completely coat the host particle surface	Acetaminophen (11 and 25 µm), ibuprofen (72 and 130 µm) ascorbic acid (223 µm), lactose (15, 22 and 53 µm), potato starch (36 µm)	[33]
LabRAM (resonant acoustic mixer)	PE wax (6.7 µm) Carnaubar wax (6.4 µm)	0-30	Ascorbic acid (56.8, 115.7, 232.4 and 521.6 µm), ibuprofen (87.2 µm)	[34]
LabRAM (resonant acoustic mixer)	PE wax (6.7 µm)	0-25	Ascorbic acid (56.8, 115.7, 232.4, 242.4 and 521.6 µm)	[35]

MAIC	Silica (0.3 μm)	1	Cornstarch (15 μm), cellulose (180/40 μm)	[36]
MAIC	Silica R972 (16 nm), A130 (16 nm)	1.5	Aluminum (3.7 μm)	[37]
MAIC and hybridizer	Silica R972 (~20 nm), EH-5 (~20 nm), OX-50 (~40 nm), Lab (~100 nm),COSMO55 (~500 nm), P500 (~2.25 μm)	0.01, 0.1, 1, 2	Cornstarch (15 μm)	[38]
MAIC	Silica	1.5	Aluminum (9.44 μm)	[37]
MAIC, hybridizer, mechanofusion	Carnubar wax (15 μm), fumed silica (0.7 μm)	1-20 for wax, 2 for silica	Magnesium (75 μm)	[39]
MAIC	Silica Cab-o-sil M-5P (~16 nm), Aerosil R972 (~16 nm)	0.5-2	Ibuprofen 110, 90 and 50 (119.6, 101.9 and 57.5 μm), acetaminophen (20.7 and10.7 μm), ascorbic acid (212.6 and14.9 μm)	[40]
Mechanofusion (Nobilta-130)	Magnesium stearate (7.9 μm), colloidal silica (CAB-O-SIL1 M-5, 0.2 – 0.3 μm)	1	Lactose (Pharmatose 450M, 19.1 μm)	[15]
Mechanofusion (Nobilta-130 or Nobilta-ASM-Mini)	Magnesium stearate (7.9 μm)	1, 2	Lactose with varying particle size (3.9 – 116.5 μm)	[24,41,42]
Mechanofusion (Nobilta-ASM-Mini)	Magnesium stearate (7.9 μm)	0.1 – 5	Lactose (Pharmatose 450M, 19.1 μm)	[16,42]
Mechanofusion (Nobilta- and Nanocular-ASM-Mini)	Magnesium stearate (7.9 μm)	5	Micronized triamcinolone acetonide, salmeterol xinafoate, salbutamol sulphate (< 4 μm)	[15]
Mechanofusion (Nobilta-ASM-Mini)	Magnesium stearate (7.9 μm)	0.5 – 10	Micronized salbutamol sulphate (< 4 μm)	[25]
Mechanofusion (Nobilta-ASM-Mini)	Magnesium stearate (7.9 μm)	0.1, 1, 5	Ibuprofen (~40 μm)	[18]

2.5.2 Coating with silica glidants

It is believed the mechanism of flow-aid function of silica glidants is that they may act based on the multiple principles of: (1) increase the distance and reduce the contact area between host particles [21,43]; (2) decrease the surface energy of host particles by covering high surface-energy sites with guest particles [44]; (3) ball bearing effect of spherical silica particles during flow of the powder [43]; (4) neutralization of electrostatic charge [45].

The mechanism of increasing distance of particles in contact has been mostly examined for both mixing and dry coating with silica glidants. It was claimed that the size of glidant had the most significant influence on flow improvement while the chemical nature had minimum impact unless the deagglomeration and coating of nano-sized glidant was significantly affected by the chemical nature – specifically their relative hydrophilic/hydrophobic properties [43]. It is worth noting that in most cases, the deagglomeration and coating quality are indeed affected by their chemical nature. For example, studies have shown that coating or mixing with hydrophobic silica acquired superior flow than those processed with hydrophilic silica [21,43]. Another explanation is the weaker adhesive force between drug and hydrophobic silica than that between drug and hydrophilic silica, whereby silica particles not only increase the distance of host particles but also contribute to the interactions between host particles [21]. Hydrophobic particles generally exhibit lower hydrogen bonding and potential capillary forces than their hydrophilic counterparts.

In reality, nano-sized silica particles form agglomerates on the host particle surface and the distribution of agglomerates can be non-homogeneous after the mixing or dry coating [43]. The ball-bearing effect and agglomerate rupture may contribute to the improved powder flow when loose silica particles or agglomerates are present on the host particle surfaces. However, during the high-shear mechanical dry coating process, the guest particles can be pushed and compressed against the host particle surface thereby partially immobilized. Under this situation, it is likely the influence of ball bearing and agglomerate rupture effects is minimized [17].

The effect of different mixing/coating processes (i.e. V-blending, dry coating by MAIC and Hybridizer) with various silica particles on the coating quality and improvement in flow for cornstarch powder were compared [21]. Dry coating approaches of MAIC achieved more homogeneous coating layer assessed by visual evaluation of SEM images; while it is noted that V-blended powder with 0.1 % w/w nano-sized glidant (EH-5) exhibited comparable improvement in flowability with a low angle of repose of 34° (raw powder, 52°; Hybridizer coated, 33°; MAIC coated, 30°) [21]. Similar findings were also reported when a milled lactose powder (particle size 19

μm, angle of repose 64.6 ± 0.9°) was either tumbling mixed (angle of repose 48.7 ± 1.1°) or dry coated with colloidal silica using a mechanofusion system (46.5 ± 0.8°) [17]. This could be because the homogenous coating of silica by high-shear processing is not always necessary for flow improvement of mildly cohesive powders, and/or the 'angle of repose' measurement technique is insensitive to differentiate flowability changes [17]. A future aspect is to examine such phenomenon in powders with increasing cohesion levels. High-shear dry coating is expected to be more effective in improving flow of more cohesive powders because it is capable to break agglomerates of both guest and host particles.

2.5.3 Coating with boundary lubricants

The mechanism of improving powder flow by coating cohesive particles with a boundary lubricant is distinctive to that of silica glidant: with a typical low surface-energy coating material such as magnesium stearate, the lamellar structure is delaminated onto the surface of high surface-energy host particles, thus reduces the cohesive forces. The reduction in attractive forces can be a combination of decreased van der Waals forces (i.e. hydrogen bonding), removed capillary forces (with substantially increased contact angles), and/or minimized electrostatic forces.

The reduction in surface free energy by dry coating with magnesium stearate has been demonstrated by inverse gas chromatography (IGC) measurement. Details of surface-energy studies are discussed in Section 5.1. Significantly decreased cohesion/adhesion forces after coating with magnesium stearate are also evident by direct force measurement using atomic force microscopy (AFM) [46].

Of particular note, Zhou *et al.* [17] demonstrated that a milled lactose powder dry-coated with 1% w/w magnesium stearate by mechanofusion (Nobilta-130, Hosokawa Micron Corporation) has achieved significantly better powder flow compared to those coated with 1% w/w colloidal silica (CAB-O-SIL M-5, Cabot Corporation) under the same coating conditions. Flowability data of two coated lactose powders are listed in Table 3. In another study, it is noted that coating of a free-

flowing silica powder (D_{50} 55 μm) with 1 or 5% w/w magnesium stearate by a Cyclomix resulted in reduced flowability: this could be due to either breakage of host particles (meaning more fine particles were present after processing) and/or a poor coating quality (as suggested by SEM images) [47]; while the flow of hybridizer-coated particles was unaffected with better coating coverage than those coated by Cyclomix [47] suggesting the Hybridizer provides a more intensive interaction during the coating process.

Table 3 Flow properties of lactose samples (Standard deviations are in parentheses, n = 4). Data are adopted from ref. [17].

	AOR (°)	CI	HR
Untreated	64.6 (0.9)	0.50 (0.01)	1.99 (0.04)
Blended with colloidal	48.7 (1.1)	0.43 (0.01)	1.75 (0.03)
Mechanofused with colloidal	46.5 (0.8)	0.37 (0.02)	1.60 (0.04)
Blended with magnesium stearate	63.9 (1.1)	0.47 (0.01)	1.88 (0.03)
Mechanofused with magnesium stearate	38.4 (1.0)	0.29 (0.01)	1.40 (0.02)
Mechanofused without additives	54.1 (0.4)	0.42 (0.02)	1.73 (0.07)

2.5.4 Effect of coating on fluidization and aerosolization

Fluidization behavior of a powder is crucial to many pharmaceutical manufacturing processes including pneumatic conveying and fluid-bed drying. Aerosolization behavior is the key determinant of formulation performance for dry powder inhalers. As the outcomes of significant reduced inter-particulate cohesive forces, dry coating was reported to substantially improve fluidization and aerosolization of cohesive pharmaceutical powders.

Dry-coated milled lactose monohydrate particles (Pharmatose® 450M with a D_{50} of 3.9 and Lactohale® LH 300 with a D_{50} of 19.2 μm) with 1 − 2 % w/w magnesium stearate by mechanofusion have exhibited superior fluidization behavior over the uncoated powders [41]. In this

study, fluidization properties were measured by an FT4 Powder Rheometer® (Freeman Technology) in the aeration mode. The improved fluidization properties of cohesive powder will not only facilitate the powder handling such as pneumatic conveying and fluid-bed drying, but also improve the aerosolization performance of dry powder inhalers (DPIs) [41].

The usefulness of dry coating to improve aerosolization performance of DPIs has been reviewed previously [9,48]. In carrier-based formulations, either lactose carrier or micronized drug particles can be coated with a force control agent (i.e. magnesium stearate). Early studies have shown improved aerosol performance of carrier-based DPI formulations when the lactose carrier particles were coated with magnesium stearate [49], which can be attributed to the reduced adhesion forces between the micronized drug particles and the coarse carrier surface [50]. However, if only carrier is coated and adhesion between carrier and drug particles is reduced, cohesive drug particles tend to agglomerate and segregation may occur [46]. Therefore, it was concluded that the most effective strategy to improve the overall performance of carrier-based DPIs is to coat both carriers and drug particles [9].

Significant improvement in aerosol performance of carrier-free formulations has been demonstrated for the coated pure drug particles of micronized salbutamol sulphate [25,51], budesonide [51], salmeterol xinafoate and triamcinolone acetonide [15]. In the study by Zhou *et al.* [15], jet-milled triamcinolone acetonide has the lowest fine particle fraction ($FPF_{emitted}$) before ($FPF_{emitted}$ = 26.4 ± 1.8) and after coating ($FPF_{emitted}$ = 51.6 ± 1.5) while with the greatest increase (95% increase in $FPF_{emitted}$) after coating. Such differences in improvement of aerosolization could be due to the effect of particulate properties (i.e. particle size, shape, surface chemistry, etc.) on coating efficiency and aerosolization. The data from a subsequent study showed that coating quality measured by X-ray photoelectron spectroscopy has strong impact on aerosolization [25].

Development of efficient DPIs for high-dose antibiotics is challenging because the prescribed doses can be higher than 100 mg, which may need multiple inhalations to reach the therapeutic dose of active ingredients [52]. For example, to use TOBI® Podhaler® (tobramycin DPI), four

capsules should be inhaled for completing a dose of 112 mg. Moreover, inhalation of large quantities of antibiotic powder may cause side effects in airways including cough and throat irritation [52,53]. Because of the high drug dose, the use of carrier is limited in antibiotic DPI formulations to avoid accommodating large volume of powder in the DPI device, which may make the inhaler large and compromise its portability [52]. Dry coating has shown the capability to increase aerosolization efficiency of inhaled high-dose antibiotics [54], which has potential to reduce the total drug dose. Furthermore, improvement in powder flowability may minimize the use of carrier and increased bulk density may reduce the bulk volume of the powder, which is promising for developing high-dose DPIs.

2.5.5 Effect of coating on tableting

Dry or wet granulation has been traditionally applied to overcome poor powder flowability due to fine particle size in pharmaceutical industries. Granulation improves the flowability and fluidization of the bulk powders by increasing the effective size of the solid. However for high-dose drug products, it is important to minimize the amounts of various excipients so as to keep the tablet size in a range acceptable to swallow [55]. For example, tablets with drug doses > 1 g, such as anti-HIV drugs and multi-vitamin supplements, can be challenging to be produced by wet granulation, but alternative dry granulation or direct compaction conventionally needs a high excipient load, giving very large tablets [56]. Moreover, the granulation process can be time-consuming and there is also a risk of product cross-contamination and product loss during the processing steps (i.e. granulation, drying, sieving) [56].

Direct compaction is popular because this provides a less complex (hence potentially less costly) way to produce tablets [57,58]. However, this process conventionally requires a critical selection of excipients because the raw materials must demonstrate good flowability and tabletability for successful operation [59]. Particle engineering by mechanical dry coating has been examined as a potential alternative approach to generate powders with satisfactory flow properties which may be

suitable for direct compaction, and is discussed here. Fig. 4 presents the flow charts to represent tableting process *via* wet granulation, dry granulation and direct compression.

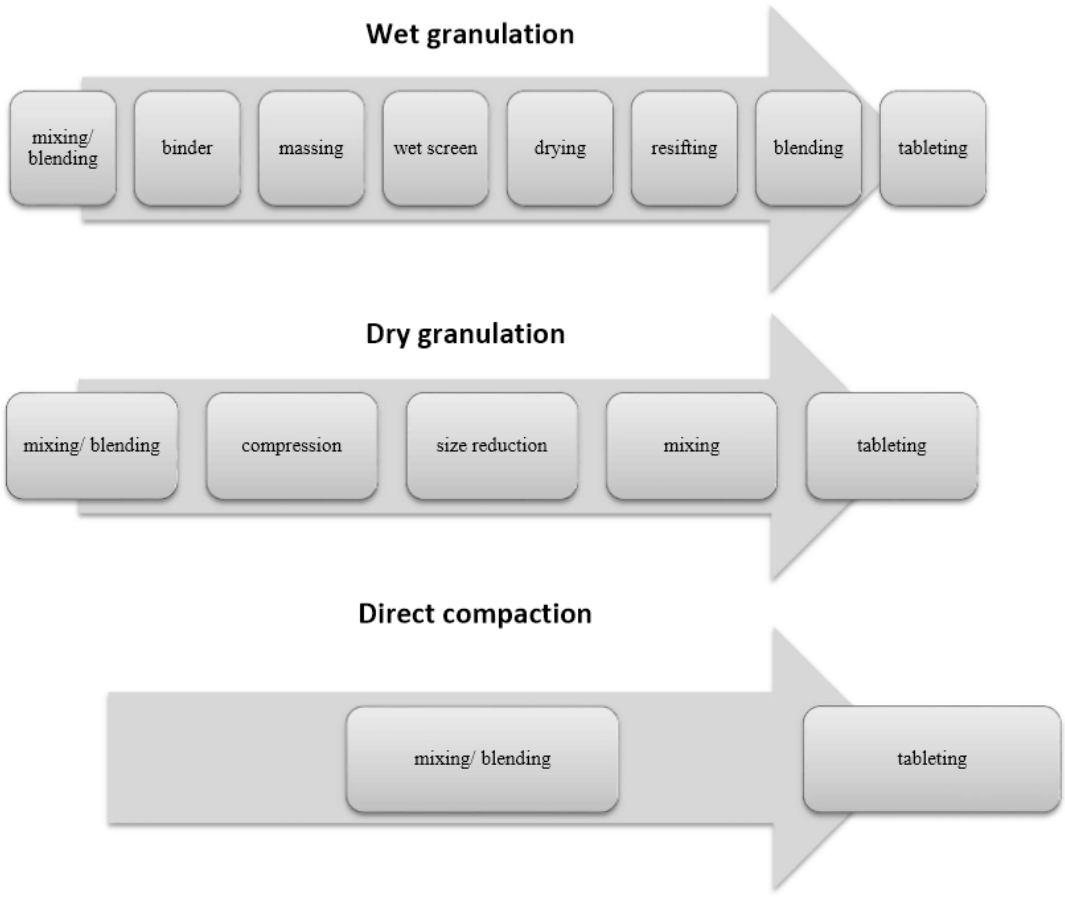

Figure 4 Flow chart of wet granulation (upper), dry granulation (middle) and direct compaction (lower) processes.

2.5.5.1 Effect of coating on tablet tensile strength

Two types of coating materials (silica glidants and boundary lubricants) have different effects on tensile strength of formed tablets consisting of coated powder. Intensive mixing of pharmaceutical powders with magnesium stearate has been reported to reduce the tensile strength of formed tablets [60,61]. This is because formation of lubricant layer on particle, agglomerate or granules decreases the bonding between particles after compaction. The reduction in tensile strength was shown to be greater for longer mixing times and higher mixing speeds for microcrystalline cellulose [60] and

starch powders [61]; and this response has been termed lubricant sensitivity. However, such effects are material and process dependent. For example, microcrystalline cellulose tends to plastically deform upon compaction; but reduction in tensile strength was not seen for dibasic calcium phosphate anhydrous powders, which were cohesive [60] or subjected to brittle fracture upon compaction [61,62]. If the brittle fracture occurs during compaction, rather than plastic deformation, new uncoated surfaces are generated and so the lubricant coating coverage is decreased [63]; thus minimizing the effect of lubricant coating on tensile strength [64,65].

For cohesive powders, it has been shown that low-shear mixing may not be able to break the agglomerates and form a uniform coating on individual particles [17,60]. Intensive mechanical dry coating of lubricant provides better coating on the cohesive particle surfaces and as a result, may lead to reduction in tensile strength of compacted tablets. Qu *et al.* [18] has shown mechanofusion of cohesive ibuprofen powder ($D_{50} \approx 40$ μm) with 1% w/w magnesium stearate produced a uniform coating and substantial improvements in flowability but resulted in a significant reduction in tensile strength of formed tablets. The reduction in tablet tensile strength appeared a function of coating quality – with more complete coating leading to weaker tensile strength. Addition of 10 % w/w binder (PVP K25) compensated for this reduction in tablet tensile strength [18], which suggested the tablets could be strong enough to withstand commercial manufacture and subsequent distribution [66].

The effect of coating with colloidal silica glidant is host-material dependent. Both increase and decrease in tablet tensile strength have been reported for dry coating of various drug powders with colloidal silica using a Comil. Zhou *et al.* reported that the tablets compacted with powder mixtures consisting of 75% of coated ibuprofen powder with hydrophilic silica (M-5P, Cab-o-sil; Cabot Corporation) and other excipients had higher tensile strength than those with uncoated drug [23]. Han *et al.* also demonstrated the increase of tensile strength for the tablet formulations comprising of ibuprofen coated with 0.6 % w/w hydrophilic silica (M-5P) [32]. Such phenomenon was also observed for three Chinese Traditional Medicines (TCM) of Danshen, Notoginseng and Borneol,

when coated with 1% w/w M-5P [28]. In contrast, the tablets compacted with the MCC powder (Avicel PH105) coated with 1% w/w M-5P silica exhibited a lower tensile strength compared to the uncoated [12]. The subsequent study showed that reduction of tablet tensile strength was greater when the silica concentration increased [29]. The increased tensile strength of coated powder for ibuprofen [23] and TCM [28] was explained as the higher bonding strength between silica and drug/excipient than that between drug/excipient particles in the powder blends. Where silica particles are sandwiched between two adjacent drug/excipient particles in the tablet, this could strengthen the adhesion and contribute to the higher tablet tensile strength [23,28]. In contrast, MCC itself has recognized compactability which suggests stronger bonding between MCC particles [67] than between MCC and silica particles during the compaction. In this case, tensile strength of MCC tablets made with the coated powder is lower than those formed with the uncoated MCC powder.

2.5.5.2 Effect of coating on tablet ejection from the die

The ejection behavior of tablets is critical to the high-speed manufacturing of pharmaceutical tablets. Pharmaceutical lubricants are commonly added into the formulation to minimize the friction and adhesion between particle/granule and punch/die so as to prevent tablet damage or sticking to the punch or die [68,69]. Effective lubrication is particularly critical for tableting of those drugs with a low melting-point such as ibuprofen [70]. It was reported a mixture consisting of ibuprofen powder coated with 1% magnesium stearate had significantly reduced ejection stress compared to the uncoated powder mixture (i.e. reduced 38% at the compaction pressure of 150 MPa) [18]. Also, addition of external lubricants [32] or pre-lubrication of tablet die and punch [28] has been reported in the tableting of silica-coated drug powder or mixtures. If additional lubricant is essential for the tableting of formulations with coated powder, coating with boundary lubricants has dual benefits of improving both flow and lubrication, which may save the usage of excipients for manufacturing high drug-dose tablets, notwithstanding its negative effect in reducing tablet

tensile strength. A balance between tablet tensile strength and lubrication is a requirement for considering the tableting of such a coated powder.

2.5.5.3 Effect of coating on dissolution

The effect of coating on the dissolution of cohesive powders and formed tablets may be complex because the coating may affect the dissolution of drug particles by two different mechanisms: (1) retardation of the dissolution rate by hydrophobic functional coatings; or (2) impact on dissolution by altering the agglomerate strength of cohesive particles. These alternative and contrasting outcomes are discussed below.

2.5.5.4 Functional coating for controlled release

The former mechanism (delayed release due to a material such as wax or polymer coated on the surface of drug particles) to achieve the controlled release has been extensively exploited in larger granules and pellets [74] but rarely applied to cohesive fine particles because the coating of cohesive particles by traditional wet coating techniques is a challenging [74]. However, Mechanofusion has been employed to coat a hydrophilic drug, acetaminophen (particle size around 300 μm) with a hydrophobic coating material of carnauba wax aiming to achieve sustained release [71]. The processing speed had a significant influence on dissolution rate of the drug; 2000 rpm was found the optimal speed for sustained release. It was proposed that a higher speed of 3000 rpm may cause the rupture of the drug particle or damage to the coating [71]; but particle size or coating quality data had not been provided to support this. Talc was co-processed with drug and coating material to improve the flowability and coating quality of the processed powder. There was a decrease in dissolution rate when the concentration of talc increased, suggesting more comprehensive coating by an indirect means [71].

Polymer coating of ascorbic acid powders with polyethylene wax was also performed using a high intensity Laboratory Resonant Acoustic Mixer (LabRAM) (Resodyn Acoustic Mixers, Butte,

Montana, USA) [35]. A continuous layer of deformed polymer particles was observed from the SEM images for large particles with sizes of 425 μm – 500 μm. It is noted the minimum processing time to obtain a continuous coating of deformed polymer increased remarkably with a decrease in particle size, and deformation of polymer was not observed for the drug particles with sizes of 45 μm – 63 μm. The bigger particles also had larger reduction in drug dissolution than the smaller ones. For example, t_{50} of particles with sizes of 425 μm – 500 μm increased from 16 s to 41 min after coating with 23.5 w/w % polymer; while t_{50} of particles of 45 μm – 63 μm only increased from 5 s to 2.8 min after coating with the same amount of polymer [35]. Since the coating layer of polymer was found intact after dissolution tests [35], a diffusion-based dissolution mechanism was hypothesized. In a subsequent study by Capece *et al.* [34], controlled release of ascorbic acid and ibuprofen was also achieved through dry coating with polyethylene wax or carnauba wax using the Laboratory Resonant Acoustic Mixer. Release of drug from the coated particles was modeled based on a diffusion mechanism [72] using the theoretically calculated coating thickness. The assumptions of the calculation are: guest and host particles are spherical; coating layer and thickness are homogenous; and all the guest particles are coated on the host particle surface without loss during the processing. In reality, particles may be non-spherical, coating layer may not be homogenous and loss of coating material may occur with guest particles being adhered on the equipment. Therefore, in the future studies, use of spherical particles and quantitative measurement of coating quality and thickness may provide more accurate information to investigate the release mechanism of coated drug powders using this diffusion model.

2.5.5.5 Effect of altered agglomerate strength on dissolution

The altered agglomerate strength of cohesive powder by dry coating also has been shown to significantly impact the dissolution. Han *et al.* have shown micronized powder (particle size of 10 μm) of a poorly water soluble drug, ibuprofen had a slower dissolution rate than the unprocessed drug powder (particle size of 102 μm) from 0 to 30 min during the test [31]. According to the well-known Noyes-Whitney Equation the dissolution rate should increase with an increase of surface

area (or decrease in particle size) [73]. When the drug powder was co-micronized with hydrophilic silica (M-5P, primary particle size of 15 nm from Cabot Corporation, MA, USA), the dissolution was markedly faster. Further increase in dissolution rate was observed when ibuprofen was co-micronized with both silica and polyvinylpyrrolidone (PVP). Such increased dissolution rate was believed attributable to the improved dispersibility (reflected by the improvement in powder flowability) and more hydrophilic particle surface. The tablets made of coated ibuprofen have also achieved enhanced dissolution [32].

It has been extensively reported that when using traditional blending, an increased mixing time or intensity with magnesium stearate and drug particles results in a retarded dissolution, as the consequence of forming a hydrophobic surface layer [74-76]. Surprisingly, there was no substantial decrease in dissolution rate when jet-milled indomethacin particles (poorly water soluble) were dry coated with magnesium stearate (0.25 and 1%, w/w) using mechanofusion [77]. There was also no retardation in the dissolution for tablets made of magnesium stearate-coated ibuprofen formulations from a mechanofusion process [18]. Furthermore, recent data has shown the dissolution rate of cohesive ibuprofen particles (particle size around 40 μm) was significantly faster when mechanofused with 1% w/w magnesium stearate, compared to the uncoated particles and those coated with sodium stearate fumarate (SSF) [78] (Fig. 5) (sodium stearate fumarate is less hydrophobic than magnesium stearate [79] but has inferior lubrication efficiency [80]). In these examples, the dissolution behavior was found to be associated with the cohesion and flowability, not the hydrophobicity of the coating material. In this study, it is proposed that the dissolution of the cohesive ibuprofen particles was dominantly controlled by the agglomerate strength. These observations were also supported by the dissolution modeling results [77].

Data from quantitative and qualitative analysis of surface coating by mechanical dry coating approaches have indicated the coating layer of magnesium stearate can be as thin as a few nanometers [16,42]. Such ultra-thin coating may not prevent or retard the penetration of the dissolution medium into the particle core. Agglomerate strength of hydrophobic cohesive drug

powders has shown as a significant influence on dissolution [81-83] and enhanced dissolution of cohesive powders has been achieved by reducing the agglomerate strength [84-86].

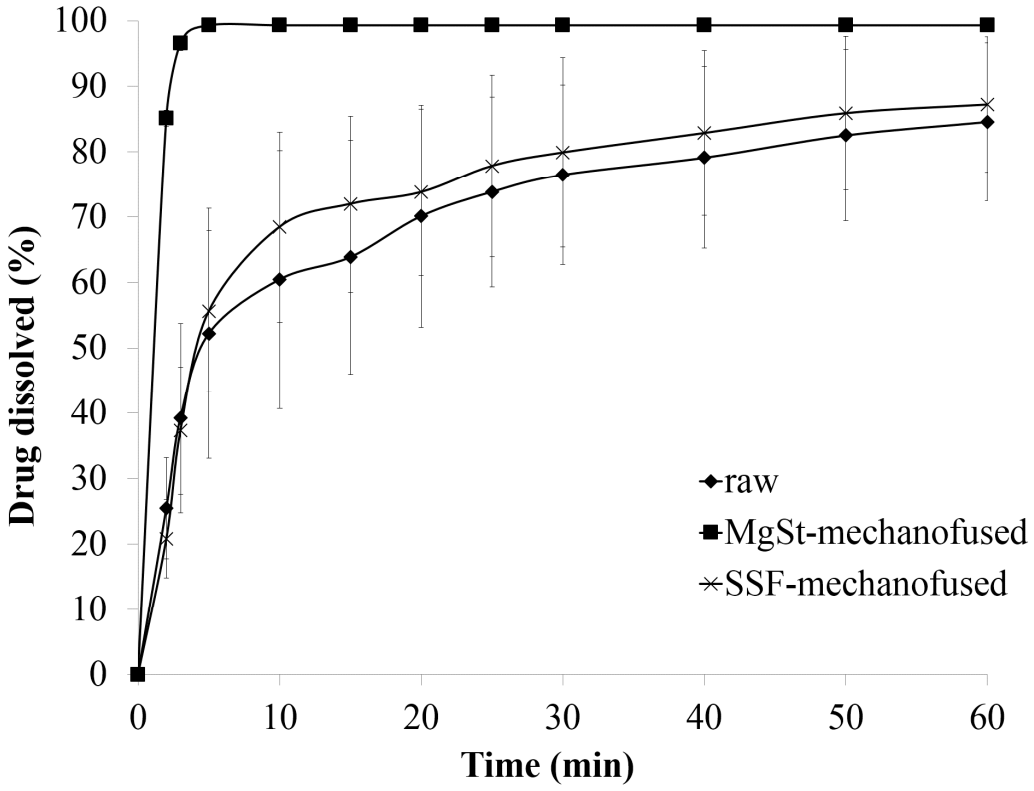

Figure 5 Dissolution profiles of ibuprofen powders either uncoated or coated with 1% w/w magnesium stearate (MgSt) or sodium stearate fumarate (SSF) by a mechanofusion dry coating device. Mean ± SD, n = 3. Data are adopted from ref [78].

2.6 Characterization of coating

2.6.1 Surface energy

In order to understand the effect of modified particle surface properties on particulate interactions, the surface energy of coated powders have been examined by several researchers. Hypothetically, the reduced powder cohesion by mechanical dry coating can be attributed to the decreased free

surface energy and attractive forces. Surface energy of powders can be measured by a number of techniques, and most commonly by either contact angle method or by inverse gas chromatography (IGC). Recently, IGC has been shown to be an efficient and non-destructive approach to measure surface energy of powders [87]. The theories of IGC measurement have been reviewed previously [88]. The surface energy properties measured by IGC have been used to help understand and predict the influence of pharmaceutical processes such as milling [89,90], mixing [91] and coating [42] on the bulk behavior of powder. Two methods of IGC measurement are available: infinite dilution and finite dilution. The infinite dilution method only probes the sites with the highest surface energy. Typically, < 1 % of the total surface is measured, which likely results in an overestimation in surface energy [92]. Using the finite dilution method, the distribution of surface energy can be examined over the more coverage of the surface, typically around 10% [87].

Surprisingly, an early study reported that dry coating with magnesium stearate increased the surface dispersive energy of milled lactose particles, as measured by the infinite dilution method of IGC [93]. This increase in the dispersive energy appears contradictory to the observed improvements in flowability and dispersibility of the coated particles [93]. Such observations were noted to be due to the limitation of the infinite dilution method because it only measures the highest surface energy sites which may represent a low proportion of the surface [94], and hence, the results from infinite dilution method can be misleading in this context. It is hypothesized that mechanical dry powder coating generates a small area of surface with high surface energy; albeit, the majority of the surface has low free surface energy.

Data from several recent studies using the finite dilution method have shown the heterogeneity in surface energy for the dry coated powders. Only very small area of surface of dry-coated powders (< 1%) possesses a relatively high dispersive surface energy and the majority of the surface has a lower dispersive energy (Fig. 6) [42]. The results from the finite dilution measurement thus explain that the reduced cohesion and improved flowability of the magnesium-stearate dry-coated powders

compared to the unprocessed and blended powders, are the outcomes of a predominantly decreased free surface energy [95].

It has been suggested that co-milling could decrease the surface energy heterogeneity of milled particles. Han *et al.* has shown co-milling ibuprofen crystal particles using a fluid energy mill with either amorphous hydrophilic nanosilica M5-P or hydrophobic nanosilica TS530 (Cabot Corporation, Billerica, Massachusetts) achieved reduced dispersive surface energy and decreased surface energy heterogeneity, compared to the uncoated and low-shear blended samples [44]. Similar observation was also reported by Stank and Steckel [96]. The micronized salbutamol sulphate co-jet-milled with magnesium stearate or glycerol monostearate had lower dispersive surface energy value and heterogeneity. Such difference in surface energy heterogeneity between the particles coated by mechanofusion and co-milling processes could be due to the different coating mechanisms and/or the properties of host/guest particles, which deserve further investigation.

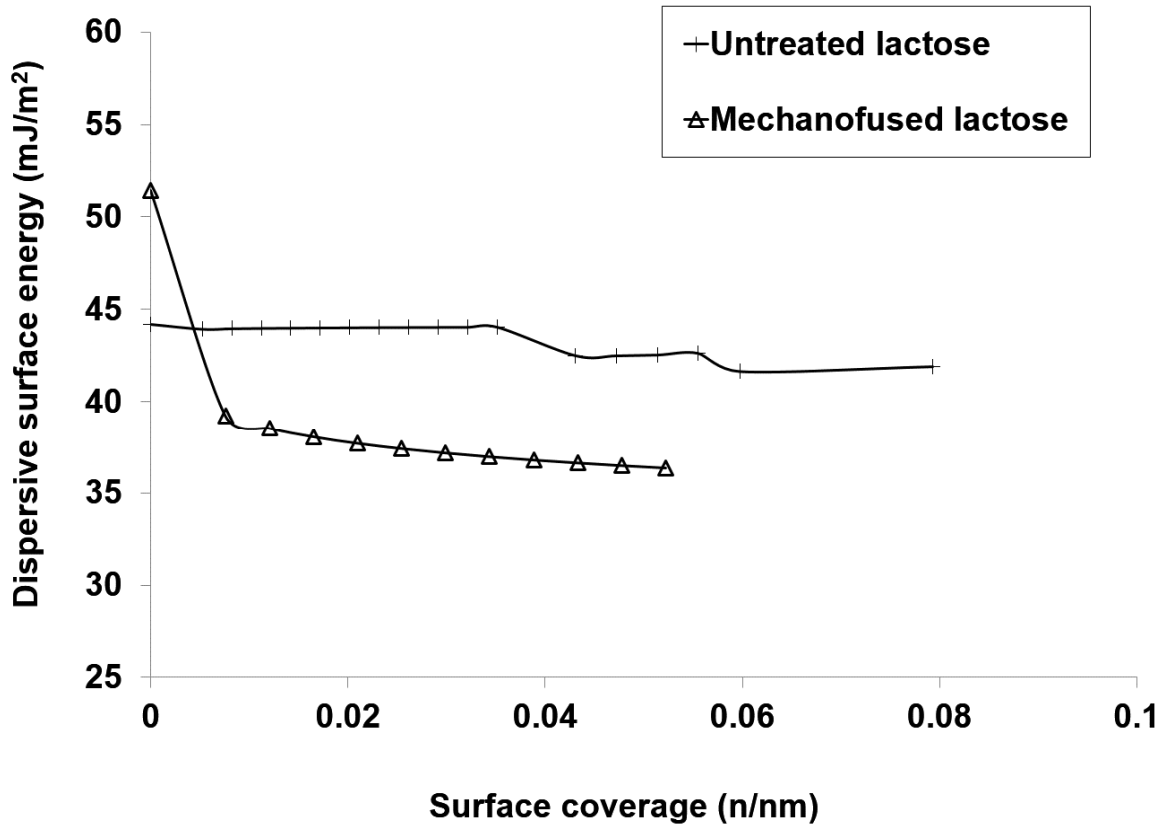

Figure 6 Only less than 1% of the mechanofused lactose particle surface has high dispersive energy; more than 99% of the surface has a lower dispersive energy than that of the milled lactose powder. Reprint from ref. [42] with permission from John Wiley and Sons.

2.6.2 Coating quality

Appropriate characterization of coating quality is crucial in examining the effect of coating on powder bulk behavior. In practice, quantitative characterization is highly challenging because often the guest particles have extremely small sizes (i.e. ~ 20 nm for AEROSIL® R-972 hydrophobic fumed silica) and/or form ultra-thin coating layers on non-flat surfaces (i.e. the thickness of magnesium stearate coating layer can be down to nano-scale [42]). Visual assessment of coating coverage based on SEM images is indirect, time-consuming (hundreds of particles should be assessed for a statistical significance) and highly subjective. Measuring the surface chemistry of coated particles is a direct and more accurate way to characterize the coating quality. To achieve a meaningful measurement, the technique should have both sufficient sensitivity in chemical element detection and high spatial resolution in detecting low mass of guest particles on the upmost surface of host particles.

Conventional energy dispersion X-ray spectroscopy systems (EDXS) were used to measure the distribution of magnesium stearate on the lubricated granules [97] or tablets [98]. It was also used to evaluate qualitatively the distribution of sub-micron silica (0.3 μm) on the coated cornstarch particle surface (15 μm) [14]. EDXS generally provides qualitative-only information and has typically low spatial resolution [99]. Raman spectroscopy has also been applied to characterize coating thickness of tablets [100,101]. However, in general Raman spectroscopy has low spatial resolution of a few micron and the probe has a penetrate depth of > 1 μm [102]. If the coating layer is thinner than the probe penetration depth, a Raman probe may penetrate the coating layer and measure both the coating and host particles. The surface coverage of coating measured by Raman

could be underestimated since the host element beneath the coating layer is also deemed as that on the upmost surface.

Recently, more sensitive chemical element detection techniques have been used for measuring the ultra-thin coating on fine particle surfaces. The state-of-the-art nano-time-of-flight secondary ion mass spectrometry (nano-ToF-SIMS) is capable of providing mapping of coating layer at a spatial resolution down to 20-100 nm; the measurement is qualitative or semi-quantitative. X-ray photoelectron spectroscopy (XPS) provides quantitative measurement of surface elements on dry-coated particles. Both techniques measure the outmost surface of < 10 nm, which ensures the data are solely from the coating layer. By combining the data obtained by these two powerful tools, for the first time both qualitative and semi-quantitative characterizations of ultra-thin coating layer on fine particles have been achieved and the correlation between coating quality and bulk behavior has been established [25,42].

Despite the success of quantifying coating quality of dry-coated particles with magnesium stearate, these sensitive characterization techniques have yet to be applied to nano-sized colloidal silica coatings.

2.7 Conclusions

Handling cohesive powders is a major challenge in designing highly-efficient pharmaceutical manufacturing processes. Literature outlined in this review indicates the potential benefits of mechanical dry coating techniques in improving bulk behavior and formulation performance of some cohesive pharmaceutical powders by favorably engineering the particle surface. Modern chemical and physical surface analytical tools such as XPS, ToF-SIMS, FT-IR and IGC are promising to determine the physical and chemical nature of the coatings and to explore the physical and chemical interactions between the host and guest particles. The true mechanisms of interaction between host and guest particles during coating and the fundamental understanding in the effect

of coating on bulk behavior remain only partially understood and deserve further investigations. Computational modelling also has the potential to better understand the coating process.

As discussed herein, the action of dry coating on bulk behavior appear to be dependent on two distinctive types of coating materials: namely nano-sized silica glidants and boundary lubricants. Effectiveness and efficiency of coating can be host, guest materials and process dependent, which means optimization may be essential for each coating process. The choice of coating materials and processes should consider the nature of the process, the properties of both guest and host particles, as well as their influence on the manufacturing and formulation performance. Future studies are warranted to better understand the mechanisms of dry coating process, and to explore new potential applications such as moisture protection [39] and taste masking [103].

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Chapter 3

Investigation of the potential for direct compaction of a fine ibuprofen powder dry-coated with magnesium stearate*

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Declaration for Thesis Chapter 3

Declaration by candidate

In the case of Chapter 3, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Study design, formation of hypothesis, laboratory work, data collection, analysis and results interpretation and the manuscript writing.	65

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Qi (Tony) Zhou	Data analysis, manuscript revision	5
Thomas Gengenbach	XPS characterization and manuscript revision	5
John A Denman	ToF-SIMS characterization and manuscript revision	5
Peter J Stewart	Supervision and manuscript revision	5
Karen P Hapgood	Supervision and manuscript revision	5
Michael Gamlen	Manuscript revision	5
David A V Morton	Supervision and manuscript revision	5

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

Candidate's Signature	[redacted]	**Date08/03/2016**
Main Supervisor's Signature	[redacted]	**Date08/03/2016**

*Note: Where the responsible author is not the candidate's main supervisor, the main supervisor should consult with the responsible author to agree on the respective contributions of the authors.

3 Investigation of the potential for direct compaction of a fine ibuprofen powder dry-coated with magnesium stearate

3.1 Commentary

In this chapter, the research aim 1 "to investigate the effect of coating concentration on the improvement of the powder flow behaviors for selected model poor-flowing drug powders" was addressed. A fine ibuprofen powder (D_{50}=25 μm) was chosen as the model drug for this study, as it is cohesive and has a low-melting point (~76°C). The ibuprofen was dry coated via mechanofusion with between 0.1 to 5% (w/w) magnesium stearate (MgSt) to examine the effects on flow and tabletability. Traditional low-shear blending was also employed as a comparison.

3.2 Abstract

This study explores the feasibility of applying a magnesium stearate (MgSt) coating using "mechanofusion", on a fine drug powder in order to form tablets with high-dose by direct compaction. Previous work has only investigated coating with flow aids such as colloidal silica, but not considered traditional lubricants. A fine ibuprofen powder, which is both cohesive and possesses a low-melting point, was dry coated via mechanofusion with between 0.1 to 5% (w/w) MgSt to examine the effects on flow and tabletability. Traditional low-shear blending was also employed as a comparison. No significant difference in particle size or shape was measured following mechanofusion. For the low-shear blended powders, only marginal improvement in flowability was obtained. However, after mechanofusion, substantial improvements in the flow properties were demonstrated. Both XPS and ToFSIMS demonstrated high degrees of coating coverage of MgSt on the particle surfaces from optimised mechanofusion. The study showed that robust tablets were produced from the selected mechanofused powders, at high-dose concentration and tablet hardness was further optimised via addition of a Polyvinylpyrrolidone (PVP) binder (10% w/w). The tablets with the mechanofused powder (with or without PVP) also exhibited

significantly lower ejection forces than those made of the raw powder, demonstrating the lubrication effect. Surprisingly, the release rate of drug from the tablets with the mechanofused powder was not retarded. This is the first study to demonstrate such a single-step dry coating of ibuprofen with MgSt, with promising flow improvement, flow-aid and lubrication effects, and also non-inhibited dissolution rate.

3.3 Introduction

In pharmaceutical industries, powder bulk behaviours such as flow and fluidization are critical to their manufacturing processes.[1] For example, consistent free flow under gravity is generally required in the case of most industrial high-speed tablet machines, aiming to obtain homogeneous and rapid transfer of powder from a hopper to give uniform die filling.[2] Fine drug particles (e.g. median size smaller than 20 to 30 μm) are often required (especially to provide desirable dissolution characteristics) but if unmodified, they generally exhibit a cohesive nature and hence poor flow, making direct manufacture impractical or compromising productivity.[2,3] Traditionally, such flow problems may be solved by particle size enlargement or adding flow-aid excipients for direct compaction.[4] However, size enlargement generally employs complex, multistage and expensive processing and can still yield powder tableting challenges.[5,6] Alternatively, the addition of large amounts of bespoke flow-aiding excipients, designed for direct compaction, may not be practical for those high-dose drugs, creating over-sized tablets and increasing the manufacturing cost. Therefore, directly compacting a fine drug powder into tablets is attractive but presents challenges for pharmaceutical manufacturing, especially for a high-dose drug powder such as ibuprofen, with a low melting point which can cause sticking and picking during tableting.[7]

Recently, dry powder coating approaches have been reported as a promising strategy to substantially improve flow, dispersion and fluidization of selected cohesive pharmaceutical powders.[8-12] However, these were generally not soft, low melting point materials. Dry coating can improve powder flow by coating of guest particles on the surfaces of the hosts to reduce powder

cohesion.[13] There are a number of dry processes reported in this context, including mechanofusion,[14] hybridizer,[15] comil,[9,16] fluid energy mills[8] and the magnetically assisted impaction coater (MAIC).[3,8] Dry powder coating is described as an attractive approach, as it is generally simpler, cheaper, safer and more environment-friendly than the solvent-based coating alternatives.[17] In earlier studies, substantially improved powder flow of a fine cohesive lactose monohydrate excipient (median particle size approximately 20 μm) was demonstrated using a mechanofusion approach to coating with magnesium stearate.[10] Mechanofusion is reported as another form of dry powder mechanical coating, similar in outcomes to the hybridizer or MAIC, which has gained recent interest.[18,19] Mechanofusion can take several forms but essentially comprises a cylindrical chamber and a process head which rotate relative to each other at high speed to create intense shear and compression of the core (host) in the presence of coating (guest) particles. The intensive forces employed in such mechanofusion and related processes may cause shape change and granulation effects.[20]

Magnesium stearate (MgSt) is the most widely used as a pharmaceutical lubricant;[21] while colloidal silica is a standard flow-aid additive.[22] Lubricants and flow aids are very different both in form and function, with flow aids acting by increasing surface roughness, in contrast to lubricant function.[23] Dry coating with the flow aid/glidant nanosized silica has been examined in a number of past studies as a means to achieve an enhancement in powder flowability.[16,24] In contrast, deliberate coating using a lubricant has been considered undesirable for tablet formulation due to the negative effect of a lubricant on forming interparticulate forces under compression.[25,26] It is interesting to note that from selected mechanofusion conditions, lactose powders dry coated with magnesium stearate were reported to give a superior flow improvement compared to those dry coated with colloidal silica.[10] This was proposed to highlight benefits specific to mechanofusion, with flow aid properties of silica being inhibited by variable embedding into the lactose surface.[10] In the case of direct tableting of dry coated ibuprofen powder with colloidal silica,[27] additional lubricant was added, which may ease ejection and prevent tablet from sticking.[25,28]

Hence, our aim for this study was:

1. to investigate if a low-melting point drug powder can be dry coated with the lubricant magnesium stearate, via mechanofusion (without significant material softening, particle granulation or other energy-induced damage).
2. would such a coating provide benefits on both powder flow improvement and tablet lubrication to minimise the use of further excipients, and exclude the need for a separate flow aid.
3. and, could tablets be formed recognising, the potential limitation that tablet tensile strength and tablet dissolution rate may be catastrophically compromised by the hydrophobic lubricant.

The employment of a mechanofusion process has been shown to create a lubricant coating that can be much thinner than that attainable by traditional blending,[29] So in this context it is not clear of the impact on a subsequent tablet formation and dissolution behaviour. In this study, dry powder PVP was then included as an optional binder function blended into the selected drug powders to explore its possible compensation effect on tablet tensile strength during compaction. Crospovidone was included as a standard tablet disintegrant.

A low melting point API, ibuprofen, was studied as a model host particle here. It is one of widely used anti-inflammatory drugs and normally formulated in tablets with high drug doses from 200 to 800 mg.[30] It is also noteworthy in this context that the high dose loading and low melting point tends to cause surface melting during high speed tableting resulting in problematic sticking to the tablet press punches and grinding production to a halt as the process needs to be stopped to clean each punch.[30] Consequently, this reduces the speed at which rotary tablet presses can run with a compound such as ibuprofen, hence increasing operational costs. This further makes ibuprofen an ideal model challenging material for this study in contrast to previous studies on simple materials such as lactose,[10,31] polymethylmethacrylate [32] and etc.

3.4 Materials and methods

3.4.1 Materials

Fine ibuprofen 25 was provided by BASF (Ludwigshafen, Deutschland). Magnesium stearate NF (MgSt) was purchased from Mallinckrodt Chemicals, Phillipsburg, USA. Polyvinylpyrrolidone (PVP K25) and Kollidon® CL-F (Crospovidone) was also supplied by BASF. Potassium phosphate monobasic, sodium dodecyl sulphate and sodium hydroxide was all purchased from Sigma-Aldrich.

3.4.2 Methods

3.4.2.1 Dry coating

Dry coating of the ibuprofen samples was performed in an AMS-Mini mechanofusion system (Hosokawa Micron Corporation, Osaka, Japan). Ibuprofen samples (approximately 20 g) were manually premixed with 0.1, 1 or 5 % (w/w) magnesium stearate using a spatula in a 125 ml cylindrical glass container and then fed to the mechanofusion process chamber. These samples were denoted as 0.1% MgSt-mechanofused, 1% MgSt-mechanofused and 5% MgSt-mechanofused, respectively.

A detailed description of mechanofusion can be found in the earlier literature.[10] In short, the premixed guest and host particles are placed into the rotating chamber and during the processing, the guest particles are fused onto the surfaces of the host particles due to the intense interaction generated by the relatively high speed shear mixing. In the current work, the mechanofusion process was conducted by slowly increasing the paddle speed to 900 rpm over 1 min and maintaining this speed for a further 5 min. Preliminary work has shown that higher rotational speeds resulted in hard deposits of ibuprofen on the mechanofusion processor internal walls. This was attributed to partial surface melting of this material, similar to that reported during high speed tableting of ibuprofen. Hence the speed and time used here was selected based on preliminary

studies as an optimum to achieve effective magnesium stearate coating but not to result in processing problems. Tap water (22 ± 2°C) was applied via circulation through a casing jacket to maintain cooling to the unit during the mechanofusion process.

3.4.2.2 Low-shear blending

Low-shear blending of ibuprofen samples with 1% (w/w) magnesium stearate was carried out using a conventional tumbling Turbula® T2F mixer (Glen Mills Inc., Clifton, NJ, USA). Approximately 19.8 g of ibuprofen plus 0.2 g of magnesium stearate were weighed into a 125 ml cylindrical glass container, which was approximately half fill level. This was blended for a relatively extensive period of 30 mins at a speed of 72 rpm. This sample is denoted as MgSt-blended.

The raw, blended and mechanofused ibuprofen powder (with 1% magnesium stearate: as described above) was subsequently blended in the Turbula T2F with 10% (w/w) PVP plus 5% crospovidone, using the same process parameters, to produce samples which are denoted as raw-PVP, blended-PVP, mechanofused-PVP, respectively.

3.4.2.3 Powder densities and Carr Index

The poured density (ρ_p) was determined by feeding sample powders slowly and carefully to a 10 ml calibrated volumetric cylinder through a funnel at a fixed height of 2 cm above the cylinder. The tapped density (ρ_T) was measured after 1250 taps using an automatic tapper (AUTOTAP™, Quantachrome Instruments, Boynton Beach, FL). This instrument ran with a 3.18 mm vertical travel at a tapping speed of 260 tap/min. The measurement was performed in triplicate. The Carr Index (CI)[33] was calculated from poured density and tapped density values.

3.4.2.4 Particle sizing

The particle size of each sample was measured by laser diffraction (Mastersizer® 2000, Malvern Instruments, Worcestershire, UK) using a small volume liquid dispersion unit. The dispersion

medium was prepared as a saturated aqueous solution of ibuprofen (temperature: 25±0.5°C). Approximately 50 mg of ibuprofen powder was dispersed in 20 ml of dispersion medium prior to measurement. The particle size distribution was averaged from three replicates of each sample. The particle size distribution was represented by D_{10} (diameter at 10% undersize), D_{50} (diameter at 50% undersize) and D_{90} (diameter at 90% undersize).

3.4.2.5 Powder flow properties

Flow properties of each sample were characterized using the Freeman FT4 Powder Rheometer in the compressibility, aeration and shear modes (Freeman Technology, Worcestershire, UK). A detailed introduction of this instrument function for coated powders can be found in previous reports.[34,35]

In the compressibility mode, a 23.5 mm diameter piston compressed powders under normal stresses of 1, 2, 4, 6, 8, 10, 12 and 15 kPa. Compressibility is a measure of volume change (in percentage) of the sample powder under a given applied normal stress. A lower compressibility value curve line generally corresponds to less cohesive properties.[1,10]

In the aeration mode, powder fluidization behaviours were investigated using the automated aeration programme that runs a sequence of tests measuring the energy to rotate a blade through the powder bed at increasing levels of air velocity traversing through the sample powder.[35] The outcome provides an assessment of ease of powder fluidisation.

In the shear mode, a maximum pre-shear normal stress of 9 kPa was induced to consolidate the powder prior to each test. Shear measurements were then conducted at normal stress of 3, 4, 5, 6 and 7 kPa. The interparticle cohesion of each sample was derived by extrapolating the yield loci according to the equation as below (1):

$$\tau = C + \sigma \tan \eta \quad (1)$$

Where τ is the shear stress (kPa), σ is the normal stress (kPa), η is the angle of friction (degrees),

and *C* is the cohesion (kPa). A lower cohesion value demonstrates a lower interparticle interaction force.

3.4.2.6 Scanning electron microscopy (SEM)

Morphology of the ibuprofen samples was evaluated using a scanning electron microscope (Phenom^{TM}, FEI Company, Hillsboro, OR, USA). A small amount of each sample was slowly sprinkled onto a double–sided sticky tape mounted on a sample holder, and gently shaken to remove the loose powder. The prepared samples were sputter coated with gold using an electrical potential of 2.0 kV at 25 mA (SCD005, BAL-TECAG, Blazers, Germany).

3.4.2.7 Particle shape

The particle shape was characterized using the Morphologi G3 (Malvern Instruments, Worcestershire, UK). The Morphologi G3 is an automated image analysis system which enables measuring the morphological characteristics (such as shape) of statistically-valid high numbers of particles using particle recognition software to provide number and volume based statistics for a large population that provide a non-subjective assessment with good resolution. The authors have developed this automated image analysis method to allow a unique study of particle shape in the context of an intensive dry coating process. All the samples were separately prepared using the integral Sample Dispersion Unit (SDU) which dry disperses powders onto the glass plate at a standardised injection pressure of 1 bar. The measurement for each sample was performed in triplicate and results were averaged.

In this study, three shape factors (circularity, elongation and convexity) were derived and used to characterize the particle shape. Circularity measures how close the shape is to a perfect circle, which is calculated as the ratio of the perimeter of a circle with the same area to the particle divided by the perimeter of the actual particle image.[36] It is defined as below equation (2):

$$\textbf{Circularity} = 4\pi A/P^2 \qquad (2)$$

Where A is the particle actual area and P is its actual perimeter. The values of circularity are between 0 and 1. Therefore, a perfect circle has a circularity of 1, whilst a needle-like object gives a circularity value closer to 0.

Elongation is stated as below equation (3):

Elongation = 1 − *width/length* **(3)**

Its values also are in range of 0 and 1. A shape symmetrical in all axes (such as a circle) will have an elongation value of 0 whereas shapes with large aspect ratios will have an elongation closer to 1. Finally, Convexity was used to evaluate the roughness of a particle calculated by dividing the convex hull perimeter by the actual particle perimeter.[36] It again has the values in the range from 0 to 1, where a shape having a very smooth surface gives a convexity approaching 1 while a very rough surface has a value closer to 0.

3.4.2.8 XPS

X-ray photoelectron spectroscopy (XPS) analysis was performed using an AXIS Ultra DLD spectrometer (Kratos Analytical Inc., Manchester, UK) with a monochromated Al Kα source at a power of 180 W (15 kV × 12 mA), a hemispherical analyser operating in the fixed analyser transmission mode and the standard aperture (analysis area: 0.3 mm × 0.7 mm). The total pressure in the main vacuum chamber during analysis was typically 10^{-8} mbar. Survey spectra were acquired at pass energy of 160 eV. To obtain more detailed information about chemical structure, oxidation states etc., high resolution spectra were recorded from individual peaks at 20 eV pass energy.

Samples were filled into shallow wells of custom-built sample holders. One lot of each sample was prepared and 2 different locations were analysed on each sample at a nominal photoelectron emission angle of 0º with respect to the surface normal. Since the actual emission angle is ill-

defined in the case of particles (ranging from 0º to 90º) the sampling depth may range from 0 nm to approximately 10 nm.

Data processing was performed using CasaXPS processing software version 2.3.15 (Casa Software Ltd., Teignmouth, UK). All elements present were identified from survey spectra. The atomic concentrations of the detected elements were calculated using integral peak intensities and the sensitivity factors supplied by the manufacturer. Binding energies were referenced to the aliphatic hydrocarbon peak at 285.0 Ev.[37]

3.4.2.9 ToF-SIMS

ToF-SIMS experiments were performed using a PHI TRIFT V nanoTOF instrument (Physical Electronics Inc., Chanhassen, MN, USA) equipped with a pulsed liquid metal $^{79+}$Au primary ion gun (LMIG), operating at 30 kV energy. Dual charge neutralization was provided by an electron flood gun and 10 eV Ar+ ions. Surface analyses were performed using "unbunched" Au1 instrument settings to optimize spatial resolution. Raw data was collected in positive SIMS mode at a number of locations typically using a 200 x 200 μm raster area, with 4 min acquisitions. Signals of Mg (m/z ~24) were collected as indicative of MgSt, while signals at m/z ~207 (M+H), ~192 (M-CH_2) and ~161 (M-COOH) were collected as indicative of ibuprofen ($C_{13}H_{18}O_2$, m/z ~206).

For purposes of statistical interrogation, 25 particles of interest were imaged per sample to collect a representative data set for qualitative comparison of surface chemistry. Region-of-interest analyses were performed on the collected raw image data using WincadenceN software (Physical Electronics Inc., Chanhassen, MN, USA). Integrated peak values of the selected ions were normalized to the total secondary ion intensities. The resulting data were then compared qualitatively by preparing plots of average normalized counts (with 95% confidence intervals) for each species of interest.

3.4.2.10 Tablet formation

Tablet formation (or tabletability) was assessed here as the capacity of a powdered material to be transformed into a specified strength disc under the effect of compaction pressure.[38] The selected sample powders were compacted directly into tablets using a GTP-1 computer controlled and instrumented tablet press (Gamlen Tableting Ltd., Nottingham, UK). The compaction force and ejection force curves were recorded for each tablet using Gamlen TP Controller Version 3.09. A flat round punch with a diameter of 6 mm was used to form standard model tablets of approximately 100 mg in weight. Five tablets were made and tested at each compaction pressure for each sample. The compaction pressure ranged from 40 MPa to 180 MPa. The fracture force of a tablet was measured using a hardness tester (ERWEKA, Heusenstamm, Germany). Tablet tensile strength was calculated from the fracture force, tablet thickness and diameter[39] as below using equation (4):

$$\sigma = 2P/\pi Dt \qquad (4)$$

Where P is fracture force (N); D is punch diameter (mm); t is tablet thickness (mm) and σ is tensile strength (MPa). Powder compaction properties were characterized by plotting tablet tensile strength as a function of compaction pressure. Ejection stress was derived using equation (5):[40]

$$ES = F/\pi Dt \qquad (5)$$

Where ES is ejection stress (MPa); F is ejection force (N); D is punch diameter (mm) and t is tablet thickness (mm).

3.4.2.11 *In vitro* dissolution studies

The dissolution tests were conducted with a dissolution apparatus (Erweka DT6; Erweka, Heusenstamm, Germany) using USP II[41] paddle method with paddle speed of 50 rpm. The dissolution medium (900 ml) consisted of a buffer solution at pH 7.2 [42] with 0.05 g/L sodium dodecyl sulphate (SDS). All dissolution medium were filtered through 0.45 μm Millipore

membrane and equilibrated to 37.0 ± 5°C in the dissolution bath. The prepared tablets were then added to the dissolution vessels. 5 mL aliquots of the dissolution medium were collected at 0, 2, 5, 10, 15, 25, 30, 40, 50 and 60 min and were replaced with equivalent volumes of fresh medium. The collected aliquots were filtered through 0.45μm filter and the dissolved content of ibuprofen (%) was measured using a validated UV spectrophotometer assay.

3.4.2.12 UV analysis of ibuprofen

A validated UV spectrophotometer method (CECIL 3021, Lab instrumentation Pty. Ltd., Australia) was used to analyse the ibuprofen content from dissolution study at a wavelength of 221 nm.[43] The Beer's calibration of plot for ibuprofen in the dissolution medium exhibited a linear relationship between absorption and ibuprofen concentrations over the range of 2 to 20 μg/ml (R^2>0.999) with accuracy and precision values ranging from 97.4-103.5% and 1.2-2.7%, respectively.

3.4.2.13 Statistical analysis

The statistical analysis of data derived from all ibuprofen samples was performed using analysis of variance (ANOVA) with Turkey's post hoc analysis at a *p*-value of 0.05 (SPSS, Version 19, IBM Inc., USA).

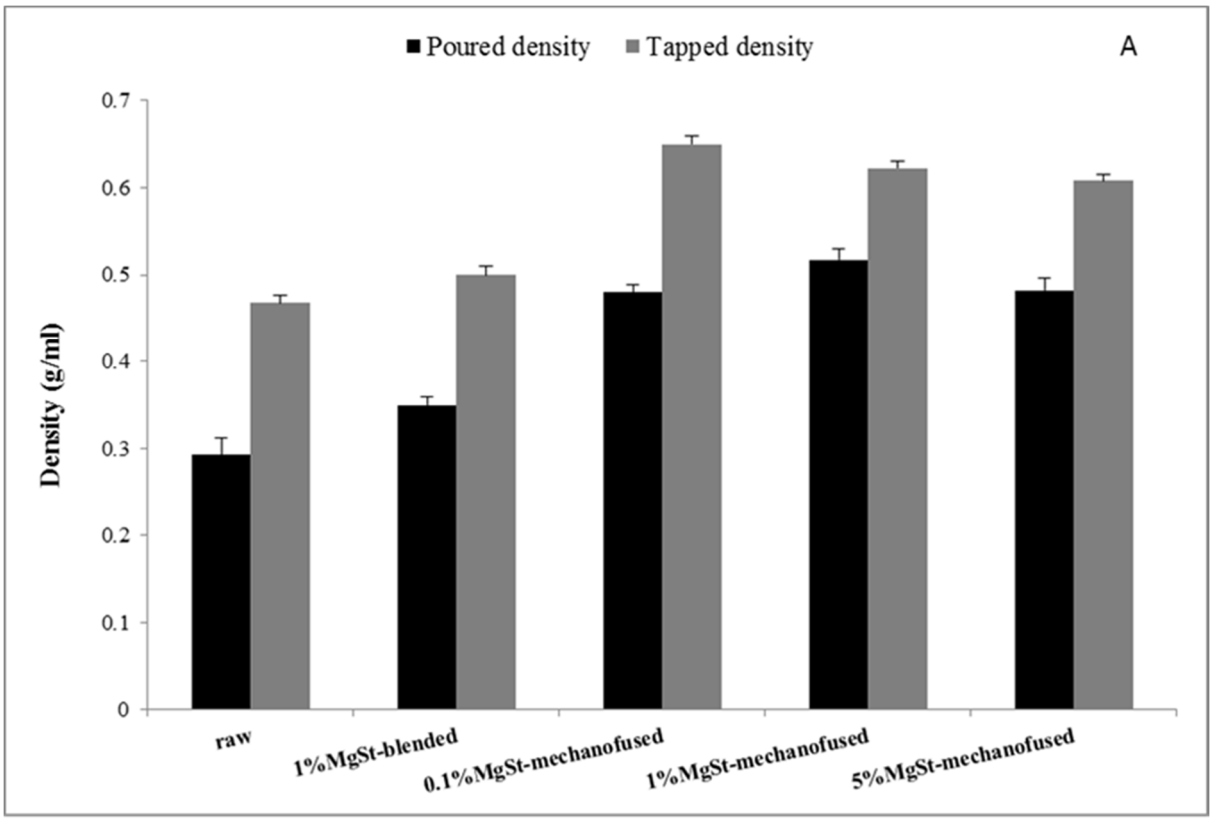
3.5 Results and discussion

3.5.1 Powder densities and Carr Index

The bulk density and Carr Index (CI) for each sample are presented in Figure 1. There was no significant difference (p>0.05) in both poured density and tapped density between the raw ibuprofen and the blended sample with 1% magnesium stearate as shown in Figure 1A. After mechanofusion with 0.1, 1 or 5% magnesium stearate, the poured density and tapped density values increased significantly in comparison to those of the raw and blended sample (p<0.001). No significant difference was shown in either poured density or tapped density values between all

mechanofused samples (p>0.05). This indicated that a prolonged conventional blend of the powder with magnesium stearate had little impact on consolidation and packing in contrast to mechanofusion with as low as 0.1%.

Figure 1B shows a slight reduction in the CI values for the blended over the raw samples, whereas more substantial decreases in CI values were obtained after mechanofusion with magnesium stearate (p<0.002). The mechanofused particles with 1% MgSt exhibited the best flowability as indicated by the lowest CI value of 0.17. Such CI values have been classified as "fair" flow.[44] Powder densities and their derived indices are widely used as indicators [45,46] to assess powder flow. After mechanofusion with magnesium stearate, the substantially increased densities and the decreases of the CI values are attributed to the formation of an extensive magnesium stearate coating layer on the particle surfaces (that is not achieved with lower shear blending) which facilitated enhanced packing of the powder as a result of reduced interparticle cohesion.



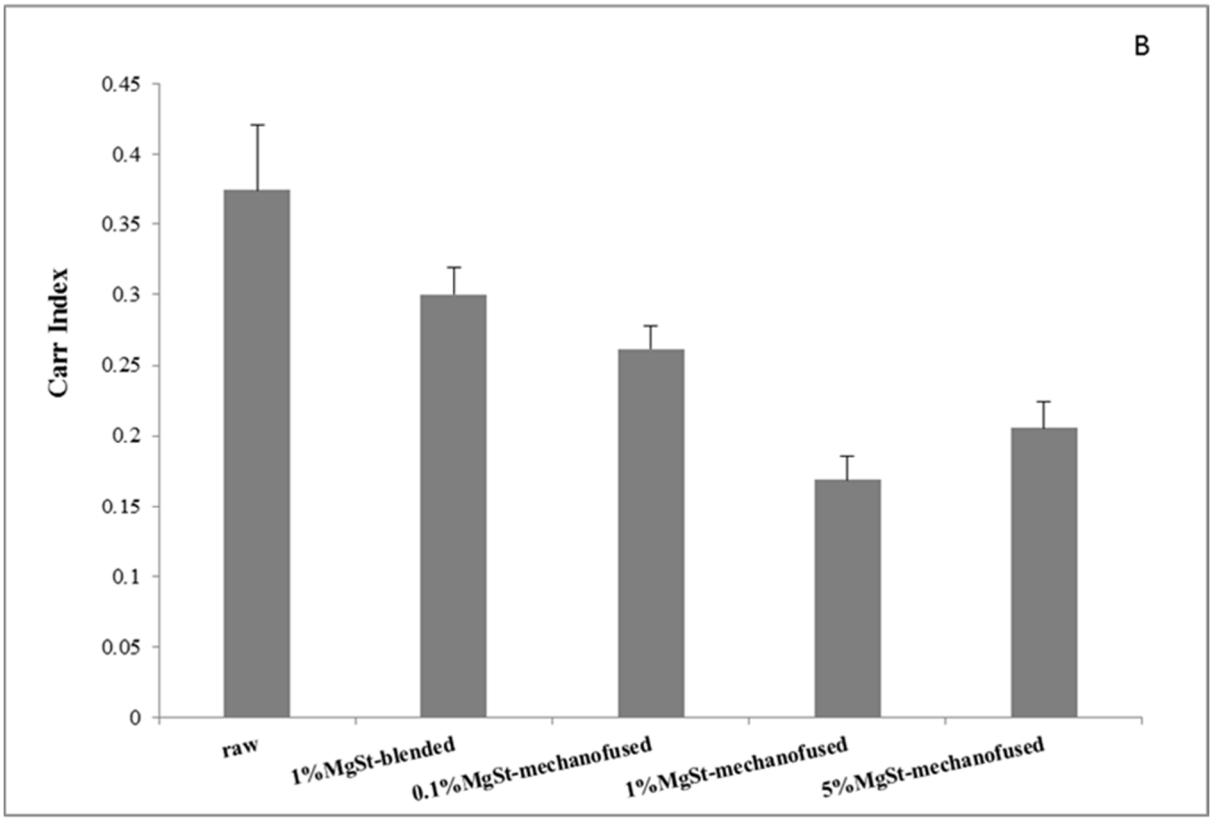


Figure 1. Densities and CI values of raw and processed ibuprofen samples (error bars represent standard deviation, n=3).

3.5.2 Powder flow properties

Cohesion and flow function (ffc) values from the FT4 powder shear tests are presented in table 1. These parameters are used to indicate the ease of flow from a consolidated state, such as from a hopper.[23] As defined by Schulze, the ffc is the ratio of major principle stress to the unconfined yield stress and used to classify the powder flow behaviour according to its value which is: ffc < 1, not flowing; 1 < ffc < 2, very cohesive; 2 < ffc < 4, cohesive; 4 < ffc < 10, easy flowing and ffc > 10, free-flowing. The raw ibuprofen powder exhibited significantly the highest cohesion values (1.24) and lowest ffc (4.02) in comparison to all others, followed by the blended powder. There was no significant difference in cohesion value between the blended ibuprofen with 1% magnesium stearate, and that mechanofused with 0.1% magnesium stearate. However, the mechanofused powders with 1% and 5% magnesium stearate showed significantly lower cohesion values (0.48 and 0.41, respectively) and higher ffc (8.8 and 10.6, respectively) than all other powders (p<0.05). This indicates the raw, blended and 0.1% mechanofused powders will flow less well from a consolidated hopper state.

Table 1. Cohesion and ffc values of ibuprofen samples (mean ± SD, n=3).

	raw	MgSt-blended	0.1%MgSt-mechanofused	1%MgSt-mechanofused	5%MgSt-mechanofused
cohesion	1.24±0.04	1.02±0.15	0.942±0.14	0.48±0.1	0.41±0.08
ffc	4.02±0.19	4.35±0.6	4.97±0.6	8.8±0.93	10.61±1.6

Figure 2 shows that the raw ibuprofen powder exhibited the highest FT4 compressibility value at all normal stresses as compared to other powders. In the context of this study, this measurement indicates raw powder with the highest interparticle cohesion.[35] The blended powder had compressibility values that were lower than those of raw powders but were significantly higher than all mechanofused samples. In contrast, the mechanofused powders with 1% and 5% magnesium stearate had similar compressibility values and patterns which were significantly lower than all others (p<0.05), while mechanofused powder with 0.1% magnesium stearate had higher compressibility values suggesting there was insufficient magnesium stearate to provide an

extensive coverage coating, thereby producing only a partial reduction in cohesion. Hence, these results indicated the mechanofusion approach resulted in a measurably higher degree of consolidation under a given stress due to particle surface modification.

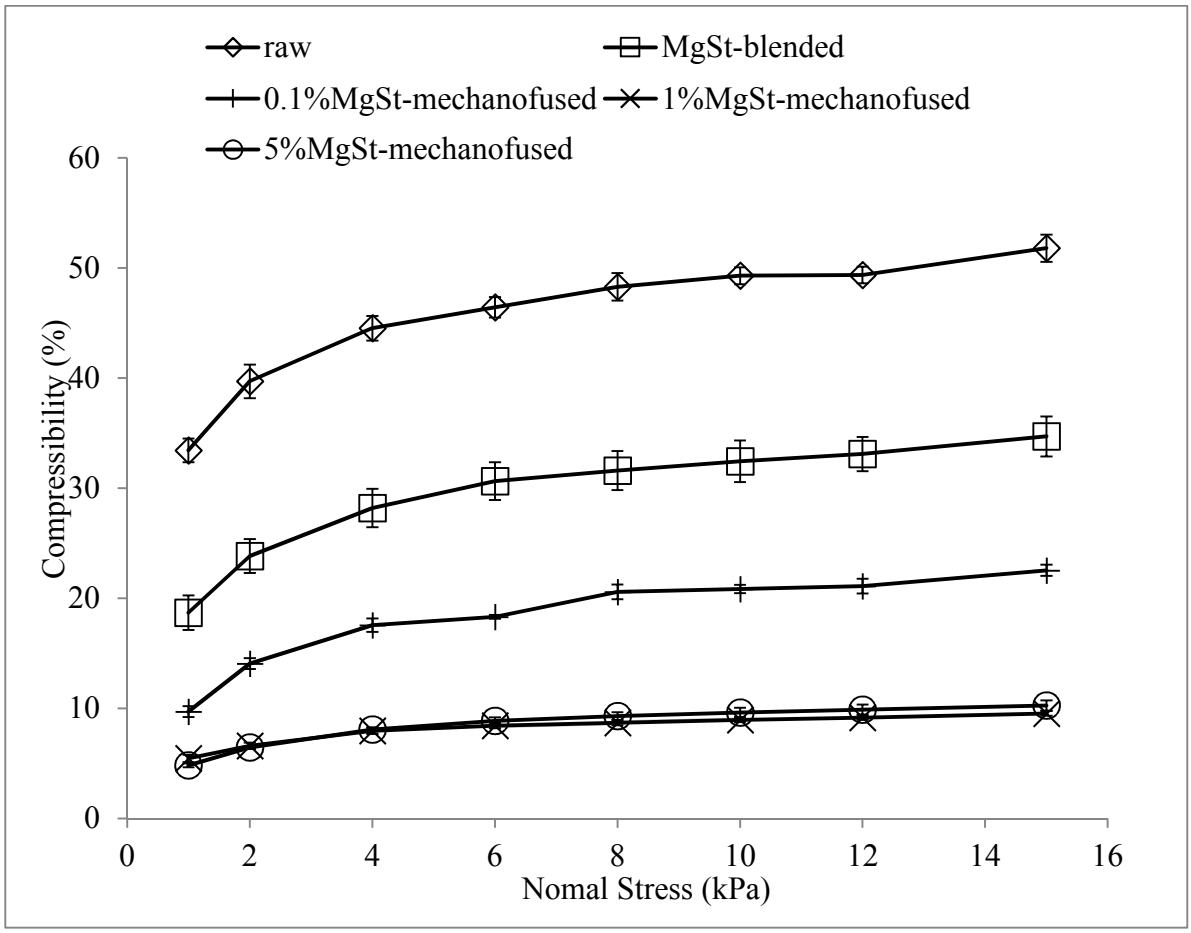


Figure 2. Compressibility values for raw and processed ibuprofen samples at different normal stresses (error bars represent standard deviations, n=3).

Figure 3 shows the powder aeration behaviour as measured on the FT4. The raw and blended samples had similar flow energy patterns and exhibited higher flow energy at each given air velocity compared to the mechanofused samples. When the air velocity was increased to 20 mm/s, the powder reached a fluidized state with around 15 mJ flow energy. In contrast, for the mechanofused samples, the flow energy was reduced to lower values, and the reduction was observed with even the minimum air velocity of 2 mm/s. Therefore, for these dry coated samples, the powders were substantially more easily fluidized and maintained this state with a minimal air flow. This enhanced fluidization property may also be a useful feature for further investigation in

future studies, in respect to powder flow, powder aeration/de-aeration and other characteristics that are relevant in tableting and related manufacture.

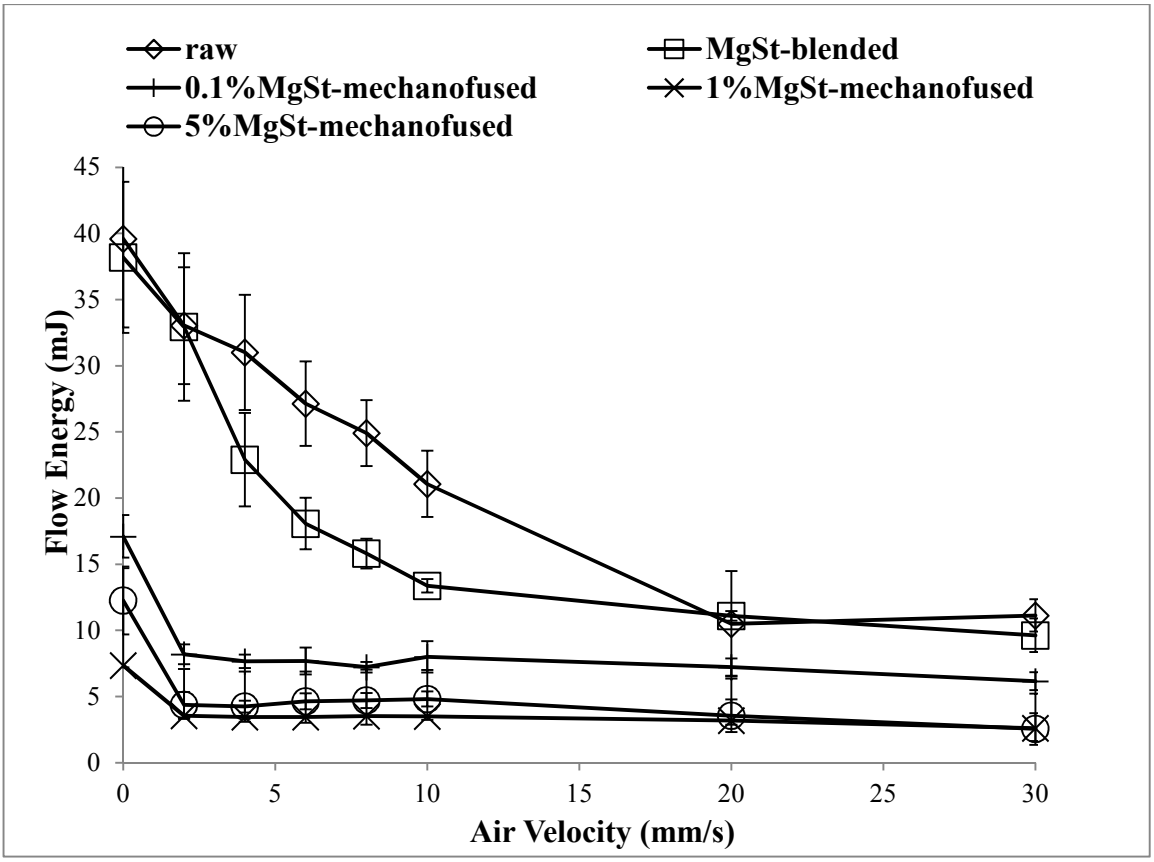


Figure 3. Flow energy at different air velocity for raw and processed ibuprofen samples (error bars represent standard deviations, n=3).

3.5.3 Particle size analysis

Table 2 shows that only marginal differences in the D_{50} values were seen between the raw, blended and mechanofused samples. The slight reductions in particle sizes after mechanofusion processing are proposed to be attributed to either slight attrition during high shear impaction or due to reduction in hard-agglomeration existing in the particles.[29] In addition, any coating layer of magnesium stearate is anticipated as very thin (i.e. of the order of a few nanometers) and therefore would not be detectable as a change in diameter by laser diffraction here. This size data also confirms that any improvement in bulk flow was not caused by particle size enlargement.

Table 2. Particle size distribution of the ibuprofen sample powders (mean ±SD, n=3).

Sample powders	D_{10}(μm)	D_{50}(μm)	D_{90}(μm)
raw	17.13±0.23	43.55±0.72	89.78±1.13
MgSt -blended	13.68±0.12	38.58±0.19	80.47±0.79
0.1% MgSt - mechanofused	14.25±0.07	34.94±0.36	66.78±1.36
1% MgSt - mechanofused	14.38±0.47	35.74±0.47	69.75±2.21
5% MgSt - mechanofused	11.48±0.29	34.14±0.21	66.65±0.27

3.5.4 SEM

Representative SEM images of the ibuprofen samples are shown in Figure 4. The raw ibuprofen particles shown in Fig. 4A exhibit a rod-like shape with smooth surface. For the ibuprofen blended with 1% magnesium stearate, Fig. 4B shows flake-shaped particles which appear to be magnesium stearate are dispersed unevenly onto the ibuprofen particles. In contrast, the mechanofused particles with either 0.1% or 1% magnesium stearate depicted in Fig. 4C and 4D, the particles exhibited relatively smooth surfaces and no flake-shaped magnesium stearate particles were observed. This observation is consistent with the high shear energy produced during mechanofusion process being far more effective at spreading and smearing the magnesium stearate onto the particle surface to achieve a relatively even thin film. Fig. 4E shows the mechanofused ibuprofen particles with 5% magnesium stearate, which instead had relatively rough surfaces. This different surface texture is proposed to be the result of visible overlapping layers of magnesium stearate. It is proposed that 5% of magnesium stearate provides an excess magnesium stearate above that required to form a uniform coating layer, and so the excess magnesium stearate flakes overlap each other on the particle surface, forming as uneven layers.[47]

Despite the low melting point of ibuprofen, no visible evidence of any melting phenomenon, such as gross shape changes or surface deformation was observed for any samples after mechanofusion.

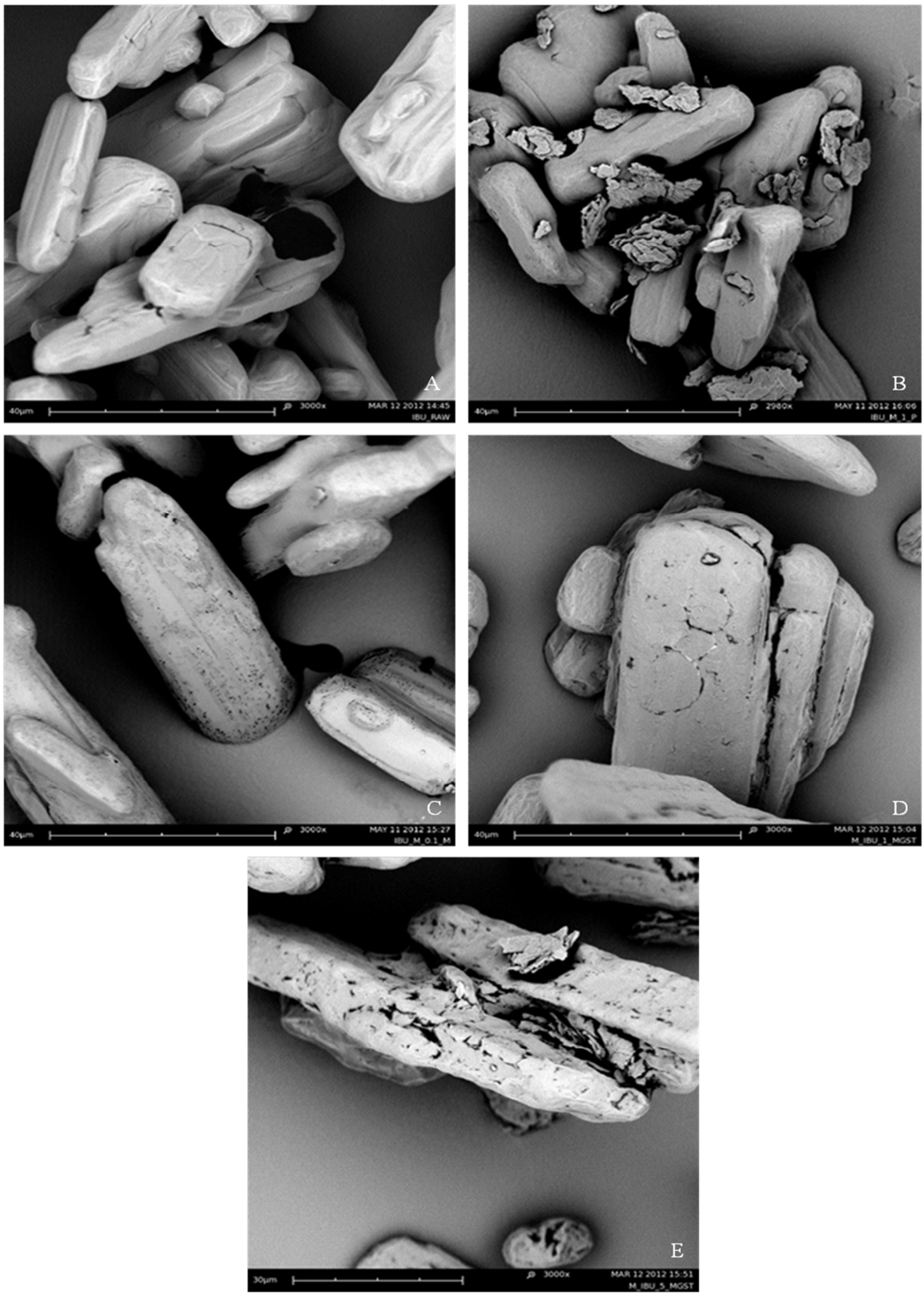


Figure 4. SEM micrographs of ibuprofen samples at magnification of 3000× (A: raw particles; B: MgSt-blended particles; C: 0.1%MgSt-mechanofused particles; D: 1%MgSt-mechanofused particles; E: 5%MgSt-mechanofused particles), scale bar represents 40 µm in micrograph of A, B, C, D and 30 um in E.

3.5.5 Particle shape

The values of particle shape factors obtained from Morphologi G3 automated analysis are shown in Figure 5. The results from this shape analysis system showed that for all the measured samples, there was no significant difference in circularity, elongation or convexity (p>0.05). These results confirmed the observation from SEM, that despite a low melting point, ibuprofen particle shape remained unchanged under the high-shear energy processing by mechanofusion, and therefore any changes in flow bulk behaviour cannot be attributed to substantial particle shape modification.

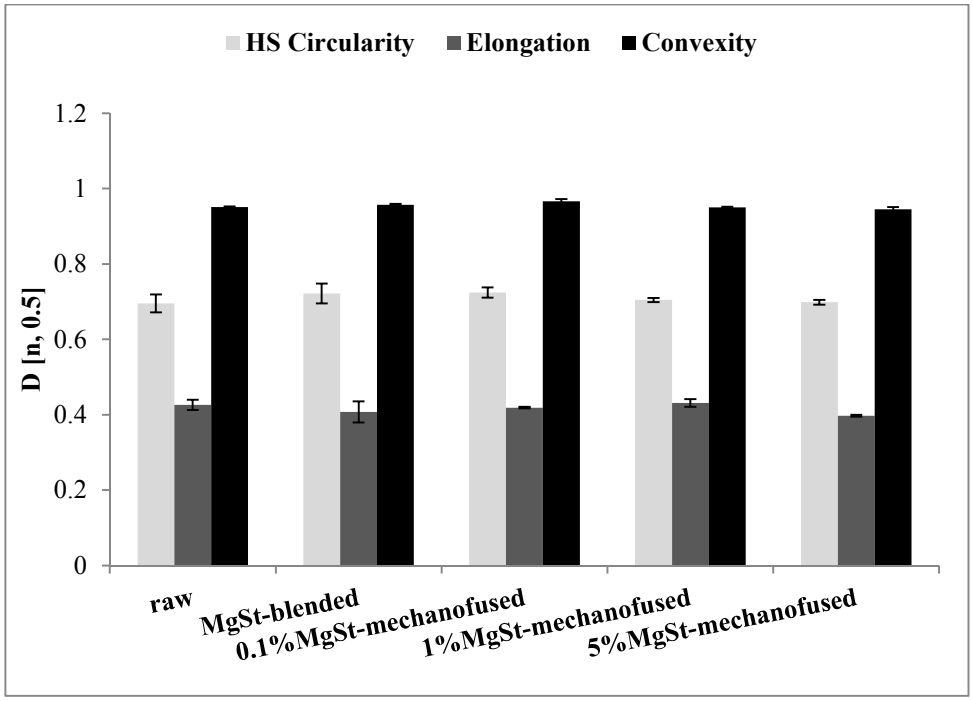


Figure 5. Values of circularity, elongation and convexity for raw and processed ibuprofen samples (error bars represent standard deviations, n=3).

3.5.6 XPS

The surface compositions of the blended particles and mechanofused particles as determined by XPS analysis are presented in Table 3 where they are compared to those of the two pure ingredients, i.e. ibuprofen and magnesium stearate. Mg, being uniquely representative of magnesium stearate, is the most reliable parameter in assessing the quality of coatings. The dry coated particles with magnesium stearate concentration of 1% and above had a level of Mg close

to that of pure magnesium stearate, indicating that all particles were coated with a layer of magnesium stearate with a thickness of at least several nanometres and free of observable coating defects (i.e. near complete coverage). Note that the somewhat lower value for 0.1% magnesium stearate (M: mechanofused) and for 1.0% magnesium stearate (P: blended) would suggest that in those two cases the coating is either thinner or that the coverage is incomplete.

The above conclusions (based on elemental surface compositions) were then further supported by analysis of the C 1s high resolution spectra, shown in Figure 6. All spectra have the dominant peak at 285.0 eV, characteristic of CH_x (C only bonded to C or H). Although there is a slight difference in binding energy between aliphatic and aromatic structures (about 0.2 eV), this difference cannot be resolved. The ibuprofen spectrum has minor peaks at 289-290 eV (carboxylic acid) and at 291-292 eV (Π -> Π* shake-up peak indicative of aromatic groups). In the case of magnesium stearate the spectrum displays a minor peak at 289 eV (COO^-). The spectra of the two mechanofused samples (1.0% and 5.0%) are identical to that of pure magnesium stearate. The aromatic shake-up peak is not present, consistently indicating that magnesium stearate effectively covers the ibuprofen particles. The spectrum of the blended sample appears to show some additional intensity above 290 - 291 eV indicating the presence of some aromatic structures near the surface (ibuprofen). This observation is again consistent with a thinner (or less complete) coating.

Table 3. Elemental surface composition of the ibuprofen sample powders as measured by XPS. Presented are atomic concentrations relative to those of carbon, i.e. atomic ratios X/C (mean ± SD, n=3). C/C = 1.000.

Element	Ibuprofen - raw	0.1% MgSt- mechanofused	1% MgSt - mechanofused	5% MgSt - mechanofused	MgSt - blended	MgSt - raw
Mg	-	0.018 ± 0.001	0.020 ± 0.001	0.020 ± 0.001	0.017 ± 0.001	0.024 ± 0.001
O	0.099 ± 0.012	0.099 ± 0.001	0.096 ± 0.001	0.094 ± 0.001	0.103 ± 0.001	0.104 ± 0.001

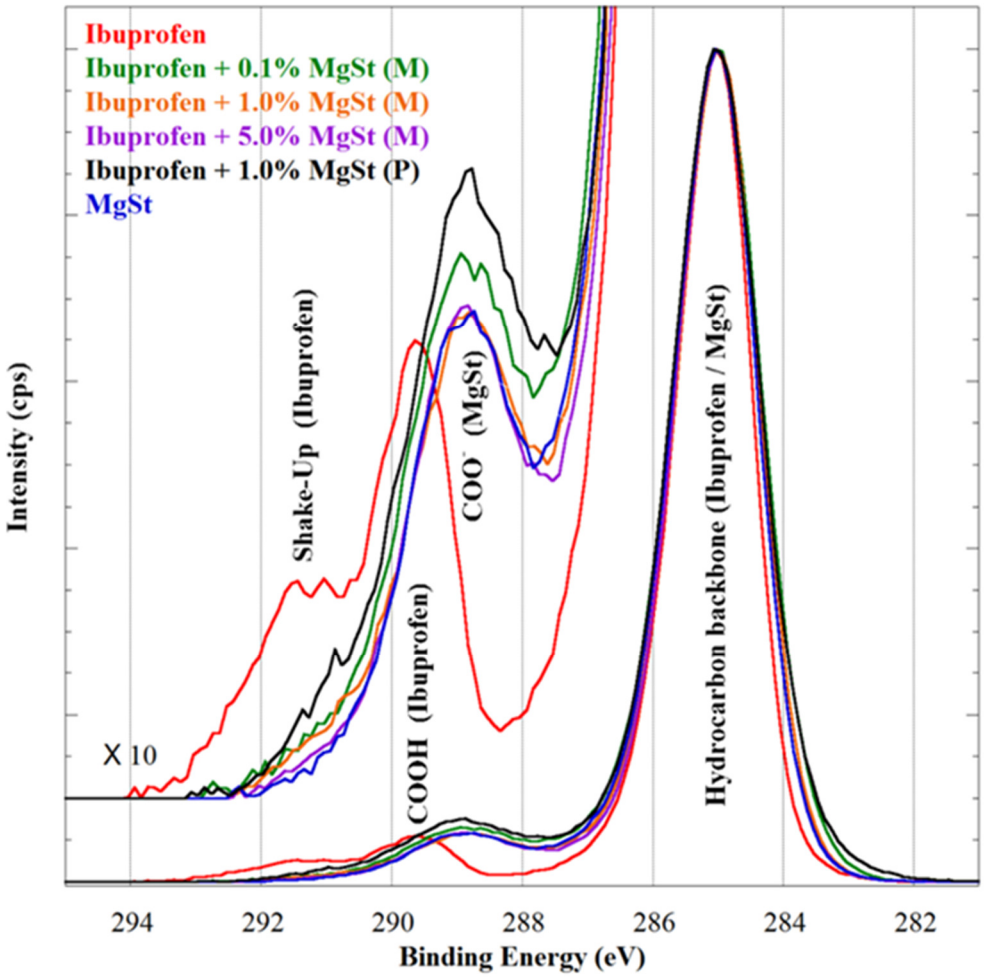


Figure 6. Representative Carbon 1s high resolution spectra from XPS surface investigation.

3.5.7 ToF-SIMS

Chemical maps of the distribution of surface species on the raw, blended and mechanofused particles are shown in Figure 7. The images showed the signals of magnesium stearate in red (Mg^+) and those of the highest intensity ibuprofen fragment (m/z~161) in green. In Fig. 7B, the particles blended with 1% MgSt exhibited inconsistent and incomplete coverage by MgSt. In comparison, the 0.1% MgSt mechanofused sample represented in Fig. 7C shows better coverage, despite the lower concentration of MgSt compared to Fig. 7B. Increasing this concentration to 1% and subsequently 5% further improved the coverage, with only very small areas of ibuprofen still visible as demonstrated in Fig. 7D and 7E, respectively.

To further investigate the particle surface chemistry, employing a more quantitative and significant basis, data were collected from at least 25 particles in each sample. Table 4 shows a qualitative

comparison of normalised intensities for MgSt and ibuprofen species on the surface of these discrete particles. Surface coverage of MgSt was drastically improved in the mechanofused samples, with increasing the MgSt concentration from 0.1-1% w/w, with less of an increase in moving to 5% w/w.

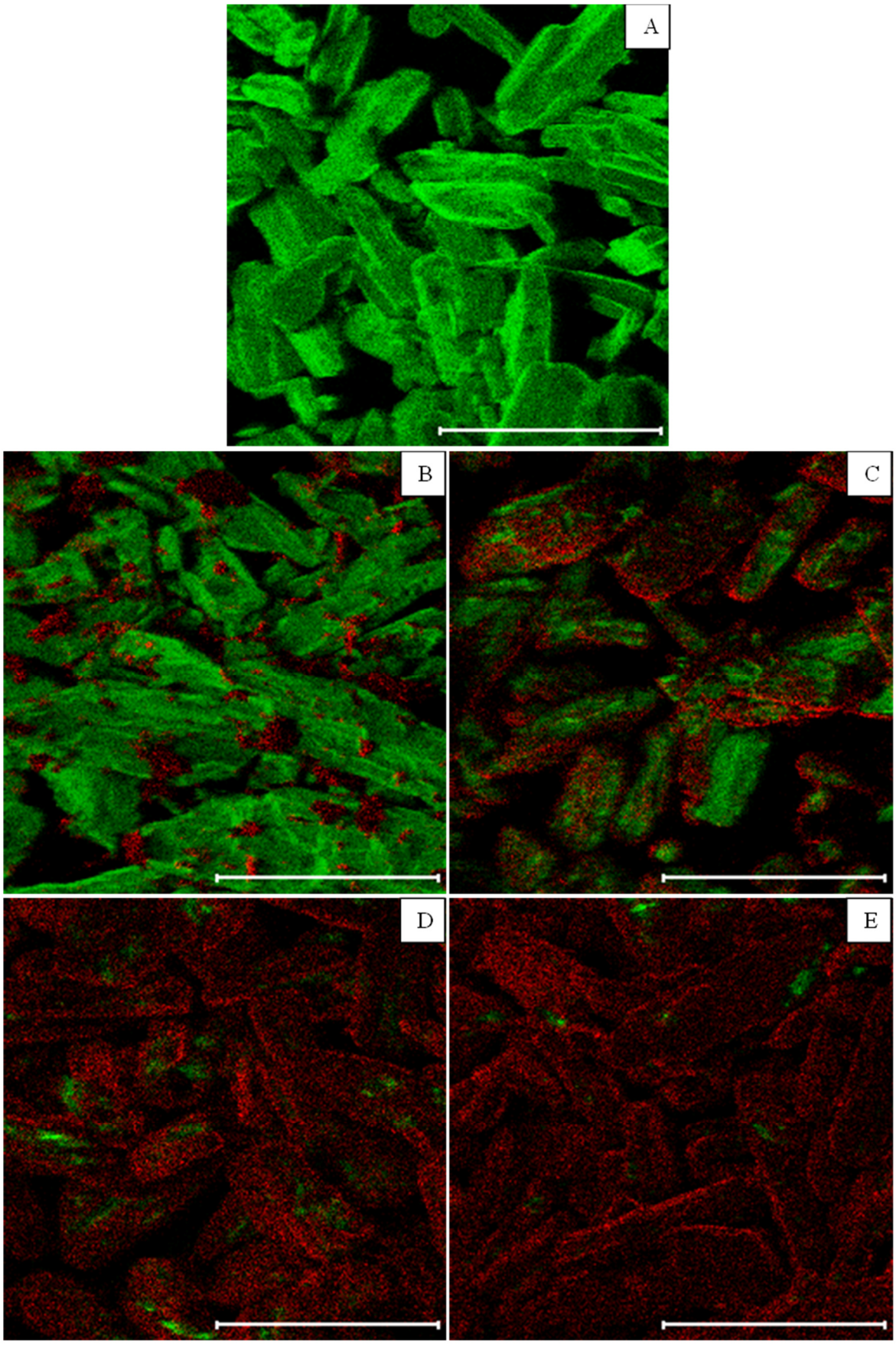

A
B
C
D
E

Figure 7. ToF-SIMS overlay images at scanning area of 200 × 200 μm^2 for ibuprofen samples as indicated as red signal for Mg (m/z 24amu) and green for ibuprofen (m/z 161amu). A: raw particles; B: MgSt-blended particles; C: 0.1%MgSt-mechanofused particles; D: 1%MgSt-mechanofused particles; E: 5%MgSt-mechanofused particles (scale = 100μm).

Table 4. Percentage of Normalized counts of Mg (m/z 24) and M-COOH (m/z 161) signals over the total ion signals of ibuprofen samples measured using ToF-SIMS at scan area of 200×200 μm (mean±SD, 95% confidence, N=25)

Element	Ibuprofen-raw	0.1% MgSt-mechanofused	1% MgSt-mechanofused	5% MgSt-mechanofused	MgSt-blended
Mg (m/z 24)	_	0.024±0.0068	0.078±0.013	0.094±0.0112	0.0064± 0.0034
[M-COOH] (m/z 161)	0.17±0.0087	0.101±0.015	0.023±0.0085	0.0104±0.006	0.16± 0.0078

3.5.8 Tablet formation

The ibuprofen powder mechanofused with 1% magnesium stearate exhibited the greatest improvement in powder flow indicators. Given also that its magnesium stearate concentration is in the recommended range of 0.25-1% (w/w) for conventional tablet compaction,[22] this mechanofused ibuprofen material with 1% magnesium stearate as well as its blends with 10% PVP binder and 5% crospovidone disintegrant were selected for powder compaction evaluation in comparison to the raw, blended with 1% magnesium stearate powder samples and their corresponding blends with 10% PVP and 5% crospovidone.

Figure 8 shows the tablet tensile strength relative to the applied compaction pressure. The tablet tensile strength values for the mechanofused powder were significantly lower than the raw and blended powder (p<0.05). This reduction in hardness is consistent with the established concept that over-lubrication with magnesium stearate can negatively affect tablet formation of pharmaceutical powders.[25,26] A well distributed magnesium stearate should provide a reduction of interparticulate bonding strength, such as van der Waals forces.[48] There was no significant

difference in tensile strength over the range of the applied compaction pressure 40-180 MPa between the raw and blended ibuprofen powders ($p>0.05$). This indicated the low shear mixing did not provide sufficient energy to extensively coat the cohesive ibuprofen powder with magnesium stearate[10] as suggested from the SEM investigation (Fig. 4B). Consequently, the effect of the tumbling blended magnesium stearate on the particle bonding strength during tableting was negligible.

The tensile strength of all tablets made with the raw, blended and mechanofused powder increased after addition of PVP. It is well known PVP as a binder is capable of improving the tablet tensile strength due to its high plastic deformation during compaction.[49-51] The tensile strength of the tablets with the mechanofused powder plus PVP increased by 42% than its corresponding tablets without PVP, in contrast to the tablets with a either blended powder plus PVP or a raw ibuprofen plus PVP, which had a tensile strength increase of around 18% in comparison with their corresponding tablets without PVP. This greater increase in tensile strength for the mechanofused powder after addition of PVP may be attributed to the more evenly distribution of PVP in the drug particle with improved flowability, which leads to improved binder bond formation.[50] In addition, the flowability of the blend consisting of the mechanofused ibuprofen and PVP plus cropovidone was substantially better than either raw or blended samples indicated by a CI value of 0.29.

All powders from this work (the raw, blended, mechanofused and their corresponding blends with PVP and crospovidone) formed tablets of suitable strength under conventional tableting conditions simulated by the Gamlen tablet press. These could be robustly handled and showed no signs of capping, lamination or other typical faults. Also the tablet tensile strength values of tablets with the mechanofused powder plus PVP were more than 1.7 MPa at the compaction pressure of around 180 MPa, which indicated such tablets were mechanically strong enough to withstand commercial manufacture and subsequent distribution.[52] This work therefore supported our aim to show that these small and well-coated particles with high surface area could be tableted under standard conditions.

The relationship between ejection stress and compaction pressure is illustrated in Figure 9. Both the blended and mechanofused ibuprofen sample, with or without PVP, gave significantly lower ejection forces than the raw powder with or without PVP under various applied compaction pressures ($p<0.05$), showing that the boundary lubricant particles (magnesium stearate) formed a resistant layer or film on the host particle or punch/die surfaces.[53] As surface heating and melting are believed to contribute to the stickiness of tableting process of ibuprofen, the reduced ejection stress during tableting of the mechanofused ibuprofen powder suggests that a further potential advantage of the lubricant coating, could be to reduce such surface heating [54] and melting problems of the APIs during high speed tableting. Hence, dry coating with magnesium stearate may provide both flow-aid and lubrication effects for the purpose of direct compaction and deserve further investigation.

In contrast to previous published studies describing direct compaction using drug powders coated with flow aids such as silica,[27] this work indicates dry coating with a lubricant such as magnesium stearate may avoid the use of an additional flow aid, allowing formation of higher drug dose loading, reduced excipient, less issues of API heating and fewer manufacturing process stages.

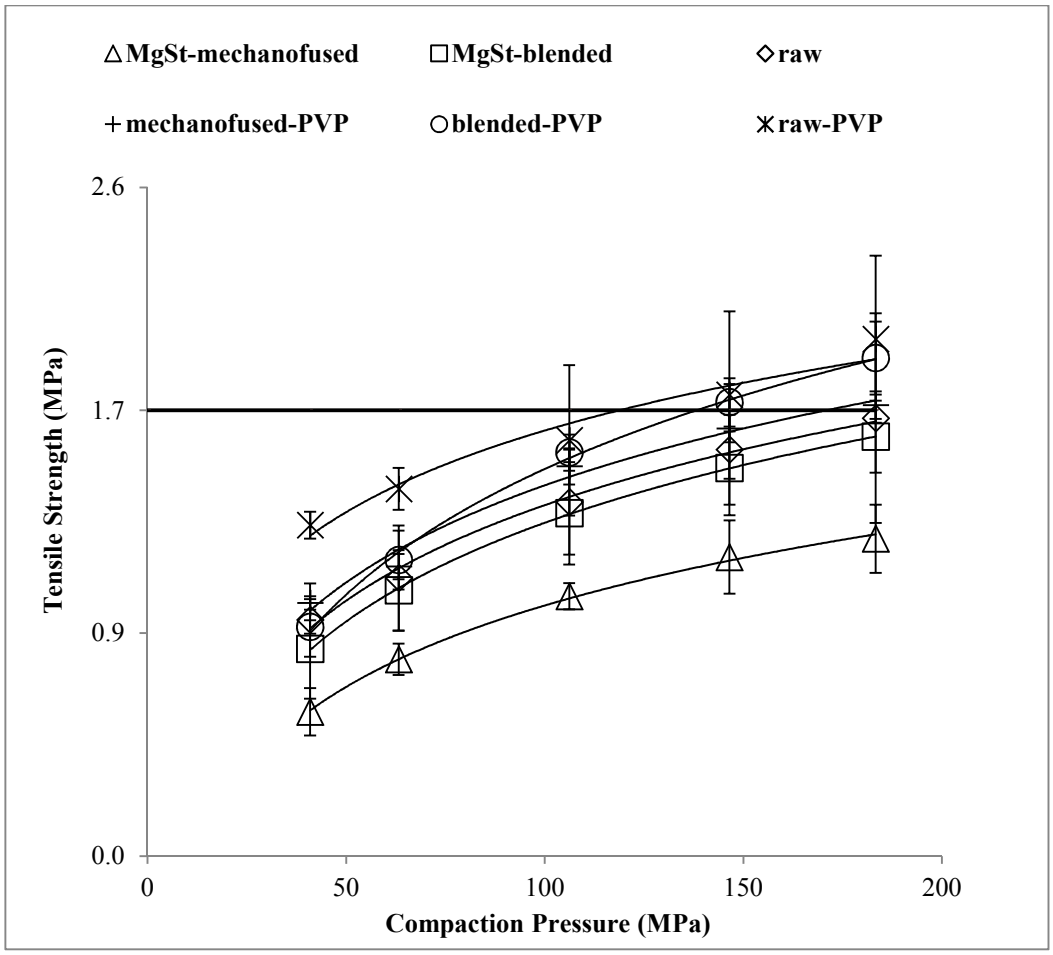


Figure 8. Tensile strength of prototype ibuprofen tablets (error bars represent standard deviations, n=5).

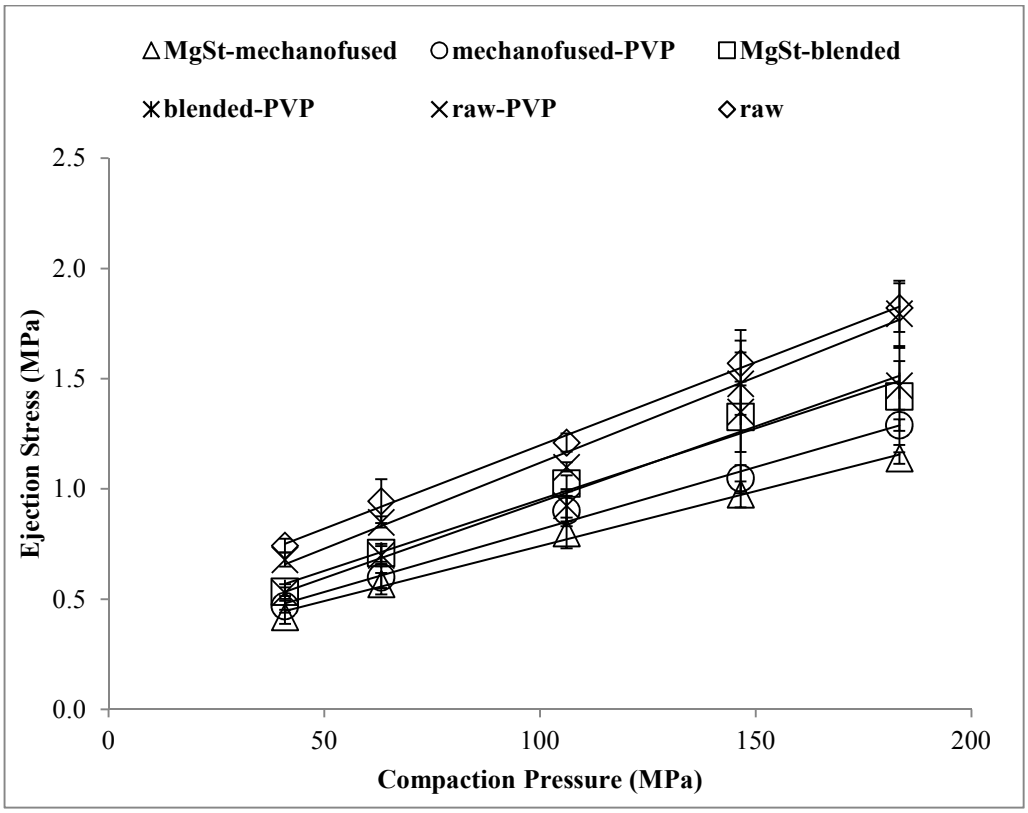


Figure 9. Ejection stress of prototype ibuprofen tablets (error bars represent standard deviations, n=5).

3.5.9 *In vitro* dissolution studies

Figure 10 showed that more than 90% of ibuprofen was dissolved in 5 min from all tested tablets formed under compaction pressure of 180 MPa. For the tablets with the mechanofused powders, the dissolved drug reached 90% within 2 minutes. This increased dissolution rate over the non-mechanofused powders was unexpected. Previous studies have reported traditional blending drug powders with MgSt would reduce the dissolution rate by applying a hydrophobic coating layer.[55] However, it has also previously been suggested that MgSt coating on the drug powder surface has the potential to reduce drug agglomeration in powders.[56] It is well known MgSt as a lubricant intends to decrease the bonding strength during tablet compaction,[53,57] and so it is proposed in this study to cause slightly weakened drug particles interfacial forces and therefore we observed enhanced deagglomeration and surface area exposed on contact with dissolution medium.

It is further proposed that the surface coating layer of MgSt by mechanofusion is much thinner than that previously produced under conventional blending technologies, and being here of the order of a few nanometers (as indicated by our surface analysis), such an unusually thin layer may not be sufficient to prevent water penetration and consequent dissolution.

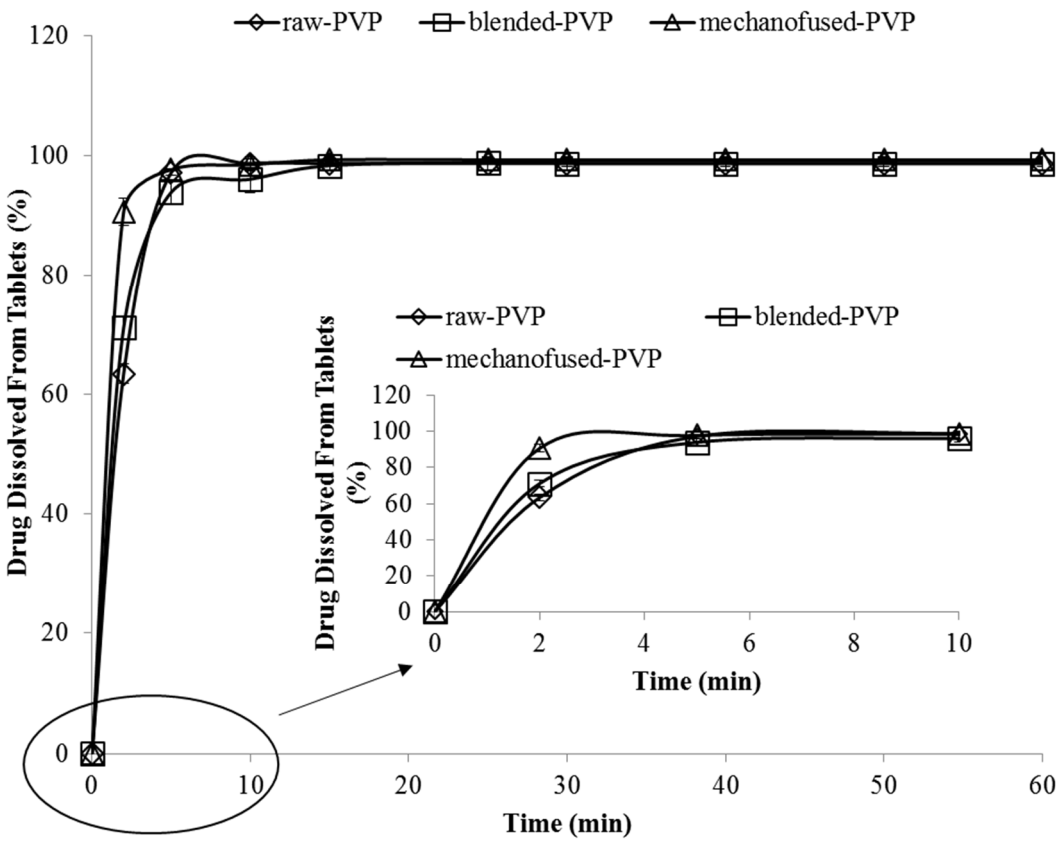


Figure 10. Dissolution profile of selected tablets (error bars represent standard deviations, n=6).

3.6 Conclusion

The aims of this work were:

1. to investigate if the low-melting point cohesive ibuprofen drug powder could be successfully mechanofusion coated with the traditional lubricant magnesium stearate.
2. this coating would give suitable powder flow improvement and tablet lubrication.
3. and tablets could be formed with satisfactory properties given historical literature suggesting otherwise.

We can report that optimal mechanofusion coating was successfully achieved under specific conditions of process head speed and duration. The effective modification of the interparticulate interactions was evidenced by substantial changes in bulk densities, Carr's Index and confirmed

with a suit of results from the range of more advanced shear and rheological powder flow testing. Advanced surface analysis of such powders demonstrated that a highly uniform coating was formed, and detailed particle characterisation proved the coating process did not affect particle shape or size, and the flow improvement resulted purely from surface coating effects. Robust tablets could be made with all powders, including the raw, mechanofused and its mixture with PVP and crospovidone powders. The addition of PVP alleviates the lower tensile strength for the tablets directly formed by the mechanofused powders, without significant increase in ejection force.

In addition, a surprising outcome was the finding is that such ultra-thin MgSt coating did not delay the drug dissolution rate.

These initial results from this innovative approach indicated this coating process may have the potential to develop novel alternative formulation strategies suitable for direct compaction of high dose drugs, including those presenting the additional challenge of a low melting point. Further work will be warranted to optimise tablet conditions further, consider other coatings or addition of further functional excipients.

3.7 Acknowledgement

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3.8 Declaration of interest

The authors report no declaration of interest.

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Chapter 4

Influence of coating material on the flowability and dissolution of dry-coated fine ibuprofen powders*

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Declaration for Thesis Chapter 4

Declaration by candidate

In the case of Chapter 4, the nature and extent of my contribution to the work was the following:

Nature of contribution	**Extent of contribution (%)**
Study design, formation of hypothesis, laboratory work, data collection, analysis and results interpretation and the manuscript writing.	75

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	**Nature of contribution**	**Extent of contribution (%) for student co-authors only**
Qi (Tony) Zhou	Manuscript revision	5
John A Denman	ToF-SIMS characterization and manuscript revision	5
Peter J Stewart	Supervision and manuscript revision	5
Karen P Hapgood	Supervision and manuscript revision	5
David A V Morton	Supervision and manuscript revision	5

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

Candidate's Signature	[redacted]	**Date08/03/2016**
Main Supervisor's Signature	[redacted]	**Date08/03/2016**

*Note: Where the responsible author is not the candidate's main supervisor, the main supervisor should consult with the responsible author to agree on the respective contributions of the authors.

4 Influence of coating material on the flowability and dissolution of dry-coated fine ibuprofen powders

4.1 Commentary

In Chapter 3, it was illustrated that the surface coating with 1% MgSt achieved the powder flow improvement. However, tablets directly formed by the mechanofused powders exhibited the lower tensile strength. Hence, various coating materials including magnesium stearate (MgSt), l-leucine, sodium stearyl fumarate (SSF) and silica-R972 was investigated.

In this chapter, the research aim 2 "To optimize the tablet compression conditions by investigating its tensile strength of such tablets formed by dry coated fine drug powders with varying coating materials as a function of compaction pressure." was addressed. Ibuprofen powder was dry coated with 1% (w/w) of magnesium stearate (MgSt), l-leucine, sodium stearyl fumarate (SSF) and silica-R972 via mechanofusion, respectively. The effect of such dry coated particles on the powder flow and tableting behaviour was examined.

4.2 Abstract

This study investigates the effects of a variety of coating materials on the flowability and dissolution of dry-coated cohesive ibuprofen powders, with the ultimate aim to use these in oral dosage forms. A mechanofusion approach was employed to apply a 1% (w/w) dry coating onto ibuprofen powder with coating materials including magnesium stearate (MgSt), l-leucine, sodium stearyl fumarate (SSF) and silica-R972. No significant difference in particle size or shape was measured following mechanofusion with any material. Powder flow behaviours characterised by the Freeman FT4 system indicated coatings of MgSt, l-leucine and silica-R972 produced a notable

surface modification and substantially improved flow compared to the unprocessed and SSF-mechanofused powders. ToF-SIMS provided a qualitative measure of coating extent, and indicated a near-complete layer on the drug particle surface after dry coating with MgSt or silica-R972. Of particular note, the dissolution rates of all mechanofused powders were enhanced even with a coating of a highly hydrophobic material such as magnesium stearate. This surprising increase in dissolution rate of the mechanofused powders was attributed to the lower cohesion and the reduced agglomeration after mechanical coating.

4.3 Introduction

Flow characteristic or "flowability" is an important factor for powder handling and processing in food and pharmaceutical industries. For example, powder free-flowing from a hopper under gravity is generally required to facilitate uniform and efficient die-filling during high-speed tablet manufacturing [1]. The dispersibility of a powder in a liquid is related to its cohesiveness [2]. A decrease in cohesive forces between particles facilitates de-agglomeration [1] and has been reported to enhance drug dissolution [3,4]. For poorly water-soluble drugs, attempts have been made to enhance their rate of dissolution by increasing the surface area of the drug through micronization [5]. However, in practice the micronized drug particles typically exhibit greater intrinsic cohesion due to the stronger van der Waals force of the attraction between particles [6] and a reduced gravitational detachment force due to the small mass of the particle. As a consequence, such powders become increasing agglomerated and enhanced dissolution is not achieved, as well as the powder having poor flow [2,7].

Conventionally, flow problems of fine pharmaceutical powders are solved by the formation of ordered mixtures [8,9], or by addition of flow aids [10]. However, the ordered mixing leads to significant dilution of the powder with a large 'carrier' excipient; flow aids can be challenging in the case of highly-cohesive powders due to difficulties in blending, for example discrete and non-uniform distribution of flow additives on the surface of particles or formation of unwanted

granulation [11-13]. In addition, segregation could occur between particles with varying sizes or densities during powder handling [14,15].

In order to obtain efficient improvement of the flowability, dispersion and fluidisation of cohesive powders, very high shear dry coating with flow additives (glidants or lubricants) has been proposed as an attractive approach to produce more uniform and more robust coating layers on the surface of host particles [13,16,17]. For example, Chattoraj *et al.* showed that enhanced flowability of microcrystalline cellulose has been achieved by surface coating with silica using a Comil® [17]. Other researchers [13,18-20] also demonstrated the flowability of cohesive powder could be improved substantially using the dry coating approaches such as fluid energy mill, magnetically assisted impaction coater or hybridizer. Our earlier work also elucidated the enhancement of flowability of fine cohesive powder by surface coating with magnesium stearate via a mechanofusion process. Mechanofusion is a form of very high shear, highly efficient mechanical dry coating approach, from which substantial improvements in powder flowability and dispersibility can be obtained [16,21,22]. Unlike milling, the mechanism of mechanofusion can fuse and/or coat guest particles onto the surface of host particles through intensive mechanical forces but with minimised host particle attrition [23].

The key criteria to select a coating (guest) material is small size powder or softness so that very small amounts can cover the surface of host particles and provide effective improvement in flowability [11]. For example, either magnesium stearate or fumed silica has been shown to substantially improve powder flowability using such dry coating approaches [23-25].

However, there is an extensive historical concern that the hydrophobic properties of some dry coating agents such as magnesium stearate will retard drug dissolution in the powder mixture when over-blended or co-ground [26,27]. Over blending of magnesium stearate is also known to have a negative effect on tableting behaviour [28-30].

We recently demonstrated that despite coating of ibuprofen powders with MgSt via mechanofusion, it was possible to generate tablets, albeit with decreased tensile strength [3]. We hypothesised from this study that alternative lubricants or glidants, which are less hydrophobic in nature, such as sodium stearate fumarate or l-leucine, facilitate the de-agglomeration of cohesive particles [31] with reduced negative effect on tabletability [32] compared to magnesium stearate. Alternatively, improved flow or dissolution may be attractive for powder used in capsules or granules as oral delivery systems. Therefore, the primary purpose of this study was to investigate the outcomes of different flow-aid additives on the coating efficiency, flow properties and dissolution rate of ibuprofen, a model high-dose drug with a low melting point. Magnesium stearate, sodium stearate fumarate and l-leucine were selected as they are commonly used lubricants in pharmaceutical manufacturing. Fumed silica was also selected because it is a typical pharmaceutical glidant.

4.4 Materials and methods

4.4.1 Materials

Ibuprofen 25 was kindly donated by BASF (Ludwigshafen, Germany). Magnesium stearate NF (MgSt) was supplied by Mallinckrodt Chemicals, Phillipsburg, USA. Hydrophobic fumed silica Aerosil® R972 (silica-R972) was provided by Evonik (Evonik Industries AG, Germany). Sodium stearate fumarate (SSF) was kindly donated by JRS Pharma (Rosenberg, Germany). L-leucine, potassium phosphate monobasic, sodium dodecyl sulphate and sodium hydroxide was all purchased from Sigma-Aldrich (Castle Hill, Australia). Sizes of MgSt, SSF, l-leucine and silica-R972 are provided in table 1-a.

Table 1-a. Median particle size of coating materials.

Name of coating materials	MgSt	SSF	l-leucine	silica
Median particle size	~ 8 μm	~ 9 μm	~ 10 μm	~ 16 nm

4.4.2 Methods

4.4.2.1 Preparation of dry coated powders

Ibuprofen powder was dry coated with selected coating materials using an AMS-Mini mechanofusion system (Hosokawa Micron Corporation, Osaka, Japan). Powder (approximately 20 g) was manually pre-blended with 1% (w/w) magnesium stearate, silica-R972, sodium stearate fumarate or l-leucine, respectively, using a spatula in a 125 ml glass vessel and then transferred to the mechanofusion processing chamber. Mechanofusion process was conducted by gradually turning the paddle speed up to 900 rpm over 1 min and keeping this speed for a further 5 min [3]. In the meantime, tap water (22 ± 2°C) was circulated through an incorporated jacket in order to cool the processing chamber. These samples were denoted as MgSt-mechanofused, l-leucine-mechanofused, SSF-mechanofused and silica-R972-mechanofused. As a comparison, untreated ibuprofen drug was denoted as "raw" in the following text.

4.4.2.2 Particle sizing

Particle size was measured by laser diffraction (Mastersizer® 2000, Malvern Instruments, Worcestershire, UK) using a wet cell module. Dispersion medium was a saturated aqueous solution of ibuprofen (temperature: 25±0.5°C). A small amount of ibuprofen powder (~50 mg) was distributed in 20 ml of dispersion medium prior to size measurement. Particle size distribution was analysed by averaging three replicates of each sample and was shown as D_{10} (diameter at 10% undersize), D_{50} (diameter at 50% undersize) and D_{90} (diameter at 90% undersize).

4.4.2.3 Powder flow properties

Investigation of flow properties was performed using a Freeman FT4 powder tester in the compressibility, aeration and shear modes (Freeman Technology, Worcestershire, UK). A detailed introduction of this instrument has been described previously [33,34].

In the compressibility mode, a vented piston consisting of a stainless steel mesh of 23.5 mm in diameter compressed powders under given normal stresses of 1, 2, 4, 6, 8, 10, 12 and 15 kPa. Compressibility is represented as percentage change of volume as a function of applied normal stress. Usually, a higher compressibility value and change in plot against normal stress demonstrated more cohesive properties [16,35].

In the aeration mode, air was introduced into the base of powder column to fluidize the powder. Flow energy was measured at various air velocities [34]. The outcome provides an assessment of powder fluidization.

In the shear testing, a pre-shear normal stress of 9 kPa was applied for consolidation of the powder prior to each test. Shear measurements were then conducted at normal stress of 3, 4, 5, 6 and 7 kPa. Inter-particle cohesion of each sample was calculated by extrapolating the yield loci using the equation as below (1):

$$\tau = C + \sigma \tan \eta \quad (1)$$

where τ is the shear stress (kPa), σ is the normal stress (kPa), η is the angle of friction (degrees), and C is the cohesion (kPa). A lower cohesion value demonstrates a lower interparticle force.

4.4.2.4 Scanning electron microscopy (SEM)

Morphology of the ibuprofen sample powders was observed using a scanning electron microscope (Phenom^{TM}, FEI Company, Hillsboro, OR, USA). A small amount of each sample was slowly poured onto a double–sided sticky tape with one side mounted on a sample holder. Loose and excess powders were removed by gently shaking of the holder. The prepared samples were sputter coated with gold using an electrical potential of 2.0 kV at 25 mA (SCD005, BAL-TECAG, Blazers, Germany).

4.4.2.5 Particle shape

Particle shape was examined using a Morphologi G3 (Malvern Instruments, Worcestershire, UK). Morphologi G3 is an automated image assessment system which uses a computer to analyze the morphological characteristics (such as shape) of statistically-valid numbers of particles through particle recognition software. This provides number and volume based statistics for a large number of particles that provides a far superior assessment and resolution compared to traditional manual image analysis. Each sample was dry dispersed onto a glass plate at a standardised injection pressure of 1 bar using an integral Sample Dispersion Unit (SDU). The measurement for each sample was performed with three replicates and results were averaged.

In this study, particle shape was assessed by investigating the circularity and convexity of the particle, respectively. Circularity is used to measure how close the shape is to a perfect circle [36]. It is calculated based on the below equation (2):

$$\textbf{Circularity} = 4\pi A/P^2 \qquad (2)$$

where A is the particle actual area and P is its actual perimeter. The values of circularity are between 0 and 1. Therefore, a perfect circle has a circularity of 1, whilst a needle-like object gives a lower circularity value.

Roughness of a particle was evaluated by convexity which was calculated by dividing the convex hull perimeter by the actual particle perimeter [37,38]. Convexity values were also in the range from 0 to 1, where a smoother surface has a higher convexity value while a rougher surface has a lower convexity value [39].

4.4.2.6 ToF-SIMS

ToF-SIMS experiments were performed using a PHI TRIFT V nano-TOF instrument (Physical Electronics Inc., Chanhassen, MN, USA) equipped with a pulsed liquid metal 79+Au primary ion gun (LMIG), operating at 30 keV energy. Dual charge neutralization was provided by an electron

flood gun and 10 eV Ar+ ions. Surface analyses were performed using "unbunched" Au1 instrument settings to optimize spatial resolution. Raw data was collected in positive SIMS mode at a number of locations typically using a 200×200 micron raster area, with 4 min acquisitions. Five areas per sample were analysed, which encompassed >50 particles, to ensure representative results were collected.

Chemical maps were produced using WincadenceN software (Physical Electronics Inc., Chanhassen, MN, USA), based on the following unique and characteristic responses: m/z = ~161 ($[M\text{-}COOH]^+$ fragment) for ibuprofen; m/z ~24 (Mg^+) for MgSt; m/z = ~132 ($[C_6H_{14}NO_2]^+$ fragment) for l-leucine; m/z = ~23 (Na^+) for SSF and m/z = ~28 (Si^+) for Silica-R972.

4.4.2.7 In vitro dissolution studies

The dissolution tests were performed according to USP34 where the detailed procedures can be found. Briefly, USP II paddle method with paddle speed of 50 rpm [40] (Erweka DT6; Erweka, Heusenstamm, Germany) was used . Dissolution medium (900 ml) was a pH 7.2 phosphate buffer solution with 0.05 g/L sodium dodecyl sulphate (SDS) [41]. Prior to use, all dissolution media were filtered through 0.45 μm Millipore membrane for degassing and equilibrated to 37.0 ± 5°C in the dissolution bath. Each sample powder (100 mg) was transferred to the dissolution vessels. 5 mL aliquots of the dissolution media were collected at 0, 2, 5, 10, 15, 25, 30, 40, 50 and 60 min and then refilled the dissolution vessels with equivalent volume of fresh medium. The aliquots of collection were filtered through a 0.45 μm filter immediately and the amount of dissolved ibuprofen (%) was measured using a validated UV assay. The solubility of ibuprofen in the dissolution medium is > 5 mg/ml [42,43]. Hence, the solubility of drug in the dissolution medium is more than 45-fold higher than the maximum drug concentration in the test, therefore sink conditions are present.

4.4.2.8 UV analysis of ibuprofen

Ibuprofen content from the dissolution study [44] was analysed using a validated UV spectrophotometer method at a wavelength of 221 nm (CECIL 3021, Lab instrumentation Pty. Ltd., Australia). Beer's calibration of plot for ibuprofen in the dissolution medium exhibited a linear relationship between absorption and ibuprofen concentrations over the range of 2 to 20 µg/ml (R^2>0.999) with accuracy and precision values ranging from 97.3-101.4% and 1.0-3.3%, respectively.

4.4.2.9 Dissolution modelling

Dissolution data were modelled using a non-linear least squares regression analysis based on the Levenberg-Marquardt algorithm [45] to identify the coefficients or parameters of the independent variables that provide the best fit between the equation and the data (SigmaPlot® 12.3; Systat Software Inc., San Jose, CA, USA).

Average of the undissolved concentrations (%) collected from all the vessels was tested against time using multi-exponential equations which include mono-exponential (two parameters), bi-exponential (four parameters) and tri-exponential (six parameters) decay equations shown as below (1-3):

$$C = C_d * \exp(-k_d * x) \quad (1)$$

$$C = C_d * \exp(-k_d * x) + C_a * \exp(-k_a * x) \quad (2)$$

$$C = C_d * \exp(-k_d * x) + C_{a1} * \exp(-k_{a1} * x) + C_{a2} * \exp(-k_{a2} * x) \quad (3)$$

where C is the concentration of undissolved drug (%) at time t; C_d and C_a are the initial concentrations (%) of dispersed particles and agglomerates, respectively; k_d and k_a (min^{-1}) represent the dissolution rate constants for dispersed and agglomerated particles, respectively. These exponential terms express dissolution performance from combinations of ''dispersed'' and ''agglomerated'' particles where dispersed particles has a greater influence on dissolution because of surface area effects [4].

Discrimination between these models was conducted mainly using several statistical parameters. For example, Akaike Information Criterion (AIC) provides a measure of goodness of fit based on maximum likelihood by relating the weighted residual sum of squares to the number of parameters that were required to obtain the fit and the model yielding the smallest value is the most suitable one; the norm value is square root of the sums of squares where a smaller value provides a superior fit of the data; F value contributes to assessing the improved fit with the use of additional parameters in which a bigger value demonstrates a better fit; correlation coefficient (R^2) is a value close to 1 indicating a greater degree of correlation and hence more favourable and dependency values (D) representing an indication of model complexity in which a value approaching to 1 implies over-parameterization.

4.4.2.10 Statistical analysis

The statistical analysis of data derived from all ibuprofen samples was performed using analysis of variance (ANOVA) with Turkey's post hoc analysis at a *p*-value of 0.05 (SPSS, Version 19, IBM Inc., USA).

4.5 Results and discussion

4.5.1 Particle size analysis

Table 1-b shows that only marginal differences in the D_{50} values were seen between the raw, blended and mechanofused samples. The slight reductions in particle sizes after mechanofusion processing are believed to be attributed to either slight attrition during high shear impaction or reduction in hard-agglomerates existing in the particles [46]. In addition, there was a significant decrease in D_{90} after mechanofusion processing possibly due to this proposed reduction in agglomerates existing in the powders. This size analysis data also demonstrated that any enhancement in bulk flowing performance was not attributed to particle size enlargement.

Table 1-b. Particle size distribution of the ibuprofen samples (mean±SD, n=3).

Sample powders	D_{10} (μm)	D_{50} (μm)	D_{90} (μm)
Raw	17.13±0.23	43.55±0.72	89.78±1.13
MgSt-mechanofused	14.36±0.46	35.74±0.47	70.75±2.21
L-leucine-mechanofused	14.39±0.68	36.29±1.4	72.21±3.6
SSF-mechanofused	14.43±0.51	36.81±1.05	75.21±2.45
Silica-R972-mechanofused	14.94±0.15	35.42±0.1	66.86±0.27

4.5.2 Powder flow properties

Figure 1 shows that the raw ibuprofen powder exhibited the highest FT4 compressibility values at all applied stresses in comparison to other powders, indicating the raw powder was the most cohesive [34]. In contrast, the compressibility values of all mechanofused powders were significantly decreased (p<0.05). Among the mechanofused powders, the SSF-mechanofused powder demonstrated the greatest compressibility. SSF is reported having a weaker lubrication effect in tablet formulation compared to MgSt [47].

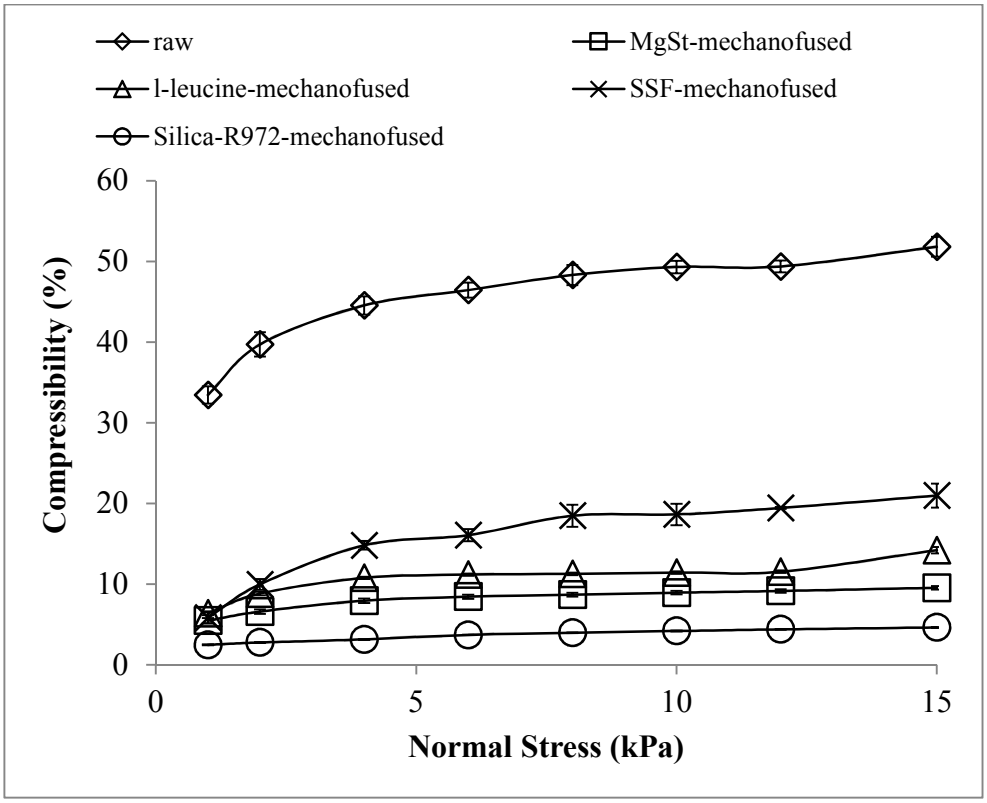

Figure 1. Compressibility values for raw and processed ibuprofen samples at different normal stresses (error bars represent standard deviations, n=3).

In Figure 2, powder aeration behaviour was assessed by the FT4. The raw ibuprofen powder exhibited higher flow energy at each given air velocity compared to all the mechanofused samples. When the air velocity was increased to 20 mm/s, the raw powder reached a fluidized state with flow energy of around 15 mJ. In contrast, the flow energy was reduced for mechanofused samples to lower values even at the minimum air velocity of 2 mm/s. The mechanofused powders with MgSt and Silica achieved the lowest flow energy values at each air velocity. This measurement indicates that the MgSt- and Silica-mechanofused powders were more easily fluidised, and the fluidisation status was maintained with a minimal air flow.

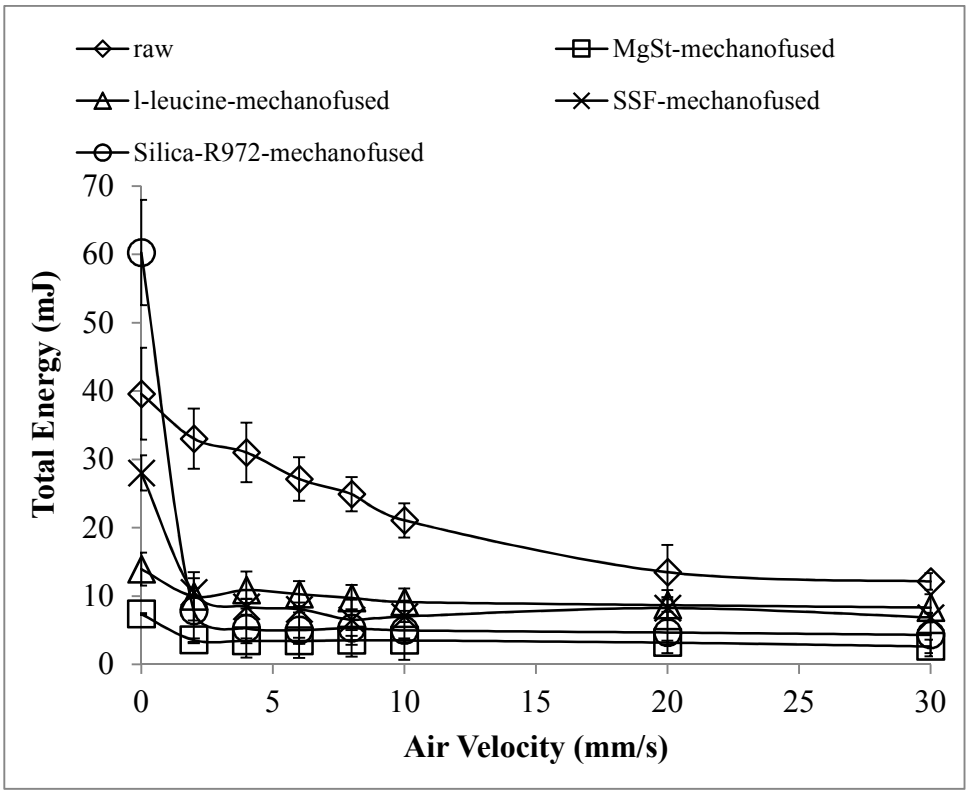

Figure 2. Flow energy at different air velocity for raw and processed ibuprofen samples (error bars represent standard deviations, n=3).

Table 2 presents cohesion and flow function (ffc) values achieved from the shear tests using the FT4. These parameters indicate the ease of powder flow in a consolidated state, such as from a hopper [48]. The ffc is defined as the ratio of major principle stress to the unconfined yield stress and

used to discriminate the powder flow behaviour: ffc < 1, not flowing; 1 < ffc < 2, very cohesive; 2 < ffc < 4, cohesive; 4 < ffc < 10, easy flowing and ffc > 10, free-flowing [48].

Table 2. Cohesion and ffc values of ibuprofen samples (mean ± SD, n=3).

	Raw	MgSt-mechanofused	L-leucine-mechanofused	SSF-mechanofused	Silica-R972-mechanofused
Cohesion (kPa)	1.24±0.04	0.40±0.05	0.41±0.06	0.88±0.05	0.41±0.08
ffc	4.02±0.19	8.78±1.03	8.34±1.60	4.47±0.20	8.61±1.60

The raw ibuprofen powder exhibited significantly the highest cohesion (1.24 kPa) and lowest ffc values (4.02) in comparison to others (p<0.05), followed by the mechanofused powders with SSF. However, the mechanofused powders with MgSt, l-leucine or silica-R972 showed significantly lower cohesion values (0.43 kPa, 0.38 kPa and 0.41 kPa, respectively) and higher ffc (8.78, 8.34 and 8.68, respectively) than all other powders (p<0.05). This implies that the three mechanofused powders will flow more easily and consistently from a hopper to the tablet die.

4.5.3 SEM

From the images of SEM presented in Figure 3, the raw ibuprofen particles (Figure 3A) possess a rod-like shape with a smooth surface. After processing with the different coating materials via mechanofusion, there is no observed change in surface texture between the MgSt-mechanofused and raw ibuprofen powders (Figure 3B). In contrast, Figure 3C, 3D and 3E all appear to show increased roughness and raised protrusions. In Figure 3E, the coating with silica created wave-like features on the drug particle surface. It is proposed that nano-sized ultra-fine silica particles form agglomerate features on the host surface due to the strong inter-particulate forces. Such silica agglomerates have been reported to have a ball-bearing effect in improving the flowability of ibuprofen particles [49]. In contrast, both l-leucine and SSF provided non-uniform flake-like (Figure 3C) or needle like (Figure 3D) coatings, respectively. These observed differences in surface textures are believed due to the varying coating behaviour of the different coating materials controlled by their physico-chemical natures such as hardness and particle size [13] .

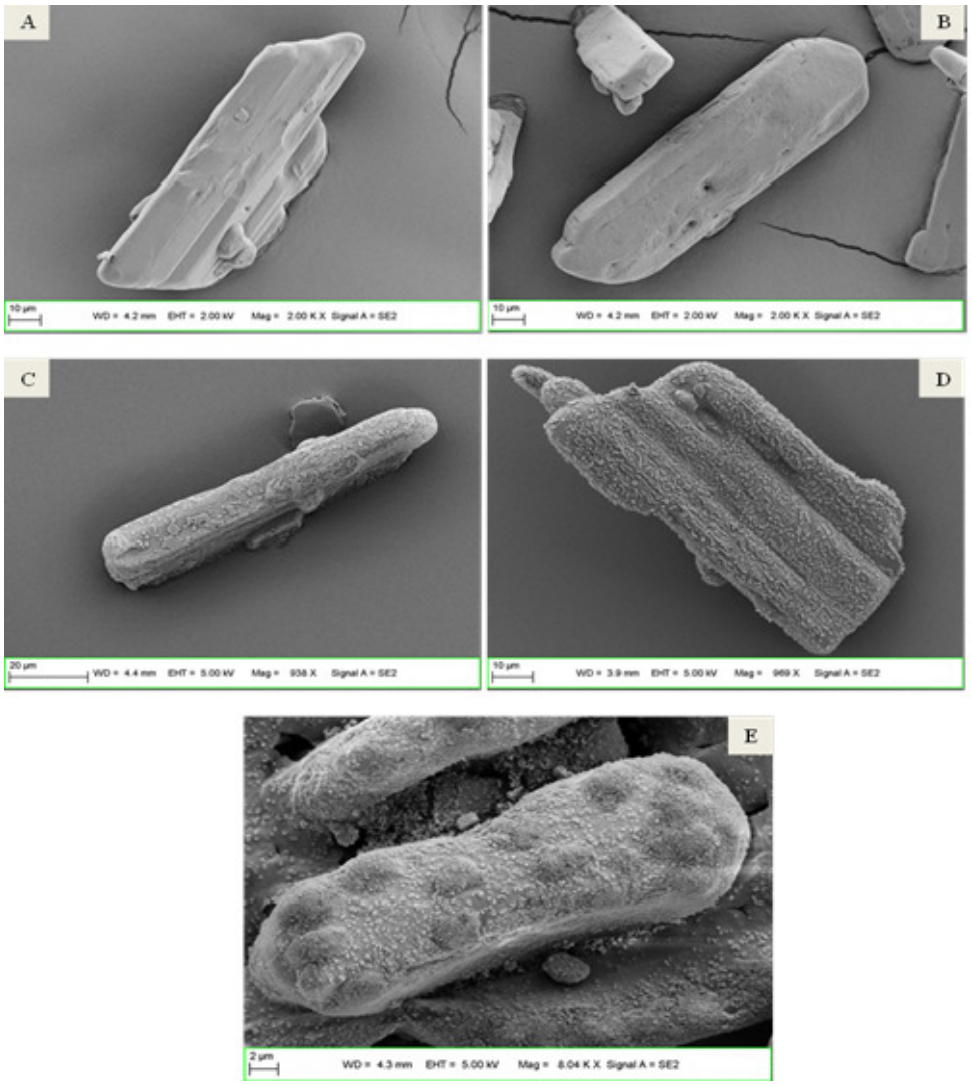

Figure 3. SEM micrographs of ibuprofen samples (A: raw ibuprofen; B: MgSt-mechanofused; C: L-leucine-mechanofused; D: Sodium stearyl fumarate (SSF)-mechanofused; Fumed silica (R972)-mechanofused), scale bar represents 10 µm in micrograph of A, B, D; 20 µm in C and 2 µm in E.

4.5.4 Particle shape

Table 3 shows the values of particle shape factors obtained using Morphologi G3 automated analysis system. No significant difference was found in circularity or convexity (p>0.05). These results were in agreement with the observation from SEM, indicating the mechanofused ibuprofen particles manufactured a similar shape to the raw particles. Therefore, any changes in flow bulk behaviour are not attributed to the substantial modification of ibuprofen particle shape.

Table 3. Values of circularity, elongation and convexity for raw and processed ibuprofen samples (mean ± SD, n=3).

Sample powders	Circularity	Elongation	Convexity
Raw	0.69±0.03	0.43±0.01	0.95±0.00
MgSt-mechanofused	0.70±0.02	0.43±0.01	0.95±0.01
L-leucine-mechanofused	0.67±0.05	0.46±0.04	0.93±0.00
SSF-mechanofused	0.66±0.02	0.43±0.02	0.94±0.00
Silica-R972-mechanofused	0.68±0.03	0.40±0.03	0.92±0.01

4.5.5 ToF-SIMS

Figure 4 presents chemical maps showing the spatial distribution of the various mechanofused surface coating species on the surface of the ibuprofen particles. The results show that both MgSt and Silica coatings provided a more complete coverage on the surface of ibuprofen powders, suggesting the superior coating performance of MgSt and colloidal silica.

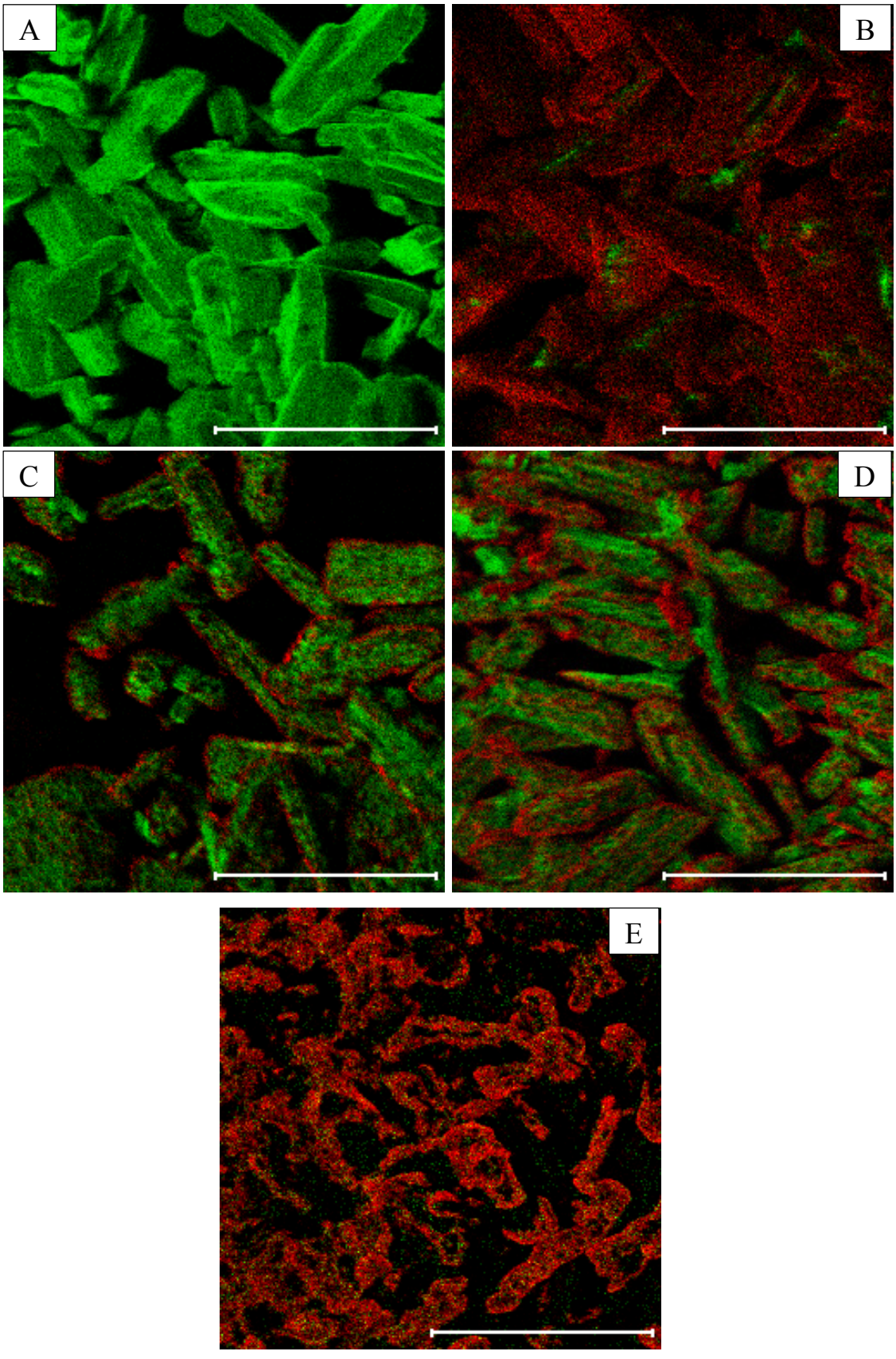

Figure 4. ToF-SIMS overlay images at scanning area of 200 × 200 µm^2 for ibuprofen samples as indicated as red signal (•) for Mg (m/z ~24amu), L-leucine (m/z ~132amu), SSF (m/z ~23amu) and silica-R972 (m/z ~28amu), respectively, and green (•) for ibuprofen (m/z

~161amu). A: raw ibuprofen; B: MgSt-mechanofused; C: l-leucine-mechanofused; D: SSF-mechanofused; E: silica-R972-mechanofused (scale = 100µm).

4.5.6 In vitro dissolution studies

Figure 5 shows the dissolution profiles of all powders. The SSF-coating did not generate a significant improvement in ibuprofen dissolution compared to the uncoated sample ($p > 0.05$). However, the dissolution rate of ibuprofen increased substantially when dry coated with MgSt, l-leucine or silica-R972. For example, the amount of dissolved drug at 2 min significantly increased from 25.4 ± 7.8% for the raw ibuprofen to 85.1 ± 1.2% after mechanofusion with MgSt ($p < 0.001$).

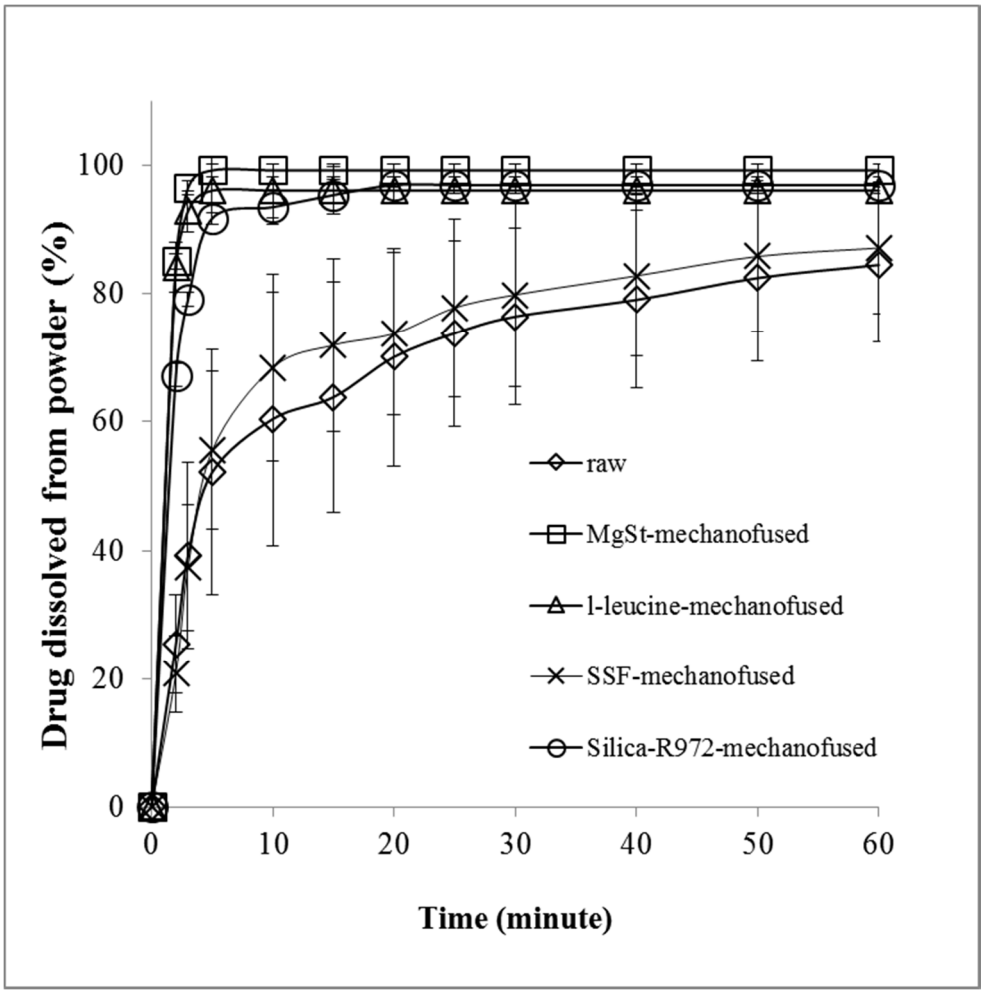

Figure 5. Dissolution profile of sample powders (error bars represent standard deviations, n=3).

Surprisingly, the powders coated with MgSt achieved the fastest dissolution. This contradicts previous reports, that co-grinding drug powders with the hydrophobic MgSt retards the dissolution of the drug in powder mixtures by preventing wetting and water penetration[26,27]. In this study, we believe the increased dissolution rate from the MgSt-mechanofused powder is due to the enhanced powder de-agglomeration. FT4 results have shown the mechanofused powder with MgSt has the lowest cohesion. Hence, agglomerates are weaker, and the increased contact surface area between the particle and dissolution medium is proposed to result in faster water wetting and penetration. Furthermore, as reported in our previous study [3], the surface coating layer of MgSt by mechanofusion is estimated to be as thin as a few nanometers. Such ultra-thin coating layers may not be able to prevent water penetration and retard dissolution.

The l-leucine-mechanofused powder also obtained increased dissolution profile although not as good as that with MgSt-coating. Surface coating with silica-R972 led to a slightly reduced increase in the dissolution rate compared to those with either MgSt or l-leucine, with 67.3 ± 1.8% of ibuprofen dissolved after 2 minutes ($p< 0.001$).

At 10 mins, the amounts of ibuprofen dissolved from all mechanofused powders, except for the SSF-mechanofused powder, was close to 100%. However, only 60.4 ± 19.7% and 68.5 ± 14.6% of ibuprofen were dissolved from the raw ibuprofen and SSF-mechanofused powders, respectively.

4.5.7 Modelling of dissolution data

To further understand the underlying relationship between the dissolution rate and coating, the dissolution data were modelled using a non-linear least squares regression analysis with multi-exponential equations as described in the Section 2.2.10 [50,51]. Fitting the dissolution data to multi-exponential equations by this approach, the dissolution parameters of initial concentration for the dispersed particles and undispersed agglomerates, and the corresponding dissolution constants were estimated. The modelling of dissolution data using this approach has been described

previously [52,53] and the details of fitting process are not described in this manuscript. The outcome of the dissolution modelling was as follows:

For the raw and SSF-mechanofused samples of ibuprofen, the dissolution data were best described by a bi-exponential model indicating that the drug was dissolved from two distributions of particles. These distributions were designated as "dispersed" particles and "agglomerated" particles. It is likely that the "dispersed' particle distribution contained not only individual particles but also some small agglomerates. The dissolution profile shown in Figure 5 can be described by two concentration terms (e.g. C_d: the initial concentration of dispersed particles and C_a: the initial concentration of agglomerated particles) in Table 4 and two dissolution rate constants (e.g. k_d: the dissolution rate constant for dissolution from dispersed particles and k_a: the dissolution rate constant for dissolution from agglomerated particles) in Table 4. The biphasic shapes of the dissolution profiles in Figure 5 are consistent with bi-exponential dissolution behaviour.

Table 4. Influence of coating materials on the estimated initial concentration of dispersed particles (C_d) and of agglomerated particles (C_a), as well as on the estimated dissolution rate constants from dispersed particles (k_d) and from agglomerated particles (k_a) for all sample powders (mean ± SD, n=3).

	Raw	MgSt-mechanofused	L-leucine-mechanofused	SSF-mechanofused	Silica-R972-mechanofused
C_d (%)	60.0±25.8	107.3±0.3	106.8±0.5	72.5±16.5	95.7±0.5
C_a (%)	43.0±23.1	-	-	32.0±16.1	-
k_d (min^{-1})	0.34±0.06	0.66±0.01	0.61±0.03	0.26±0.02	0.64±0.04
k_a (min^{-1})	0.02±0.01	-	-	0.02±0.01	-

The dissolution data for the MgSt-mechanofused, silica-R972-mechanofused and l-leucine-mechanofused samples of ibuprofen were best fitted by the mono-exponential equations. Higher order fits did not improve the fit. This indicates that the dissolution occurred from a single distribution of mechanofused particles with the estimated parameters of initial concentration of ibuprofen and the dissolution rate constant for dissolution from the particular distribution of particles.

The estimated parameters for the initial concentration of particles and the dissolution rate constants are shown in Table 4. For the powder samples where the dissolution data is fitted by a mono-exponential model, the estimated initial concentration of particles is around 100%. In some cases, the initial concentration is slightly greater than 100% and this may have resulted from fitting the data to a model which assumes that the particle distribution does not change. There may have been changes to the distribution during the dissolution process, e.g. the "dispersed" particle distribution may have become more dispersed. The dissolution rate constants for the dissolution of magnesium stearate, silica and l-leucine-mechanofused samples are not significantly different and are between 0.6 to 0.7 min^{-1}. The outcome from this modelling suggests the mechanofused powders with MgSt, l-leucine, and silica were better dispersed during the dissolution, attributable to the effect of efficient surface coating [4]. These results were in agreement with the fact that the cohesion was reduced and flow properties were significantly improved by mechanofusion with MgSt, l-leucine or silica, with resulting lower degree of agglomeration.

The estimated parameters for the dissolution of raw ibuprofen and SSF mechanofused ibuprofen are shown in Table 4. Both powders model in a similar manner with there being no significant difference between the concentration parameters and the rate constant parameters.

For all samples, the estimated parameters of concentration of dispersed particles (C_d) and dissolution rate constants (k_d) were shown in Table 4. In terms of the dispersed particle concentration, both the estimated concentrations and dissolution rate constants for magnesium stearate, l-leucine, and silica-mechanofused samples were significantly higher than those of the raw and SSF-mechanofused samples ($p<0.05$).

4.6 Conclusions

This study investigated the effect of coating material on the flowability and dissolution of dry-coated fine ibuprofen powders. Effective modification of the inter-particulate interactions with MgSt, l-leucine and silica was evidenced by substantial changes in flow behaviour measured by

the advanced shear and rheological powder flow testing approaches. Advanced image analysis of such powders demonstrated that the coating process did not affect particle shape or size, and the flow improvement resulted purely from surface coating effects. ToF-SIMS gave an indication of the coating quality achieved with each material by interrogation of its spatial distribution on the ibuprofen particle surfaces. Surprisingly, it was found that despite the notorious hydrophobic nature of MgSt and past reported behaviour of co-ground MgSt-drug powders, with the controlled ultra-high shear provided by mechanofusion, coating of hydrophobic magnesium stearate and colloidal silica enhanced the dissolution rate of ibuprofen compared to the raw powder. The dissolution modelling approach used here indicated that the underlying mechanism for this novel dissolution behaviour is that the drug powder dissolution rate depends more on the powder dispersibility rather than its surface coating hydrophobicity. It is also proposed that the mechanofusion provides a coating quality that is much better dispersed, and hence thinner than traditional blending methods reported for oral delivery.

Results from this work indicate surface engineering of cohesive powders not only improve the bulk flow but also enhance the drug dissolution. This shows promise in leading to the development of novel formulations suitable for oral delivery of high-dose drugs. Further work will be warranted to evaluate if such modified powders are suitable to be produced into tablets by direct compaction, filled directly into capsules or formed into granules for either tablets or capsules.

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4.8 Declaration of interest

The authors report no declaration of interest.

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Chapter 5

Single-step co-processing of cohesive powder via mechanofusion for direct compression*

*Submitted as **Qu, L.,** Qi (Tony) Zhou, Peter J Stewart, Karen P Hapgood, Satu Lakio David A V Morton. Single-step co-processing of cohesive ibuprofen powder with excipients via mechanofusion for direct-tableting.

Declaration for Thesis Chapter 5

Declaration by candidate

In the case of Chapter 5, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Study design, formation of hypothesis, laboratory work, data collection, analysis and results interpretation and the manuscript writing.	70

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Qi (Tony) Zhou	Manuscript revision	5
Peter J Stewart	Supervision and manuscript revision	5
Karen P Hapgood	Supervision and manuscript revision	5
Satu Lakio	Manuscript revision	5
David A V Morton	Supervision and manuscript revision	10

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

Candidate's Signature	[redacted]	**Date08/03/2016**
Main Supervisor's Signature	[redacted]	**Date08/03/2016**

*Note: Where the responsible author is not the candidate's main supervisor, the main supervisor should consult with the responsible author to agree on the respective contributions of the authors.

5 Single-step co-processing of cohesive powder via mechanofusion for direct compression

5.1 Commentary

In this chapter, the research aim "To optimize the tablet compression conditions by investigating its tensile strength of such tablets formed by dry coated fine drug powders with varying coating materials as a function of compaction pressure" was addressed. The effect of varying coating materials on the flowability and tabletability of processed powder mixtures was investigated. Mechanofusion was applied to coat the ibuprofen, dry binder (PVP 25) and superdisintegrant (crospovidone) with various coating materials including magnesium stearate (MgSt), l-leucine and silica-R972. The tablets were made directly with the co-mechanofused powder to achieve a single-step direct tablet production. Both disintegration and dissolution behaviours of these tablets were also examined.

5.2 Abstract

This study aims to test the feasibility of developing a single-step platform via a mechanofusion process to produce a powder mixture of active and inactive excipients for direct compression. A Hosokawa Micron AMS Mini (Nobilta) unit was used to dry process ibuprofen powder with various coating materials in the presence of a binder (PVP 25) and a superdisintegrant (crospovidone). Magnesium stearate (MgSt), l-leucine, and silica were selected as coating materials (1% w/w) in this process. A benchmark control blend, without any coating material was also produced. The resulting particle size distribution measured following mechanofusion was significantly smaller than the control batch. Coating with MgSt, l-leucine, or silica produced significantly improved powder flow in comparison to the control batch. Robust tablets were produced from the mechanofused powders in the presence of each of the coating materials. The tablets compacted using the mechanofused powder with MgSt and l-leucine also exhibited

significantly lower tablet ejection forces than the control batch, demonstrating their lubrication effect. Furthermore, the disintegration time and dissolution rates of these tablets made of the processed powders were enhanced, even for those coated with the hydrophobic material such as MgSt, which has been previously reported to inhibit such performance. However, the tablets made with silica-mechanofused powders would not disintegrate under the same condition. This study indicated the feasibility of a single-step dry process to be developed to produce powders via mechanofusion with both flow-aid and lubrication effects, and which are suitable for direct compression.

5.3 Introduction

Oral solid dosage forms (primarily tablets), are the most commonly used drug delivery system. Tablets offer convenient drug administration[1], are generally more stable than comparable liquid forms, and are cost effective and easy for patients to use compared to alternative dosage forms[2,3]. During the formulation and manufacturing of oral solid dosage forms, tableting problems may arise from the properties of particles, including small particle size distributions, particle shape factors and a range of particle surface properties, which may cause flowability and/or tabletability issues[4-6]. In the pharmaceutical industry, dry or wet granulation has been traditionally applied as the most popular forms of such transformation/modification in order to overcome the flowability problems caused by cohesive powders[7]. However, these traditional granulation approaches generally require complex, multistep and hence cost-increasing processing steps and increased cost of infrastructure[2,8,9].

In this context, direct compression approaches are attractive as the continually-modernizing pharmaceutical industry strives to improve its manufacturing output while reducing operational costs[10]. In contrast to wet or dry granulation, direct compression offers the potential advantages of a simple and lower cost manufacturing process, with reduced risk of contamination, and heat/solvent induced instability[8,11,12]. Direct compression requires that the powder blend of

excipients and active pharmaceutical ingredients (APIs) have suitable flow, uniformity, compactibility and lubrication[9,10]. In order to meet these requirements, relatively large particles or large amounts of excipients must be usually used[8]. Many API powders have poor flowability resulting in problems with blending, and with blend uniformity. Segregation is considered a common issue occurring during handling, processing, manufacturing and/or storage of blended dry particulate materials for direct compression[13-15] and the combined flowability and uniformity properties of the powder blend for direct compression is a key feature[2,10].

Intensive mechanical dry particle coating has been reported in a number of contexts as a simple and efficient technique for improvement of flowability of cohesive powders. In general, dry coating is found to be simpler, cheaper, quicker and more environmentally acceptable than the solvent-based coating alternatives because no solvent is used[16-18]. There are several types of dry coating devices and systems available including those termed as mechanofusion[19], the hybridizer[20], the comil[21,22], fluid energy mills[23], the magnetically assisted impaction coater (MAIC)[23,24] and the Laboratory Resonant Acoustic Mixer[18]. Their principles they share in common are the employment of high energy and/or high shear processes to coat additive "guest" excipients onto the surfaces of "host" particles. In previous studies, mechanofusion has been found to be an effective and efficient approach for dry particle coating[25,26], which showed promising potential to facilitate direct compression by improving flowability of cohesive powders[27,28]. However, to date, few studies have addressed optimisation of both flowability and tabletability of such dry coated powders as well as the dissolution of corresponding compressed tablets[29,30].

Therefore, the primary aim of this study was to test the feasibility of a series of direct compression dry-coated powder mixtures produced by a single mechanofusion step. In this study, the fine cohesive ibuprofen powder is selected as a model high-dose drug with a low melting point and poor solubility in water. Cohesive ibuprofen powders were co-processed with varying coating materials, a binder and a superdisintegrant. Powder flowability, tabletability of such processed powders and dissolution behaviour of corresponding tablets were examined.

5.4 Materials and methods

5.4.1 Materials

Ibuprofen 25 powder, polyvinylpyrrolidone (PVP K25) and Kollidon® CL-F (Crospovidone) were donated by BASF (Ludwigshafen, Germany). Magnesium stearate NF (MgSt) was provided by Mallinckrodt Chemicals, Phillipsburg, NJ, USA. Hydrophobic fumed silica Aerosil® R972 (silica) was donated by from Evonik (Evonik Industries AG, Germany). L-leucine, potassium phosphate monobasic, sodium dodecyl sulphate and sodium hydroxide were all purchased from Sigma-Aldrich (St. Louis, MO, USA). Sizes of all the powders are given in Table 1.

Table 1. Median particle size of materials

Name of materials	Ibuprofen 25	MgSt	l-leucine	silica	PVP K25	Kollidon CL-F
Median particle size	~ 35 µm	~ 8 µm	~ 10 µm	~ 16 nm	~ 88 µm	~ 50 µm

5.4.2 Methods

5.4.2.1 Preparation of dry coated powders

The composition of the tablets is provided in Table 2. Approximately 20 g batches of active and inactive ingredients were weighed and manually pre-blended using a spatula in a 125 ml glass vessel and then transferred to the mechanofusion processing chamber. The powder mixtures were processed using an AMS-Mini Mechanofusion system (Hosokawa Micron Corporation, Osaka, Japan) with Nobilta processing configuration. The mechanofusion process was conducted by a slow increase in speed up to 900 rpm over 1 min and remaining this speed for a further 5 min[27]. Cooling water (22 ± 2°C) was applied via circulation through an incorporated jacket in order to maintain the processing chamber temperature at around 25°C during the process. Processed sample powders and their corresponding tablets were denoted by relevant guest material as MgSt, l-leucine and silica. As a comparison, the powder without any coating guest material was denoted as a control batch.

Table 2. Formulation of tablets (20 g/batch, 100 mg/tablet)

	Amount in formulation (%, w/w)			
	Ibuprofen	Coating material (MgSt, l-leucine, silica-R972)	PVP K-25	Kollidon CL-F
Control batch	85 %	0	10%	5%
Blends with coating material	84 %	1%	10%	5%

5.4.2.2 Powder densities and Carr Index

Poured density (ρ_p) and tapped density (ρ_t) were measured via previously reported methods with tapping requiring 1250 taps in an automatic tapper (AUTOTAP^{TM}, Quantachrome Instruments, Boynton Beach, FL) set with a 3.18 mm vertical travel at a tapping speed of 260 tap/min. Each measurement was run in triplicate. Carr Index (CI)[31] was calculated according to the obtained values of poured density and tapped density.

5.4.2.3 Particle sizing

Particle size was measured using a Morphologi G3 (Malvern Instruments, Worcestershire, UK). The Morphologi G3 is an optical microscope image analysis-based system, which permits not just particle size distributions to be directly measured, but also the morphological characteristics of statistically-valid high numbers of particles. Particle recognition software provide number and volume based statistics. Each sample was dry dispersed onto a glass plate at a standardised injection pressure of 1 bar using an integral Sample Dispersion Unit. The measurement for each sample was performed with three replicates. The particle size distribution was shown as D_{10} (diameter at 10% undersize), D_{50} (diameter at 50% undersize) and D_{90} (diameter at 90% undersize) and the results were averaged.

5.4.2.4 Powder flow properties

Powder flow and fluidisation properties were measured using a Freeman FT4 system in the shear cell and aeration modules, respectively (Freeman Technology, Worcestershire, UK). A detailed description of the instrument has been addressed previously[32,33] .Briefly, in the shear cell test, a pre-shear normal stress of 9 kPa was applied to consolidate the powder prior to each test. Shear measurements were then conducted at normal stress of 3, 4, 5, 6 and 7 kPa. Interparticle cohesion of each sample was calculated by extrapolating the yield loci using the equation as below (1):

$$\tau = C + \sigma \tan \eta \quad (1)$$

Where τ is the shear stress (kPa), σ is the normal stress (kPa), η is the angle of friction (degrees), and C is the cohesion (kPa). A lower cohesion value demonstrates a lower interparticle force.

In the aeration mode, air was introduced from the base of powder column to fluidize the powder. Flow energy was measured as a resistance to a blade moving through the bed at various air velocities[33]. The outcome provides an assessment of relative powder fluidization behaviour.

5.4.2.5 Scanning electron microscopy (SEM)

Detailed morphology of the ibuprofen sample powders was further assessed by a scanning electron microscope (SEM, Phenom^{TM}, FEI Company, Hillsboro, OR, USA). A small amount of each sample was slowly poured onto a double–sided carbon tape with one side mounted on a sample holder. Loose and excess powder was removed by slightly shaking the holder. The prepared samples were sputter coated with gold using an electrical potential of 2.0 kV at 25 mA (SCD005, BAL-TECAG, Blazers, Germany).

5.4.2.6 Tablet Formation

Compactibility was assessed here as the capacity of a powdered material to be transformed into a specified strength disc under the specific compaction pressure[34]. The selected sample powders were compacted directly into tablets using a GTP-1 computer controlled tablet press (Gamlen

Tableting Ltd., Nottingham, UK). The compaction force and ejection force curves were recorded for each tablet using Gamlen TP Controller software (Version 3.09). A flat round punch with a diameter of 6 mm was used. Tablets were approximately 100 mg in weight. Five tablets were made and tested at each compaction pressure for each sample powder. The compaction pressure ranged from 40 MPa to 180 MPa. The breaking force of tablets was measured using a hardness tester (ERWEKA, Heusenstamm, Germany). Tablet tensile strength was calculated from the fracture force, tablet thickness and diameter[35] using equation (2):

$$\sigma = \frac{2P}{\pi Dt} \quad \textbf{(2)}$$

Where σ is tensile strength (MPa), P is fracture force (N), D is punch diameter (mm) and t is tablet thickness (mm). Compactibility of the powders was characterized by plotting tablet tensile strength as a function of compaction pressure. Ejection stress was derived using equation (3)[36] :

$$ES = \frac{F}{\pi Dt} \quad \textbf{(3)}$$

Where ES is ejection stress (MPa), F is ejection force (N), D is punch diameter (mm) and t is tablet thickness (mm).

5.4.2.7 Disintegration of tablets

The disintegration time of 6 selected tablets made at compaction pressure of 180 MPa was determined at 37°C in distilled water with a USP XXIII apparatus with discs (Erweka ZT 3U, Erweka Apparatebau, Heusenstamm, Germany).

5.4.2.8 *In vitro* dissolution studies

The dissolution tests were conducted according to the US Pharmacopeia with a dissolution apparatus (Erweka DT6; Erweka, Heusenstamm, Germany) using USP II paddle method[37] with a paddle speed of 50 rpm. The dissolution medium (900 ml) consisted of a buffer solution at pH 7.2 [38] with 0.05 g/l sodium dodecyl sulphate. All dissolution medium were filtered through 0.45 µm

Millipore membrane and equilibrated to 37.0 ± 5°C in the dissolution bath. The prepared tablets were then added to the dissolution vessels. An aliquot of the dissolution medium (5 ml) was collected at 0, 2, 5, 10, 15, 25, 30, 40, 50 and 60 min and equivalent volume of fresh medium was added after each medium withdraw. The collected aliquots were filtered through a 0.45μm filter and the dissolved content of ibuprofen (%) was measured using a validated UV spectrophotometer assay as described below.

5.4.2.9 UV analysis of ibuprofen

A validated UV spectrophotometer method (CECIL 3021, Lab instrumentation Pty. Ltd., Australia) was used to analyse the ibuprofen content from the dissolution study at a wavelength of 221 nm[39]. The Beer's calibration of plot for ibuprofen in the dissolution medium exhibited a linear relationship between UV absorption and ibuprofen concentrations over the range of 2 to 20 μg/ml ($R^2 > 0.999$) with accuracy and precision values ranging from 97.4 −103.5% and 1.2 − 2.7%, respectively.

5.4.2.10 Statistical analysis

The statistical analysis of data derived from all ibuprofen samples was performed using analysis of variance (ANOVA) with Turkey's post hoc analysis at a *p*-value of 0.05 (SPSS, Version 19, IBM Inc., Chicago, IL, USA).

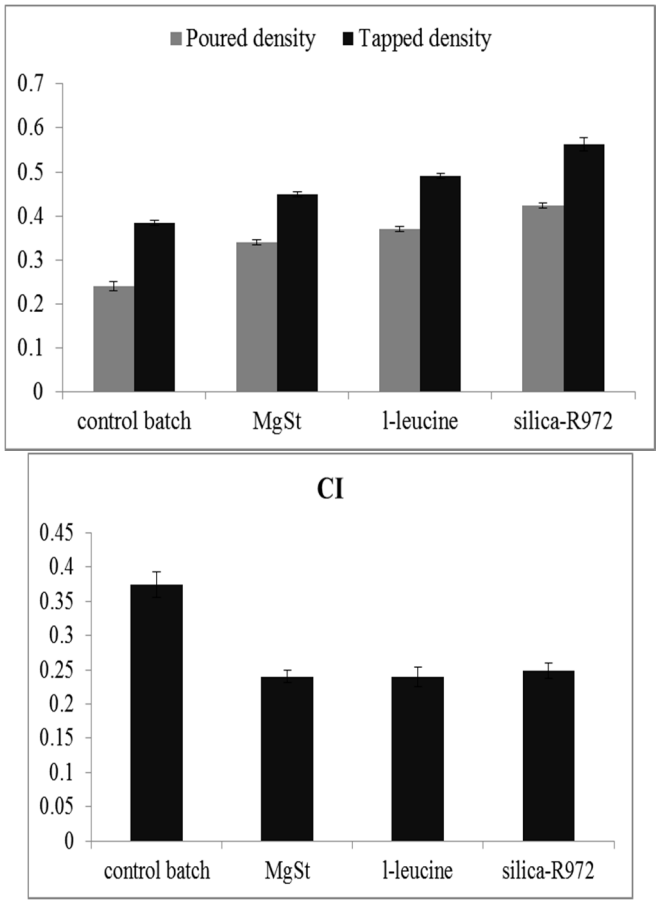
5.5 Results and discussion

5.5.1 Powder densities and Carr Index (CI)

The bulk density and CI for each sample are illustrated in Figure 1. There were significant increases ($p < 0.05$) in both poured density and tapped density after mechanofusion compared to the control batch. For the mechanofused powders with MgSt, l-leucine and silica, the values of CI were 0.24 ± 0.01, 0.24 ± 0.02 and 0.25 ± 0.01, respectively. These resulting CI values have been

classified as "passable" flow[40] and ideal for roller compaction[41]. In contrast, for the control batch, the highest value of CI (0.37 ± 0.02) was observed which presents "very poor" flow[40]. The substantially increased bulk densities and the decreased CI values of the mechanofused samples were attributed to the more efficient packing of the powder as a result of a reduced interparticle cohesion. These reductions in CI values indicated the flowability of the mechanofused powders with guest additives was substantially improved in comparison to the control batch.

A



B

Figure 1. Densities and CI values of raw and co-processed ibuprofen samples (error bars represent standard deviation, n = 3).

5.5.2 Powder flow properties

Cohesion and flow function (*ffc*) values from the FT4 powder shear tests are presented in Table 3. These parameters are used to reflect the bulk behaviour of a powder under a consolidated state, such as flow from a hopper[42]. As defined by Schulze[42], the *ffc* is the ratio of major principle stress to the unconfined yield stress and has been widely used to classify the powder flow behaviour: *ffc*

< 1, not flowing; 1 < *ffc* < 2, very cohesive; 2 < *ffc* < 4, cohesive; 4 < *ffc* < 10, easy flowing and *ffc* > 10, free flowing. The control batch powder exhibited the highest cohesion values (1.73 ± 0.05 kPa) and lowest *ffc* (3.52 ± 0.12). There was no significant difference in cohesion and *ffc* values between the mechanofused powders with either MgSt or l-leucine. However, the mechanofused powders with silica showed the lowest cohesion (0.24 ± 0.01) and highest *ffc* value (18.1 ± 0.01) among all tested powders ($p < 0.05$). This indicates the mechanofused powder with silica achieved best flowability under consolidated states, and this is believed to be due to the "ball-bearing" interfacial effect formed with the silica agglomerates[43,44] on the surfaces of host particles.

Table 3. Cohesion and *ffc* values of ibuprofen samples (mean ± SD, n = 3)

	Control batch	MgSt	l-leucine	silica-R972
Cohesion (kPa)	1.33 ± 0.05	1.06 ± 0.09	0.93 ± 0.07	0.24 ± 0.04
ffc	3.52 ± 0.12	4.01 ± 0.27	5.06 ± 0.2	18.1 ± 3.0

Figure 2 shows the powder aeration behaviour obtained from the FT4 measurements. The control batch exhibited a consistently high flow energy at each air velocity among all samples, and did not reach a clear minimum, even at 30mm/s air flow. In contrast, for the mechanofused samples, the flow energy was reduced to a minimum value even at the lowest air velocity of 2 mm/s. Therefore, the processed samples were shown to be substantially more easily fluidized.

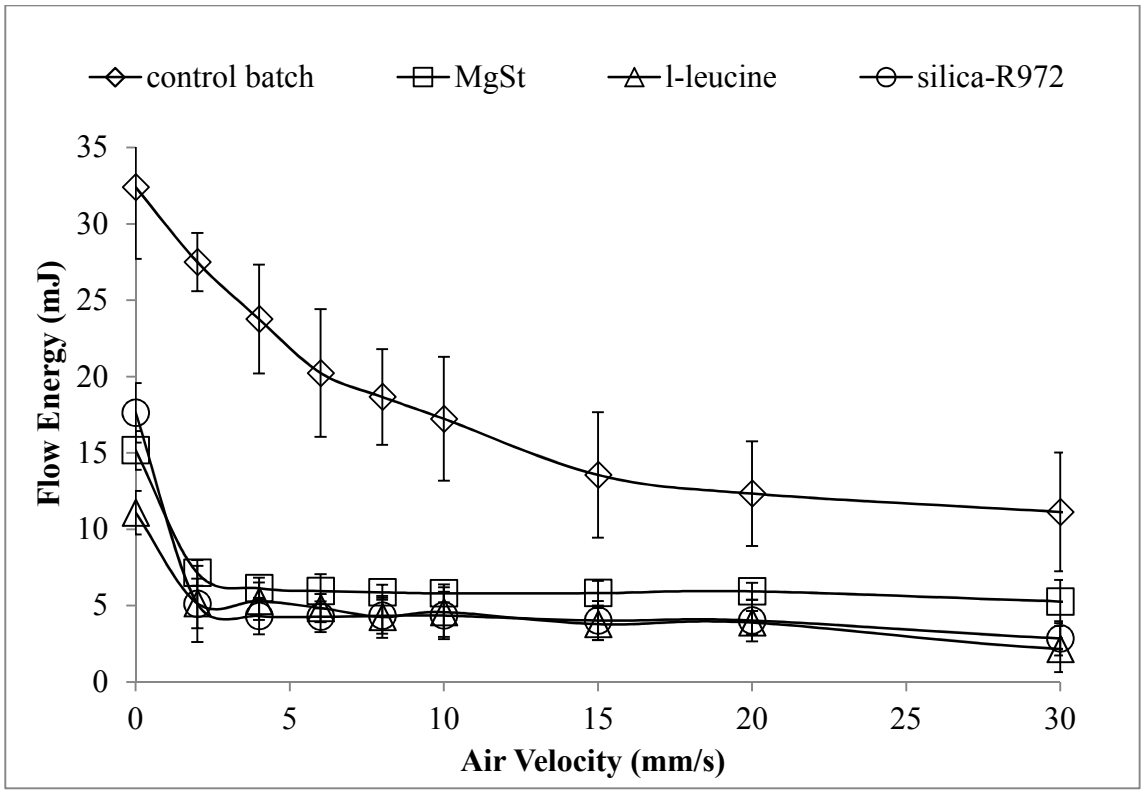


Figure 2. Flow energy at different air velocity for control batch and co-processed ibuprofen samples (error bars represent standard deviations, n = 3).

5.5.3 Particle size analysis

Table 4 shows that there were slight differences in the both D_{50} and D_{90} values between the control batch and mechanofused samples, although the D_{10} remained approximately constant. The lower particle sizes after mechanofusion with additives is proposed to be due to be a reduced formation of hard-agglomerates existing in the particles[45] due to the presence of lubricants and glidant. This particle size data also indicates that any change in bulk flow performance was not achieved by enlarging particle size.

Table 4. Particle size for control batch and co-processed ibuprofen samples (error bars represent standard deviations, n = 3).

	Particle size distribution		
	D_{10}(μm)	D_{50} (μm)	D_{90} (μm)
Control batch	42.13±2.5	116.2±4.5	281±39.3
MgSt	41.84±6.5	87.52±1.4	205.9±32
l-leucine	47.6±5.2	86.8±4.9	191.1±22.1
Silica-R972	38.9±2.5	76.6±7.9	169.1±50.8

5.5.4 Scanning electron microscopy

Representative SEM images of the ibuprofen sample powders are shown in Figure 3. The control batch particles (Fig. 3A) exhibited as either agglomerates or individual particles. The observed agglomerates consist of components with distinctive shapes: drug particles (rod-like), superdisintegrant crospovidone (as porous nodules) and PVP (as dimpled spherical shapes). The PVP is consistently seen in figures 3A, C and D as providing a core for the other particle types to adhere to.

For the MgSt-mechanofused particles, (Fig 3B), the surface texture of particles was similar to the control batch. Figure 3C shows the l-leucine-mechanofused particles, and there is a visible indication the ibuprofen particles had rougher surface textures. This possiblely suggests that l-leucine formed a more patch-like coating on the particle surfaces, given that it is not as effective a lubricant as MgSt in its ability to laminate on the surfaces uniformly and lubricate the powder flow.

For the silica-mechanofused particles (Fig. 3D), a fine lumpy texture was observed on the surfaces of both individual particles and whole agglomerates. These structures possibly show silica acts to increase surface roughness as small rigid nano-sized beads to improve powder flowability[44].

Despite the low melting point of ibuprofen, no visible evidence of any significant melting phenomenon was observed for any samples after mechanofusion, which is consistent with a previous mechanofusion study[27].

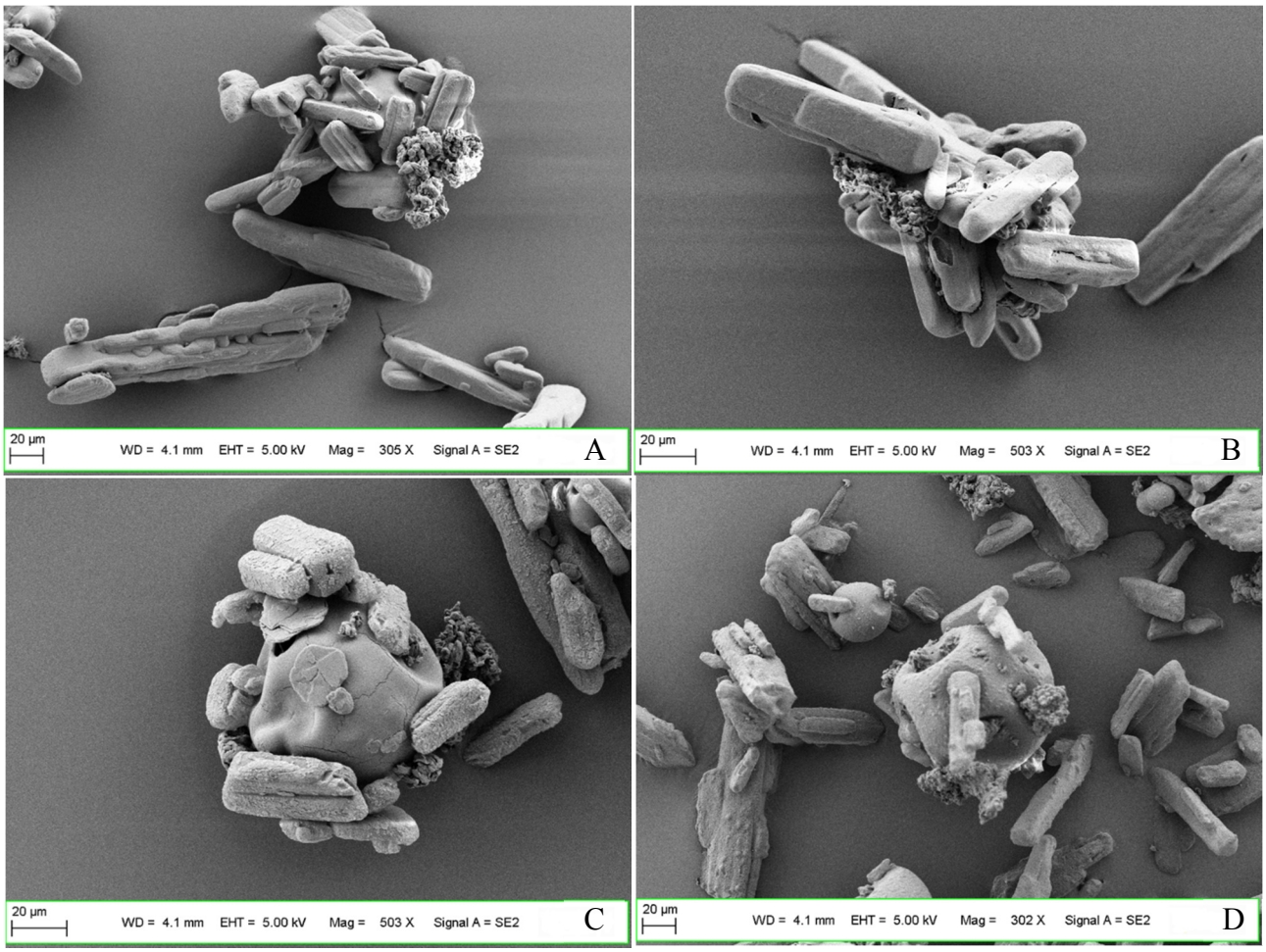


Figure 3. SEM micrographs of ibuprofen samples. A. control batch, B. MgSt, C. l-leucine, D. silica. Scale bar represents 20 µm in micrographs.

5.5.5 Tablet compaction

The relationship between ejection stress (ES) and compaction pressure is provided in Figure 4. The MgSt- and l-leucine-mechanofused powders gave significantly lower ES values than the control batch and silica-mechanofused powders under the applied compaction pressures ($p < 0.05$). Such lubrication effect could be attributed to the formation of an effective lubricant layer or film on the host particle or punch/die surfaces[46]. No significant difference in ES were observed between the tablets made with the control batch and silica-mechanofused powders. This illustrates that silica lacks any lubrication effect on tablet ejection.

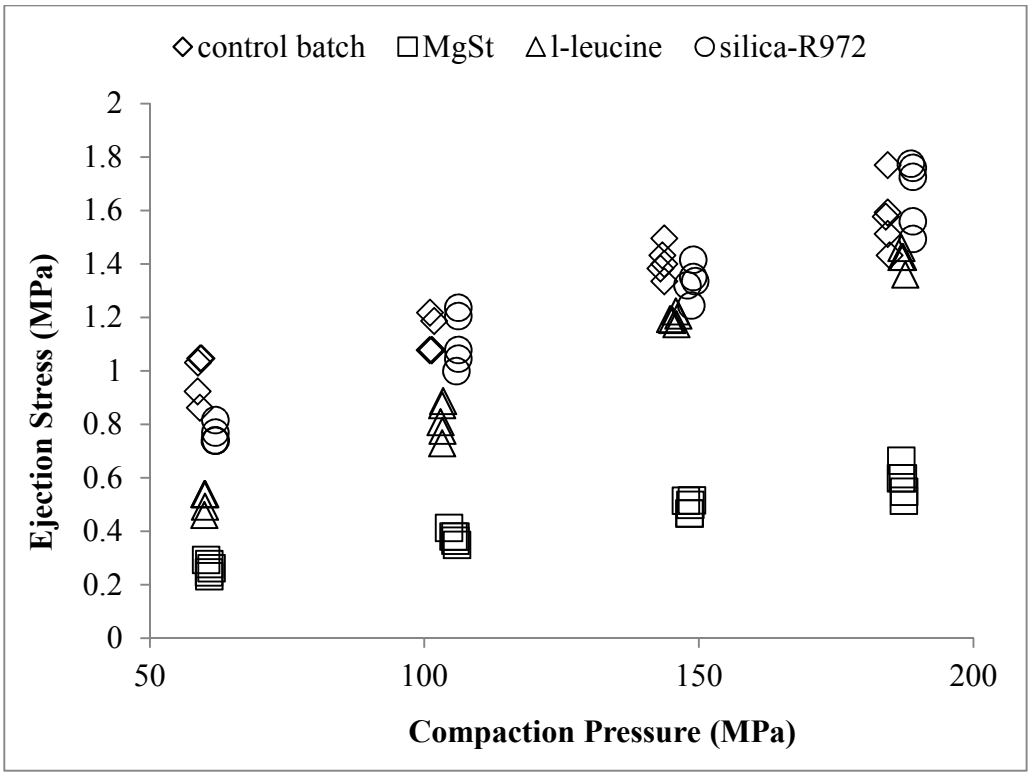


Figure 4. Ejection stress of prototype ibuprofen tablets (n = 5).

During the manufacturing of tablets, ejection behaviour is critical to the success of high-speed production because high ES usually causes capping, lamination and adhesion to the die or punches[47-49], particularly for drugs with a low melting point such as ibuprofen[50,51], and external addition of lubricants is essential for the high-speed tableting of ibuprofen. Of particular note, the current study demonstrates that a simple single-step mechanofusion process that can achieve both flow-aid and lubrication effects, where the guest additive is a lubricant. However, this duel function was not achieved with a classical flow aid silica.

All sample powders (the control and mechanofused samples) formed intact tablets under the applied compaction pressure, without adding any further external excipients. Capping, lamination, or other typical faults in tablets were not observed.

Figure 5 shows the tablet tensile strength relative to the applied compaction pressure. At the applied compaction pressure of 110, 150 and 180 MPa, the tablet tensile strength for the MgSt-mechanofused powder showed the lowest values relative to other powders. This reduction in tensile strength was in agreement with the established concept that over-lubrication of powders

with MgSt can negatively affect bond formation of pharmaceutical powders[27,52,53]. In contrast, the tablets made with silica-mechanofused powders demonstrated highest tensile strength values. The interpretation of this increasing tensile strength is probably that the hard nano-sized silica provides an additional bonding area between the contacting softer particles resulting in a stronger interparticle strength[54-58] and the bonding strength between the ibuprofen powder and silica was stronger than that between ibuprofen powders, which is in agreement with the findings from other independent research group[59,30].

There was no significant difference in tensile strength over the range of the applied compaction pressure 110 - 180 MPa between the tablets made with the control batch, silica-mechanofused and l-leucine-mechanofused powders ($p > 0.05$).

At the compaction pressure of around 180 MPa, the tensile strength values of tablets with all mechanofused powders other than the MgSt-mechanofused powder were more than 1.7 MPa. This value has been reported to indicate mechanical strength sufficient to withstand commercial manufacturing and subsequent distribution[60].

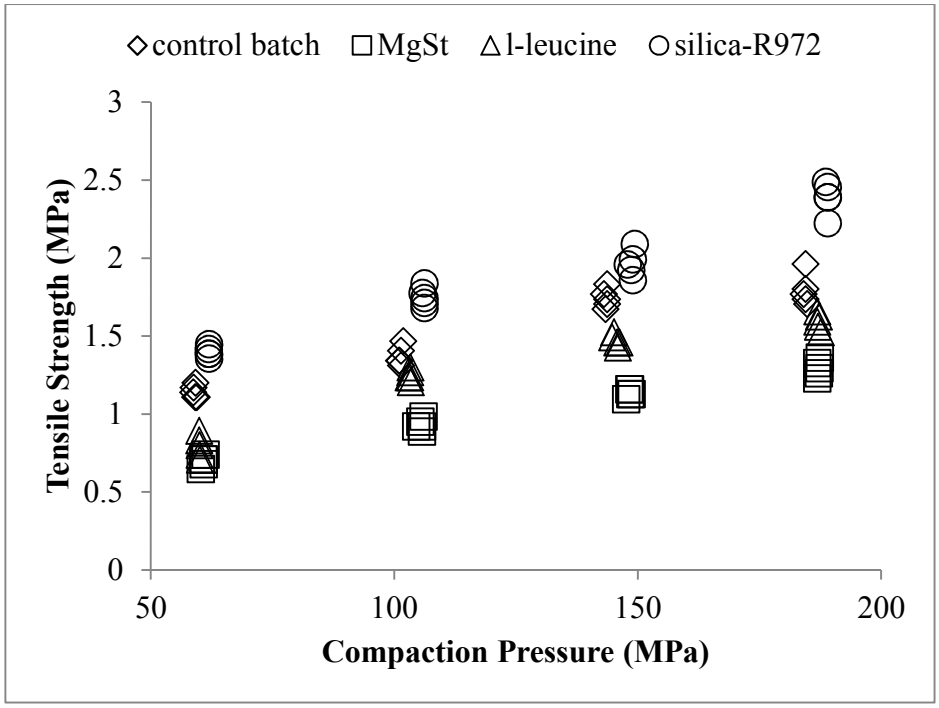


Figure 5. Tensile strength of prototype ibuprofen tablets (n = 5).

The data indicate that a balance between lubrication and tensile strength effects may be achieved. For example, the coating with l-leucine appears best placed to strike a balance between lubrication and tensile strength, which has the potential to improve powder flowability, provide lubrication while avoiding negative effects on tensile strength of the final tablets. Therefore the work supports a hypothesis that a single-step mechanofusion process could be developed to produce a powder mixture with combined properties for direct compression as an alternative to the traditional multi-step granulation processes. Furthermore, the single-step particulate structure engineering process may allow a reduced amount of speciality excipients usually associated with a direct compression formulation. This could reduce tablet size in high dose tablets and therefore ease swallowing of large-sized tablets and also save in the manufacturing costs[50].

5.5.6 Disintegration of tablets

Disintegration behavior of the produced tablets (made using compaction pressure 180 MPa) is shown in Table 5. The tablets of the silica-mechanofused powder did not disintegrate under the test conditions. The disintegration time of the tablets made of the control powder was more than 15 min, in contrast the tablets made of the mechanofused powders with either MgSt or l-leucine was less than 5 minutes.

Table 5. Disintegration of sample tablets (compaction pressure 180 MPa)

Tablets	Control batch	MgSt	l-leucine	silica
Disintegration time (min)	> 15	< 5	< 5	N/A (the tablets are too hard to break up)

This substantially shorter disintegration time of the tablets made of the MgSt-mechanofused and l-leucine-mechanofused powders, implies that the coating of MgSt and l-leucine facilitates deagglomeration. Surprisingly for the case of MgSt, coating does not have a substantial impact to

prevent water ingress. However, the tablets made of the silica-mechanofused powder could not break up at all due to the strong tensile strength of the tablets.

5.5.7 *In vitro* dissolution studies

Figure 6 showed that more than 90% of ibuprofen was dissolved from the tablets within 5 min from tablets made with MgSt or leucine lubricants. In our previous studies, it has been reported that hydrophobic MgSt coating on the drug powder surface may act to reduce drug agglomeration in powders in order to achieve increasing dissolution rate of the corresponding tablets[27].

The tablets made with the silica-mechanofused powder did not dissolve over the time duration of 60 min, which was consistent with the results from the disintegration tests. So while silica can provide good flow enhancement, it does not facilitate other tablet properties, and most notably cannot facilitate tablets penetrated by the dissolution medium.

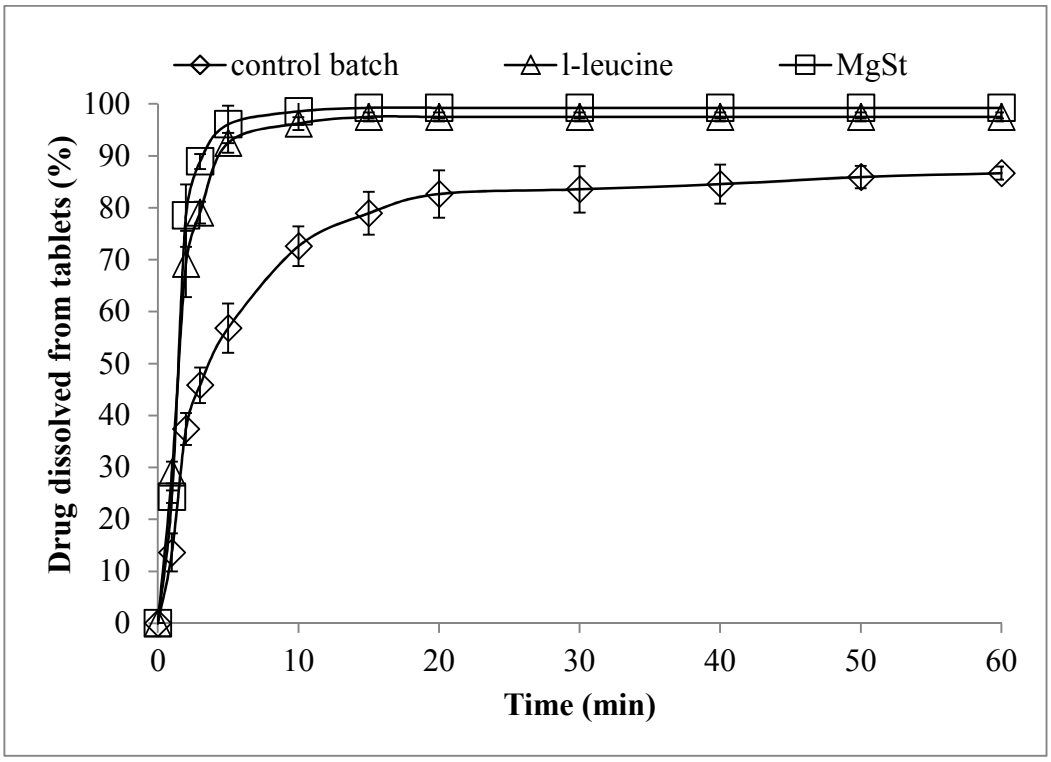


Figure 6. Dissolution profile of sample tablets (error bars represent standard deviations, n = 3). The tested tablets were made using 180 MPa.

Traditionally, l-leucine is used in tablets as a hydrophilic lubricant intend to have less negative effect on dissolution rate of the tablets as an alternative to MgSt[61,62]. It may be required at a concentration up to 10% (w/w)[61,63]. In this study, the dissolution rate of tablets made with l-leucine-mechanofused powder was increased significantly, and it appears the dissolution medium was able to penetrate into the tablets more easily (given its hydrophilic nature) and thus facilitate the superdisintegrant action of crospovidone

5.6 Conclusions

The co-processing of ibuprofen powder with different coating materials in addition of PVP and crospovidone via mechanofusion has shown:

1. The effective modification of the interparticulate interactions as evidenced by substantial changes in bulk densities, Carr's Index and confirmed with a suit of results from the range of more advanced shear and rheological powder flow testing.
2. Detailed particle characterisation proved the coating process did not affect particle shape or size, and the flow improvement resulted from surface coating effects.
3. Robust tablets could be made with all resulting processed powders.

The l-leucine-mechanofused material appeared to provide the best balance of tabletting outcomes in this context with decreasing disintegration time and improved dissolution rate as well as acceptable tensile strength. The co-processing drug powders with l-leucine in addition of binder and superdisintegrant may have the potential to manufacture tablet efficiently in a single step, while further work is warranted to optimise process and powder compositions across various aspects of this work with regard to the specific range of properties including powder flowability and corresponding tabletability.

5.7 Acknowledgement

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5.8 Declaration of interest

The authors report no declaration of interest.

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Chapter 6

Effects of particle size of coating material L-leucine on flow, tableting and dissolution behaviour of dry-coated ibuprofen powders*

*Submitted as **Qu, L.**, John A Denman, Peter J Stewart, Karen P Hapgood, Qi (Tony) Zhou, David A V Morton. Effect of l-leucine particle size on flow, tableting and dissolution behaviour of dry-coated ibuprofen powders.

Declaration for Thesis Chapter 6

Declaration by candidate

In the case of Chapter 4, the nature and extent of my contribution to the work was the following:

Nature of contribution	**Extent of contribution (%)**
Study design, formation of hypothesis, laboratory work, data collection, analysis and results interpretation and the manuscript writing.	65

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	**Nature of contribution**	**Extent of contribution (%) for student co-authors only**
John A Denman	ToF-SIMS characterization and manuscript revision	5
Peter J Stewart	Supervision and manuscript revision	5
Karen P Hapgood	Supervision and manuscript revision	5
Qi (Tony) Zhou	Manuscript revision	10
David A V Morton	Supervision and manuscript revision	10

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

Candidate's Signature	[redacted]	**Date** **08/03/2016**

Main Supervisor's Signature	[redacted]	Date 08/03/2016

*Note: Where the responsible author is not the candidate's main supervisor, the main supervisor should consult with the responsible author to agree on the respective contributions of the authors.

6 Effect of l-leucine particle size on flow, compaction and dissolution behaviour of dry-coated ibuprofen powders

6.1 Commentary

The data achieved from chapter 4 and 5 showed that l-leucine as a coating material has been found to have promising capacity of improving flowability of fine cohesive drug powder after mechanofusion process. Also such processed powder was able to be compacted into tablets directly. Thus in this chapter, the influence of particle size of l-leucine on the flowability, tabletting and dissolution behaviour of cohesive ibuprofen powder mechanofused with different particle sizes of l-leucine was evaluated. Mechanofusion was applied to coat different l-leucine with the range of D_{50} from 10-260 μm onto ibuprofen powder. The tabletability of such dry coated powders with external addition of PVP K25 and crospovidone was investigated by measuring its tensile strength, ejection force and dissolution behaviour.

6.2 Abstract

Pharmaceutical lubricants are recognized as effective in coating powdered materials; however, the effects of particle size of lubricants as additives in coating material, and resulting impact on the

coating quality, bulk flow, compaction and dissolution of coated powders and formed compacts has not been closely studied. L-leucine has previously been investigated as a lubricant in this context, and the purpose of this work was to evaluate the impact of L-leucine particle size of as a coating material on behaviours of L-leucine dry-coated cohesive ibuprofen powders. Cohesive ibuprofen powders were dry-coated by mechanofusion with L-leucine of various median sizes in the range of 10 – 260 μm. Powder flow testing with the Freeman FT4, showed dry coating of L-leucine with the particle size range from 10 – 110 μm produced a significantly improved flow compared to both the unprocessed and the mechanofused powders with the L-leucine size of 260 μm. ToF-SIMS results demonstrated an increasing trend of L-leucine coverage on the drug particle surface with the decreasing particle size of L-leucine. Dissolution of the drug powders was studied using the USP paddle method. The obtained dissolution data were fitted into mono-exponential and bi-exponential models, representing dissolution from the dispersed and agglomerated particles, respectively. Tablets made of the mechanofused ibuprofen powders by direct compaction were robust. Dissolution rate of the formed tablets with the mechanofusion powders was enhanced compared to those made of Turbular-blended with L-leucine of 260 μm. The present study revealed the significant influence of the particle size of coating material, L-leucine, on the formulation performance of coated drug powder and the formed tablets.

6.3 Introduction

More than 80% of all pharmaceutical dosage forms are tablets, with popularity ascribed to patient acceptability [1,2]. During the production of tablets, the handling of fine particulates is very common as part of the processing. However, most fine drug particles (e.g. median size smaller than 20 to 30 μm) have poor flowability, which can cause problems in handling, processing or storage during the tablets manufacturing. Larger drug particles may also present flow problems due to particle surface properties. The success of the handling and manufacturing of these powders as well as their formulation performance is dependent on their powder bulk behaviours (i.e. flow, fluidization and dispersion) [3]. For example, free-flowing solids are generally required for the industrial high-

speed tableting, aiming to obtain rapid transfer of the powder from the hopper to the die [4]. Many strategies have been employed to enhance powder flowability such as granulation [5] or adding flow-aid excipients for direct compaction [6,7].

In general, direct compaction has fewer processing steps than tableting of granules, leading to lower costs [5,8]. Furthermore, without using solvents and the needs for drying, direct compaction is particularly more suitable for those drugs sensitive to heat or liquid [9]. However, the powders to be direct compacted must exhibit satisfactory flow.

Recently, dry powder coating techniques have been demonstrated as a promising approach to substantially improve flow, fluidization and dispersion of selected cohesive pharmaceutical powders by reducing powder cohesion [10-14]. An advantage is that compared to the traditional liquid-based coating, no organic solvent or water is used in this dry process. There are a number of dry coating approaches documented in pharmaceutical applications, including mechanofusion [15], the Hybridizer [13], the Comil [12,14], fluid energy mills [16] and the magnetically assisted impaction coater (MAIC) [17-19]. Mechanofusion has been examined for a number of pharmaceutical purposes [20]. Substantially improved powder flow of either a fine cohesive lactose monohydrate excipient (median particle size approximately 20 μm) [15] or fine ibuprofen drug powder (median particle size approximately 30 μm) [7] was demonstrated using a mechanofusion approach to coating with magnesium stearate.

Magnesium stearate (MgSt) and colloidal silica are the most widely used coating materials in dry coating processes. Our previous study has compared the effect of coating material on the flow, fluidization and dissolution of dry-coated ibuprofen powders [21]. The data have shown that the dry-coated ibuprofen powders with magnesium stearate had the best flow, but led to a significant decrease of tensile strength of tablets. In addition, the tablets made with the silica dry-coated ibuprofen powder failed to disintegrate even with addition of 5% w/w of disintegrant, crospovidone. It was found that coating with L-leucine has achieved a better balance between powder flow and tablet tensile strength. However, there was a lack of information on the effect of

L-leucine coating on flowability, tabletability and dissolution of the coated powder and formed tablets. Moreover, the previous studies found that particle size of the coating material of colloidal silica may have significant impacts on dry coating quality [22,23]; however, such effects have not been examined for the lubricant type of coating materials. Therefore, the aim of this study is to examine the influence of initial L-leucine particle size on the flowability and the tabletability of resulting dry-coated ibuprofen powder, as well as the dissolution performance of direct compacted tablets formed.

6.4 Materials and methods

6.4.1 Materials

Ibuprofen 25 was donated by BASF (Ludwigshafen, Germany). Magnesium stearate NF (MgSt) was provided by Mallinckrodt Chemicals, Phillipsburg, USA. L-leucine, potassium phosphate monobasic, sodium dodecyl sulphate and sodium hydroxide was supplied by Sigma-Aldrich (Castle Hill, Australia).

6.4.2 Methods

6.4.2.1 Preparation of L-leucine with various particle sizes

L-leucine (approximately 5 g) with median particle size around 260 μm was milled down to the median particle size around 110 μm, 60 μm and 10 μm, respectively, using a ball mill (Pulverisette 6, FRITSCH, Idar-Oberstein, Germany). Ball milling with 25 stainless steel balls was performed at speed of 250 rpm for 1 min, 350 rpm for 1 min and 550 rpm for 2 min respectively to achieve corresponding L-leucine particle size of 110 μm, 60 μm and 10 μm. A ball size of 5 mm in diameter was used.

6.4.2.2 Dry coating

Ibuprofen powder was dry coated with resulting various particle size L-leucine (260, 110, 60, and 10 μm) using an AMS-Mini mechanofusion system (Hosokawa Micron Corporation, Osaka, Japan). Powder (approximately 20 g) was manually pre-mixed comprising 99% ibuprofen with 1% (w/w) various particle size L-leucine, respectively, using a spatula in a 125 ml glass vessel and then transferred to the mechanofusion processing chamber. Mechanofusion process was carried out by slowly increasing the blade speed up to 900 rpm within 1 min and maintaining this speed for a further 5 min [7]. The Mechanofusion vessel was water cooled (22 C +/- 2) with an incorporated jacket in order to prevent the processing chamber from significant heating during the process. These samples were denoted as l-leu-260, l-leu-110, l-leu-60 and l-leu-10, respectively. The untreated ibuprofen drug powder was denoted as raw in the following sections.

6.4.2.3 Preparation of powder mixture for tableting

All mechanofused ibuprofen powders (l-leu-260, l-leu-110, l-leu-60 and l-leu-10) were subsequently blended with 10% (w/w) PVP (binder) and 5% crospovidone (disintegrant), for 30 min at a speed of 72 rpm using a conventional tumbling Turbula® T2F mixer (Glen Mills Inc., Clifton, NJ, USA). As a comparison, raw ibuprofen powder was also blended with 1% (w/w) L-leucine with a particle size of 260 μm, 10% (w/w) PVP and 5% crospovidone using the same tumbling blending parameters. These samples are donated as l-leu-260-T, l-leu-110-T, l-leu-60-T and l-leu-10-T, l-leu-260-blended-T, respectively.

6.4.2.4 Particle sizing

Particle sizes were measured by laser diffraction (Mastersizer® 2000, Malvern Instruments, Worcestershire, UK) with a wet cell module according to a previously validated method [7]. A saturated aqueous solution of ibuprofen (temperature: 25±0.5°C) was used as the dispersion medium. Around 50 mg of ibuprofen powder was dispersed in 20 ml of dispersion medium prior

to start measuring. Particle size distribution was obtained by averaging three replicates of each sample and was shown as D10 (diameter at 10% undersize), D50 (diameter at 50% undersize) and D90 (diameter at 90% undersize).

6.4.2.5 Powder flow properties

Flow properties of sample powders were examined using a Freeman FT4 Powder Rheometer in the aeration and shear modules (Freeman Technology, Worcestershire, UK). A detailed introduction of this instrument has been well documented in the literature [24,25].

Briefly, in the compressibility mode, a vented piston was utilized to compress powders under a range of normal stresses from 1 to 15 kPa. Compressibility is a way to measure the volume change (in percentage) of the sample powder under increasing normal stress. A lower value in compressibility generally corresponds to less cohesion between examined particles [26].

Shear testing requires a pre-shear normal stress of 9 kPa to be applied for consolidation of the powder prior to each test. Shear measurements were then conducted at a range of normal stress from 3 to 7 kPa [27]. Inter-particle cohesion of each sample was addressed by extrapolating the yield loci using the equation as below (1):

$$\tau = C + \sigma \tan \eta \quad (1)$$

where τ is the shear stress (kPa), σ is the normal stress (kPa), η is the angle of friction (degrees), and C is the cohesion (kPa). A lower cohesion number represents a lower interparticle cohesive force indicating better flow properties of powders.

The ffc is defined as the ratio of major principle stress to the unconfined yield stress and used to classify the powder flow behaviour: ffc < 1, not flowing; 1 < ffc < 2, very cohesive; 2 < ffc < 4, cohesive; 4 < ffc < 10, easy flowing and ffc > 10, free-flowing [28].

6.4.2.6 Scanning electron microscopy (SEM)

Ibuprofen sample powders were mounted onto a double–sided adhesive tape with one side adhering to a sample holder. The prepared samples were then sputter coated with gold using an electrical potential of 2.0 kV at 25 mA (SCD005, BAL-TECAG, Blazers, Germany). The surface morphology of the particles was carried out using a scanning electron microscope (PhenomTM, FEI Company, Hillsboro, OR, USA).

6.4.2.7 ToF-SIMS

ToF-SIMS experiments were performed using a PHI TRIFT V nanoTOF instrument (Physical Electronics Inc., Chanhassen, MN, USA) equipped with a pulsed liquid metal 79+Au primary ion gun (LMIG), operating at 30 keV energy. Dual charge neutralization was provided by an electron flood gun and 10 eV Ar+ ions. Surface analyses were performed using "unbunched" Au1 instrument settings to optimize spatial resolution. Raw data were collected in positive SIMS mode at a number of locations typically using a 200x200 micron raster area, with 4 min acquisitions. Five areas per sample were analysed, which encompassed >50 particles, to ensure representative results were collected.

Chemical maps were produced using WincadenceN software (Physical Electronics Inc., Chanhassen, MN, USA), based on the following unique and characteristic responses: m/z = ~161 ([M-COOH]+ fragment) for ibuprofen and m/z = ~132 ([C6H14NO2]+ fragment) for L-leucine.

6.4.2.8 Tablet formation

The above prepared sample powder mixtures were tableted by direct compaction using a GTP-1 computer controlled tablet press (Gamlen Tableting Ltd., Nottingham, UK). A flat round punch with a diameter of 6 mm was used to form standard sample tablets of approximately 70 mg in weight. Five tablets were made and tested at each compaction pressure for each sample mixture. The compaction pressure was in the range from 40 MPa to 180 MPa. The fracture force of a tablet

was measured using a hardness tester (ERWEKA, Heusenstamm, Germany). Tablet tensile strength was calculated from the fracture force, tablet thickness and diameter[29] as below using equation (2):

$$\sigma = 2P/\pi Dt \quad (2)$$

Where P is fracture force (N); D is punch diameter (mm); t is tablet thickness (mm) and σ is tensile strength (MPa). Powder compaction properties were characterized by plotting tablet tensile strength against compaction pressure.

6.4.2.9 *In vitro* dissolution studies of sample powders and tablets

The dissolution studies of both coated powders and formed tablets were conducted according to the USP II paddle method with a paddle speed of 50 rpm [30] (Erweka DT6; Erweka, Heusenstamm, Germany). Dissolution medium (900 ml) consisted of a pH 7.2 phosphate buffer solution with 0.05 g/L sodium dodecyl sulphate (SDS) [7,21]. Prior to operation, all dissolution media were filtered through 0.45 µm Millipore membrane for degassing and equilibrated to 37.0 ± 5°C in the dissolution bath. Each sample powder (100 mg) or the tablet (70 mg/tablet) was transferred to the dissolution vessels. 5 mL aliquots of the dissolution media were collected at 0, 2, 5, 10, 15, 25, 30, 40, 50 and 60 min and then the dissolution vessels were refilled with equivalent volume of fresh medium. The aliquots of collection were filtered through a 0.45 µm filter immediately and the amount of dissolved ibuprofen (%) was measured using a validated UV assay.

6.4.2.10 UV analysis of ibuprofen

The content analysis of ibuprofen from the dissolution study was carried out using a validated UV spectrophotometer method at a wavelength of 221 nm (CECIL 3021, Lab instrumentation Pty. Ltd., Australia) [7,21]. Beer's calibration of plot for ibuprofen in the dissolution medium exhibited a linear relationship between absorption and ibuprofen concentrations over the range of 2 to 20 µg/ml

(R^2>0.999) with accuracy and precision values ranging from 98.5-102.1% and 1.4-3.5%, respectively.

6.4.2.11 Dissolution modelling of sample powders

Dissolution data obtained from the tested sample powders were modelled with a non-linear least squares regression analysis according to the Levenberg-Marquardt algorithm[31] to analyse the coefficients or parameters of the independent variables that supply the best fit between the equation and the data (SigmaPlot® 12.3; Systat Software Inc., San Jose, CA, USA).

Modelling of the undissolved drug (%) in the vessels was performed using multi-exponential equations which consist of mono-exponential (two parameters), bi-exponential (four parameters) and tri-exponential (six parameters) decay equations listed as below (3-5):

$$C = C_d * \exp(-k_d * x) \quad (3)$$

$$C = C_d * \exp(-k_d * x) + C_a * \exp(-k_a * x) \quad (4)$$

$$C = C_d * \exp(-k_d * x) + C_{a1} * \exp(-k_{a1} * x) + C_{a2} * \exp(-k_{a2} * x) \quad (5)$$

where C is the concentration of undissolved drug (%) at time t; C_d and C_a are the initial concentrations (%) of dispersed particles and agglomerates, respectively; k_d and k_a (min^{-1}) represent the dissolution rate constants for dispersed and agglomerated particles, respectively. These exponential terms express dissolution behaviour from combinations of ‘‘dispersed’’ and ‘‘agglomerated’’ particles where dispersed particles have a significant effect on dissolution performance which is attributed to surface area influence [32].

Discrimination between the models were carried out with several statistical parameters. For example, Akaike Information Criterion (AIC) provides analysis of goodness of fit according to maximum likelihood by correlating the weighted residual sum of squares to the number of parameters that were needed to achieve the fit and the model obtaining the smallest value is the most suitable one; the norm value is square root of the sums of squares in which a smaller number supplies a better fit of the data; F value contributes to assessing the improved fit with the use of

additional parameters in which a bigger value demonstrates a superior fit; correlation coefficient (R^2) is a value near 1 indicating a greater degree of correlation and hence more favourable and dependency values (D) demonstrating an indication of model complexity where a value reaching 1 indicates over-parameterization.

6.4.2.12 Statistical analysis

The statistical analysis of data derived from all ibuprofen samples was performed using analysis of variance (ANOVA) with Turkey's post hoc analysis at a *p*-value of 0.05 (SPSS, Version 19, IBM Inc., USA).

6.5 Results and discussion

6.5.1 Particle sizing

Table 1 shows that only marginal differences in the D50 values were seen between the raw and mechanofused samples. The slight reductions in particle sizes after mechanofusion processing could be attributed to either little attrition resulting from high shear impaction, or decrease in hard-agglomerates existing in the particles; this observation is consistent with previous studies [7,21,33]. These size analyses data demonstrated that any enhancement in bulk flowing performance could not be attributed to size enlargement and granulation.

Table 1. Particle size distribution of the ibuprofen samples (mean±SD, n=3).

Sample powder	D_{10} (μm)	D_{50} (μm)	D_{90} (μm)
Raw	17.13±0.23	43.55±0.72	89.78±1.13
l-leu-260	15.21±0.09	36.98±0.12	72.07±0.27
l-leu-110	13.59±0.18	33.69±1.4	69.21±4.6
l-leu-60	14.34±1.01	34.81±1.05	72.01±2.45
l-leu-10	14.44±0.15	34.52±0.72	68.86±2.27

6.5.2 Powder flow properties

Figure 1 shows that the raw ibuprofen powder exhibited the highest FT4 compressibility values at all applied stresses in comparison to other powders, indicating the raw powder was the most cohesive [25]. In contrast, the compressibility values of all mechanofused powders were significantly reduced ($p<0.05$). Among the mechanofused powders, the l-leu-260-mechanofusion powder showed the greatest compressibility indicating higher cohesive forces between particles,

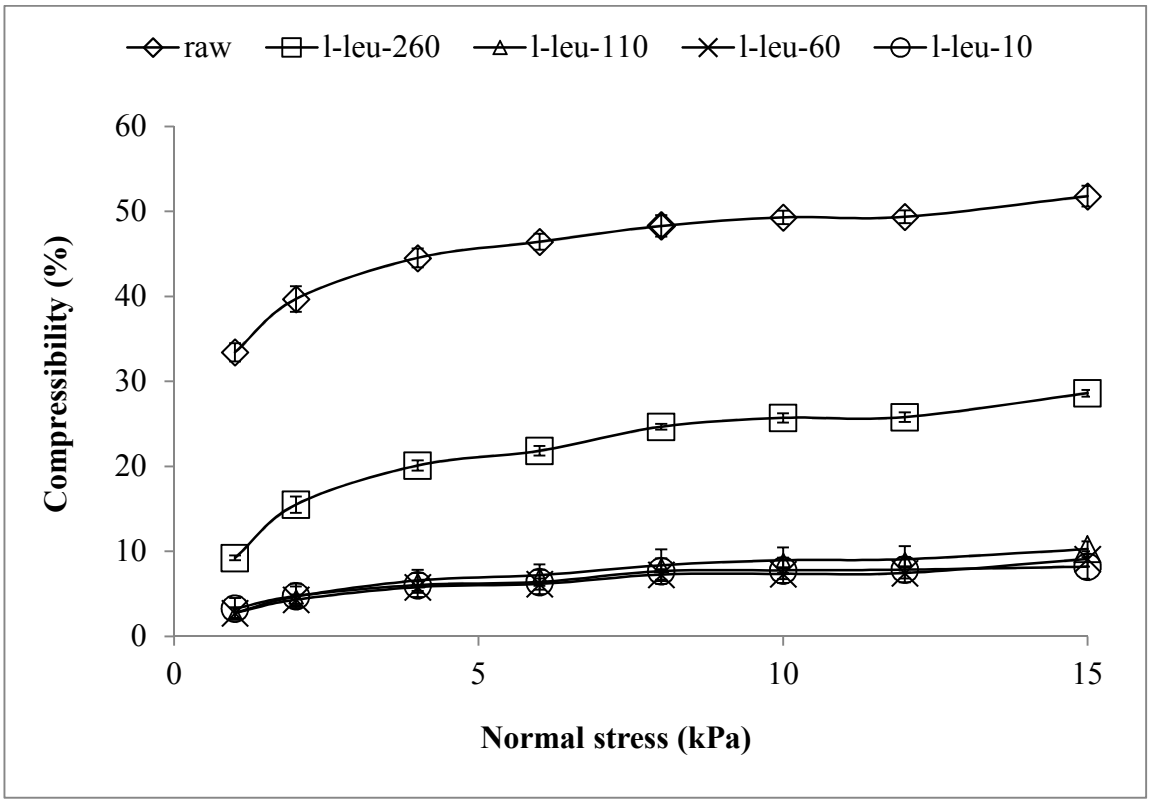

Figure 1 Compressibility of sample powders (n = 3).

Cohesion values derived from shear testing are provided in Table 2. The raw ibuprofen powder exhibited the highest cohesion (1.24 kPa) and lowest ffc values (4.02) followed by the mechanofused powders with l-leu-260 ($p<0.05$). Among the mechanofused powders, the l-leu-260-mechanofusion powder also showed a higher cohesion value, while the mechanofused powders with smaller size L-leucine (110, 60, and 10 µm, respectively) showed significantly lower cohesion (0.71 kPa, 0.53 kPa and 0.38 kPa, respectively) and higher ffc (4.78, 8.1 and 11.61,

respectively) ($p<0.05$). These results demonstrate that an increase in coating material particle size leads to the higher cohesion and poorer flowability, in agreement with the compressibility data.

Table 2. Cohesion and ffc values of the ibuprofen samples (mean±SD, n=3).

	Raw	l-leu-260	l-leu-110	l-leu-60	l-leu-10
Cohesion (kPa)	1.24±0.04	1.15±0.04	0.71±0.13	0.53±0.09	0.38±0.10
ffc	4.02±0.19	4.18±0.18	4.78±0.48	8.10±1.29	11.61±2.60

6.5.3 Dissolution of sample powders

Figure 2 illustrates the dissolution profiles of the raw and mechanofused powders. The l-leu-260-coating did not generate a significant improvement in ibuprofen dissolution compared to the raw ibuprofen sample ($p > 0.05$). However, the dissolution rate of ibuprofen increased substantially when dry coated with L-leucine in a range of smaller particle size (110, 60 and 10 μm, respectively). For example, the dissolved drug at 2 min significantly increased from 17.4 ± 1.6% for the raw ibuprofen to 82.4 ± 3.2% for the coated l-leu-10 powder ($p < 0.001$).

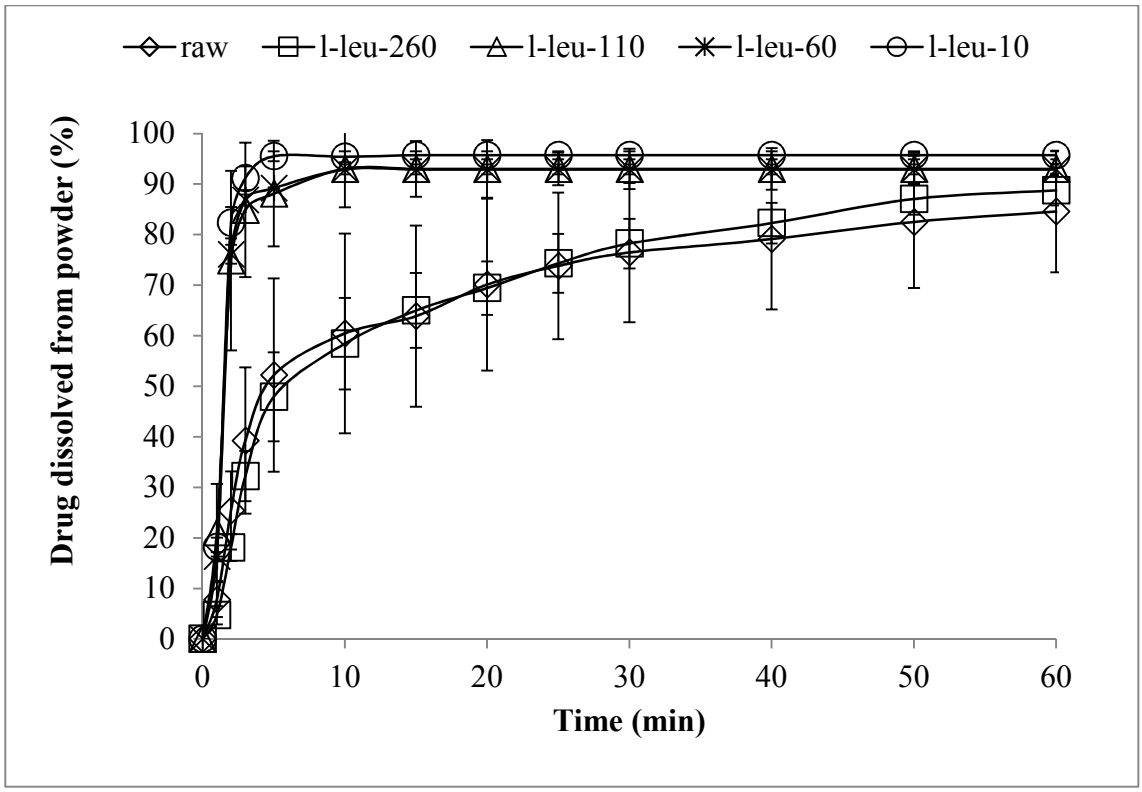

Figure 2 Dissolution profiles of sample powders (n=3).

It was observed that the powders coated with the smallest particle size (10 μm) L-leucine achieved the fastest dissolution. This is consistent with our previous reports, where increased dissolution rate corresponds with improved flowability which may be attributed to enhanced powder de-agglomeration [21]. The FT4 results have shown the mechanofused l-leu-10 powder has the lowest cohesion. Hence, agglomerates are considered as weaker, and an increased contact surface area between the particle and dissolution medium is proposed to result in faster water wetting and penetration. The mechanofused powder with smaller particle sizes (110 and 60, respectively) also obtained an increased dissolution profile similar to the l-leu-10. However, there is no improvement of dissolution rate in mechanofused powder with l-leu-260 ($p > 0.05$). Therefore, it was concluded that the particle size of starting L-leucine had a significant influence on the dissolution behaviours of the mechanofused powders.

6.5.4 Modelling of powder dissolution data

In order to further understand the underlying relationship between the dissolution rate and particle size of L-leucine, attempts were made to fit the dissolution data to a multi-exponential equations using non-linear least squares regression analysis as described in the Materials and Methods section. Using this approach, the dissolution parameters of initial concentration for the dispersed particles and undispersed agglomerates, and the corresponding dissolution constants were calculated.

For the raw and l-leu-260-mechanofused samples, the dissolution data were best fitted by a bi-exponential model indicating that the drug was dissolved from two population types of particles. These two populations were designated as the "dispersed" particles and "agglomerated" particles. It is likely that the "dispersed' particle distribution contained not only individual particles but also some small agglomerates. The dissolution profile shown in Fig.2 can be described by two concentration terms (e.g. C_d: the initial concentration of dispersed particles and C_a: the initial concentration of agglomerated particles) in Table 3 and two dissolution rate constants (e.g. k_d: the dissolution rate constant for dissolution from dispersed particles and k_a: the dissolution rate constant for dissolution from agglomerated particles) in Table 3. The biphasic shapes of the dissolution profiles in Fig.2 are consistent with bi-exponential dissolution behaviour.

The dissolution data for the l-leu-110, l-leu-60 and l-leu-10-mechanofused samples of ibuprofen were best fitted by the mono-exponential equations. Advanced order equations did not improve the fit. This is consistent with the dissolution occuring from a single distribution of mechanofused particles with the estimated parameters of initial concentration of ibuprofen and the dissolution rate constant for dissolution from the particular distribution of particles.

The estimated parameters for the initial concentration of particles and the dissolution rate constants are shown in Table 3. For the powder samples where the dissolution data is fitted by a mono-exponential model, the estimated initial concentration of particles was around 100%. In some cases,

the initial concentration was slightly greater than 100% and this may have resulted from fitting the data to a model which assumes that the particle distribution does not change. There may have been changes to the distribution during the dissolution process, e.g. the "dispersed" particle distribution may have become more dispersed. The dissolution rate constants for the dissolution of l-leu-110, l-leu-60 and l-leu-10-mechanofused samples are not significantly different and are between 0.5 to 0.6 min^{-1}. The outcome from this modelling suggests the mechanofused powders with smaller L-leucine particle sizes (10, 60 and 110 μm) were better dispersed during the dissolution tests than other two coated powders, which is attributed to the efficient surface coating made with smaller particle sizes leucine [34].

The estimated parameters for the dissolution of raw ibuprofen and l-leu-260 mechanofused ibuprofen are shown in Table 3. Both powders model in a similar manner with there being no significant difference between the concentration parameters and the rate constant parameters. For all samples, the estimated parameters of concentration of dispersed particles (C_d) and dissolution rate constants (k_d) are also shown. In terms of the dispersed particle concentration, both the estimated concentrations and dissolution rate constants for smaller particle sizes L-leucine-mechanofused samples were significantly higher than those of the raw and l-leu-260-mechanofused samples ($p<0.05$).

Table 3. Influence of particle size of L-leucine on the estimated initial concentration of dispersed particles (C_d) and of agglomerated particles (C_a), as well as on the estimated dissolution rate constants from dispersed particles (k_d) and from agglomerated particles (k_a) for all sample powders (mean ± SD, n=3).

	Raw	l-leu-260	l-leu-110	l-leu-60	l-leu-10
C_d (%)	60.0±25.8	57.1±14..3	104.8±1.5	106.1±1.1	106.8±0.5
C_a (%)	43.0±23.1	47.3±13.3	-	-	-
k_d (min^{-1})	0.34±0.06	0.27±0.04	0.52±0.01	0.53±0.01	0.61±0.03

k_a (min^{-1})	0.02±0.01	0.02±0.01	-	-	-

All the data in compressibility, flowability and dissolution rate indicated a threshold in effective coating was reached after the particle size of the coating material was reduced to 110 μm or less. Such distinctive bulk behavior of coated powders are likely attributed to the different coating quality. Hence, SEM and ToF-SIMS were employed to assess the quality of coating layer generated with L-leucine of various particle sizes.

6.5.5 SEM

Fig. 3 provides a series of representative SEM images. These images indicate that after dry coating with L-leucine, the overall particle shape was unchanged, which is in agreement with the previous findings [21]. However, it was noted that the coating with L-leucine of various particle sizes generated different textures on the ibuprofen particles surfaces. This may relate to the different flowability behaviour. The l-leu-260 coating produced discrete patches, which may be of coating material; while all other coating materials formed a more homogeneous roughened surface. We propose that due to the large particle size of l-leu-260, L-leucine is less efficiently delaminated and so unable to be as effectively spread and coated onto the host particle surface. To further confirm the poorer coating quality by l-leu-260, ToF-SIMS was employed to provide qualitative analysis of surface chemistry of the coated particles.

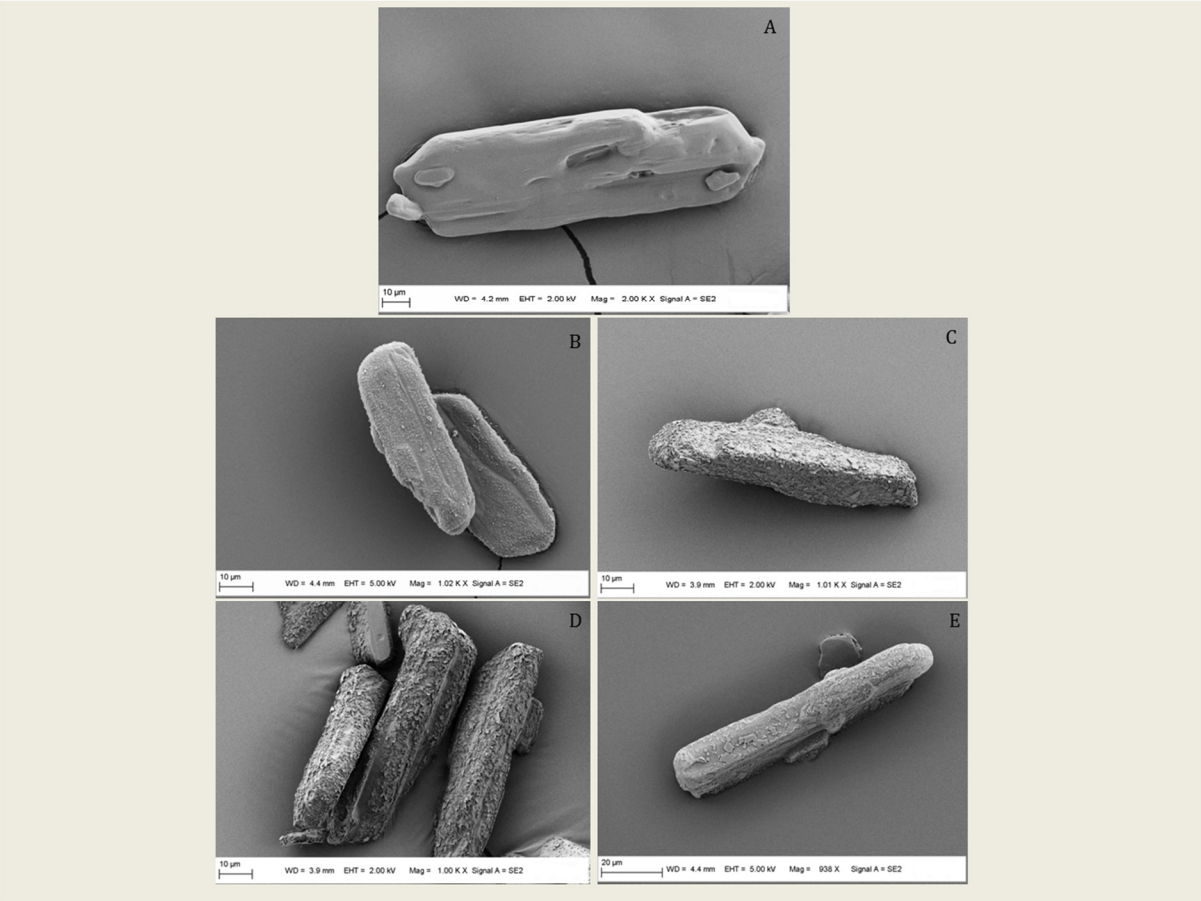

Figure 3. SEM micrographs of sample powders (A: raw; B: l-leu-260; C: l-leu-110; D: l-leu-60; E: l-leu-10), scale bar represents 10 µm in micrograph of A, B, C, D; 20 µm in E.

6.5.6 ToF-SIMS

Fig. 4 shows the chemical distributions of the coating material, L-leucine (red), and the drug, ibuprofen (green), on the upmost particle surface. It can be observed that L-leucine surface coverage is relatively lower for the l-leu-260 coating, while markedly higher for the l-leu-110, l-leu-60 and l-leu-10 coatings. A qualitative comparison of the surface chemistry was also conducted by averaging the normalised response of L-leucine fragment $[C6H14NO2]^+$ to the total ion signals from 25 particles. Fig. 5 shows that L-leucine surface coverage was significantly higher when the L-leucine particle size was decreased from 260 to 110 µm; however, further decrease in particle size did not correspond to a significantly higher surface coating coverage. The ToF-SIMS results therefore complement the SEM analysis and also the flowability data in showing that the effective

coating of the ibuprofen particle surface was achieved with the L-leucine particle size of and below the threshold 110 µm.

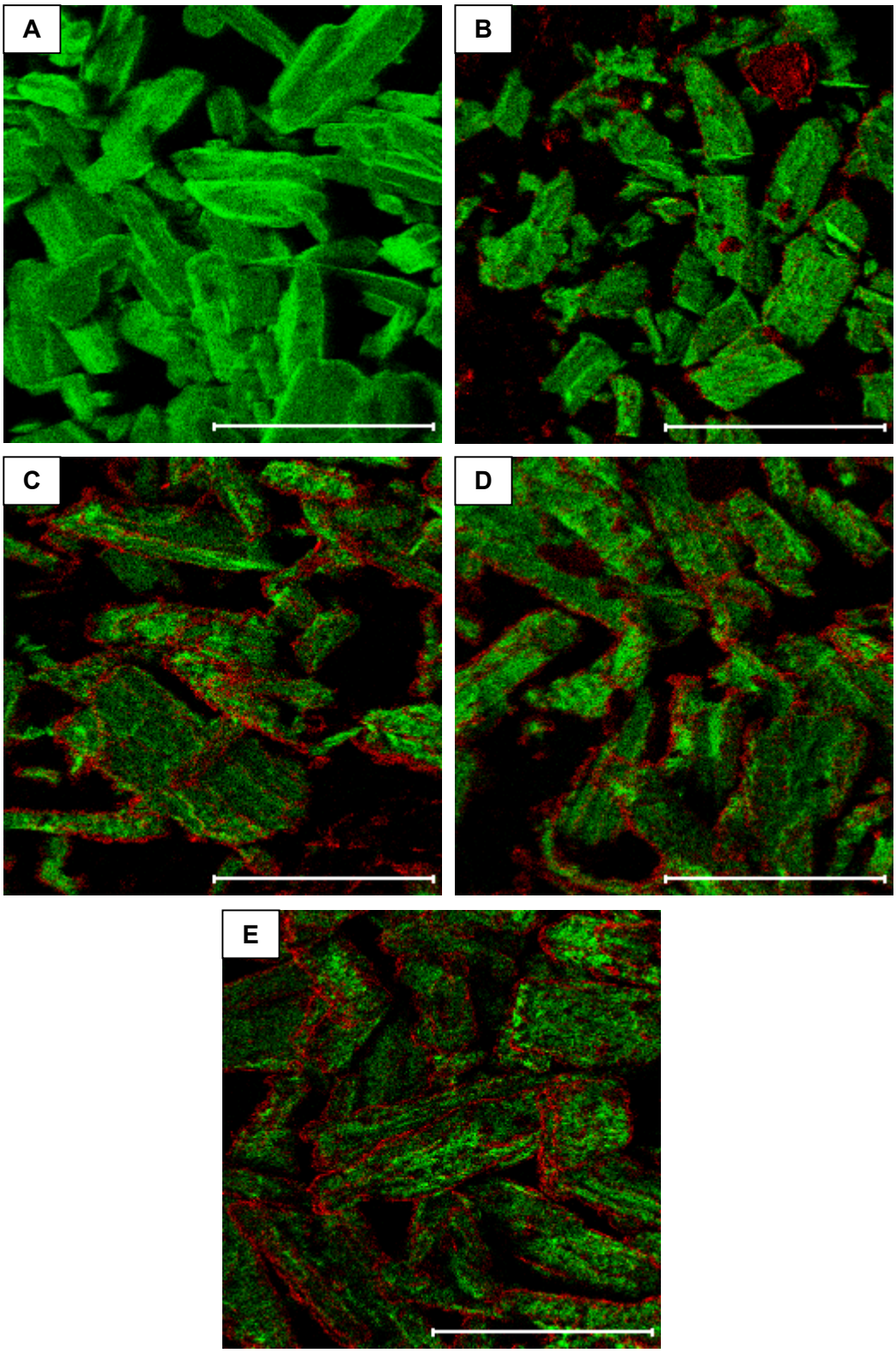

Figure 4. Distribution of L-leucine (red) on the surface of ibuprofen (green) measured by ToF-SIMS for: A: raw; B: l-leu-260; C: l-leu-110; D: l-leu-60; E: l-leu-10. Scale bar = 100 micron.

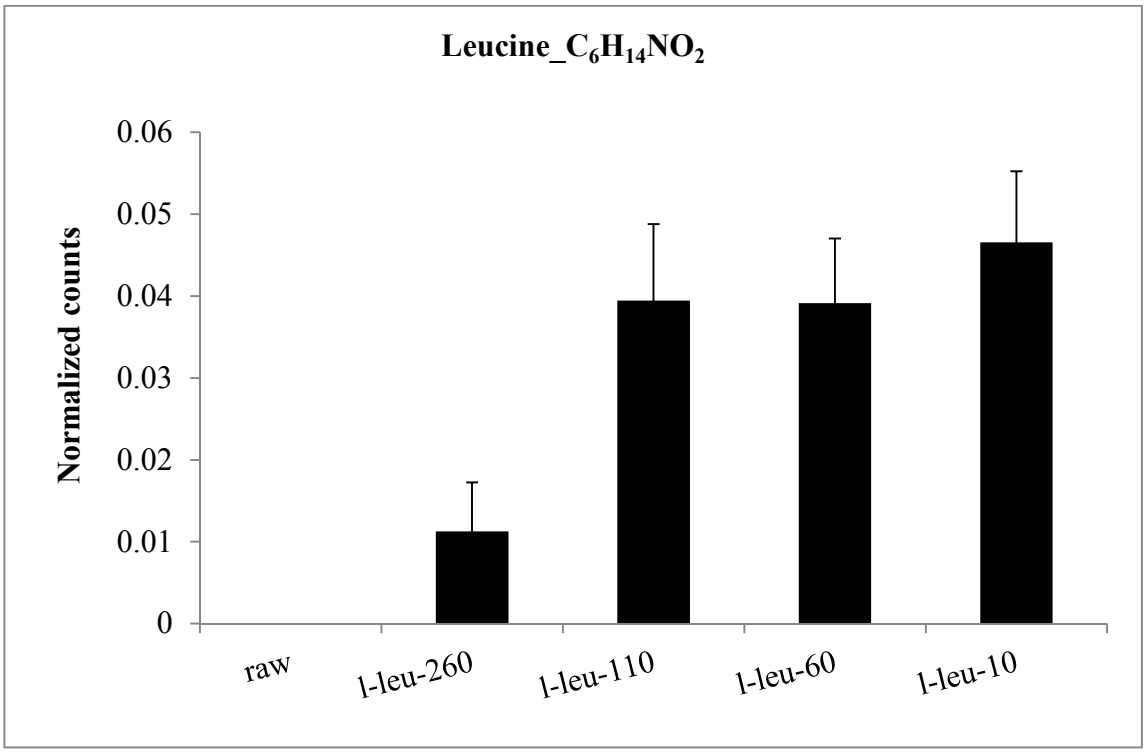

Figure 5. Normalized signal response of L-leucine on the particle surfaces measured by ToF-SIMS. Results represent surface chemistry as an average of 25 particles, with 95% confidence error bars.

6.5.7 Tablet formation

Fig. 6 shows that the tablet tensile strength values for the mechanofused powder were only slightly lower than the blended powder. This suggests coating of L-leucine has only a small negative impact on tablet formation of sample powders, and less impact compared to the previously studied magnesium stearate coating [7]. There was no significant difference in tensile strength over the range of the applied compaction pressure 40-180 MPa between the mechanofused ibuprofen powders (p>0.05). This indicated the particle size of L-leucine did not influence the tensile strength of tested powders.

Tablets showed no signs of capping, lamination or other typical tablet faults. The tablet tensile strength was more than 1.7 MPa under a certain pressure of 180 MPa, which indicated such tablets were mechanically strong enough to satisfy commercial manufacture, package and transport [35]. This work therefore supported the hypothesis that the L-leucine coated ibuprofen powders could have the potential to be tableted through direct compaction under standard manufacturing conditions.

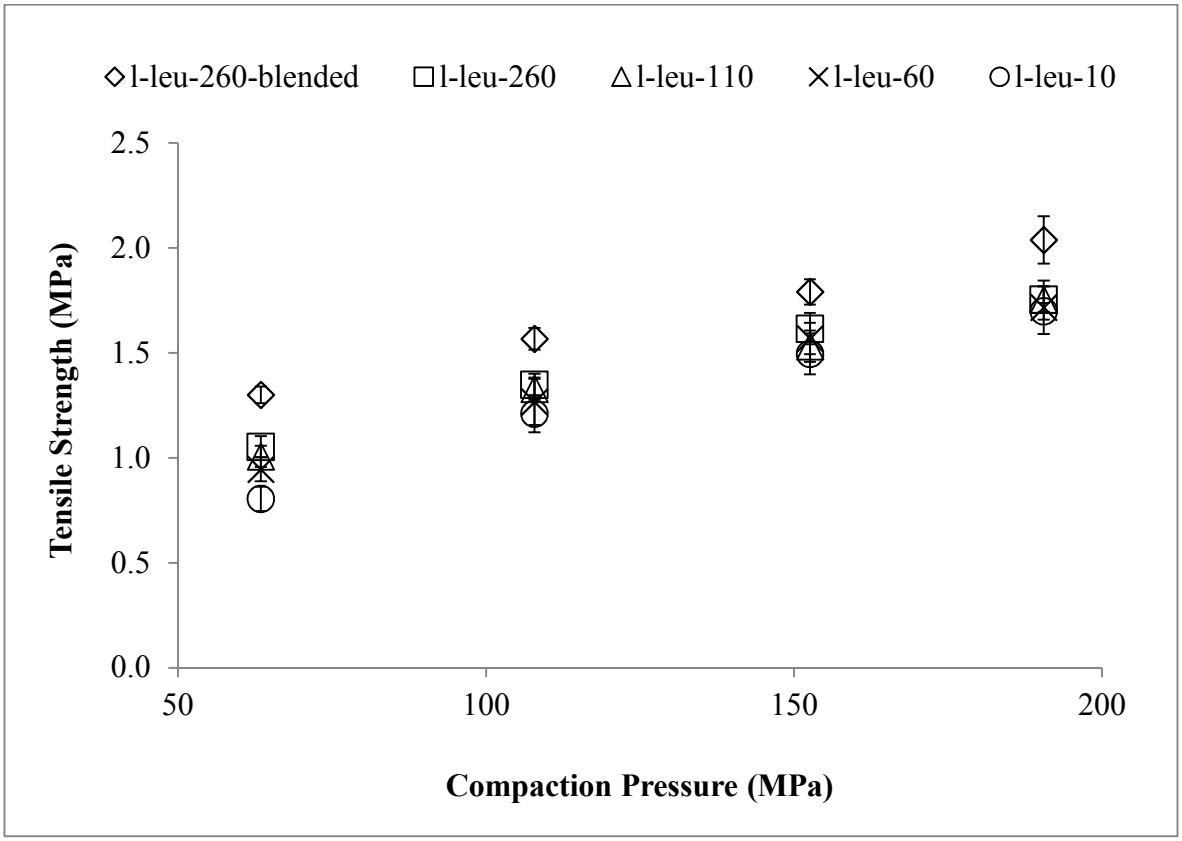

Figure 6. Tensile strength of formed tablets made at various compaction pressured (n=3).

6.5.8 *In vitro* dissolution studies of tablets

Figure 7 showed that for the tablets made of the blended powder, only around 40% of ibuprofen was dissolved in 60 min. However, more than 90% of ibuprofen was dissolved in 5 min from the tablets made of the mechanofused powders with L-leucine in the particle size ranges from 10-110 um. This is consistent with the aforementioned powder dissolution results. Therefore, the significant improvement in dissolution rate of the tablets is attributed to the improved dispersion

of the coated sample powders with less agglomeration and increased solid-liquid contact surface area [6,7] after the tablets disintegrate in the dissolution medium.

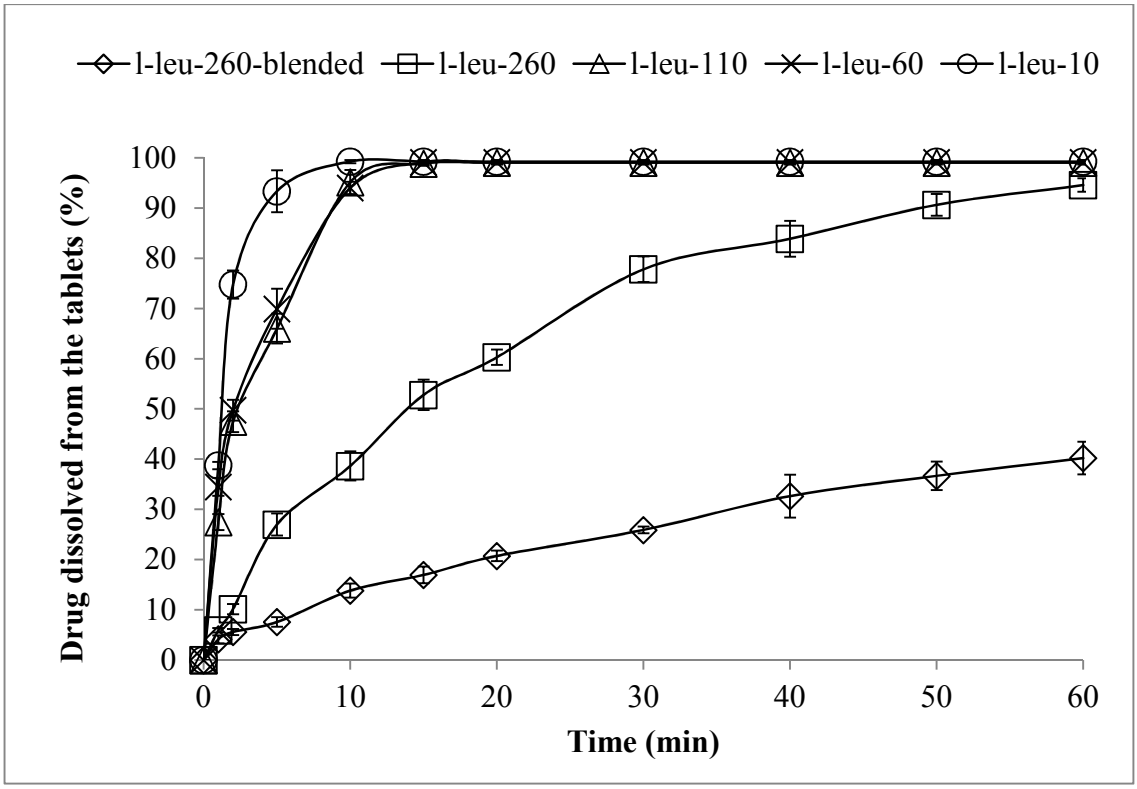

Figure 7 Dissolution Profiles of the formed tablets (n=3).

6.6 Conclusion

This study for the first time identified a significant impact of the particle size of a lubricant coating material, L-leucine, on the flowability, dissolution, and tabletability of dry-coated fine ibuprofen powders. Effective modification of the interparticulate interactions with L-leucine coating of the size range 10 μm to 110 μm was evidenced by powder flow data, indicating that smaller L-leucine provides a larger reduction in the cohesive force. In addition, such reduced powder cohesion was transferred to the enhanced dissolution rate by increasing the powder dispersibility in the medium, in which the underlying mechanism was elucidated by the dissolution modelling. SEM micrographs and the data from ToF-SIMS supported that L-leucine particle size has a significant influence on coating quality. It was shown that L-leucine particles in the size range of 10 to 110

μm provided a higher level of coating coverage on the surface of ibuprofen particles than the larger L-leucine particles with a size of 260 μm.

Results from this work demonstrate that coating with smaller particle size of L-leucine enhances the dissolution not only for the drug powder, but also for the corresponding formed tablets. Importantly, the tensile strength of tablets made of L-leucine coated ibuprofen powders was not remarkably reduced like the magnesium stearate coated formulations, which indicates L-leucine has a great potential to be used as a coating material for developing novel formulations suitable for direct compaction of high-dose drugs. Further work is warranted to evaluate if such modified powders are suitable to be scaled up for commercial manufacturing.

6.7 Acknowledgement

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6.8 Declaration of interest

The authors report no declaration of interest.

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Chapter 7

General conclusions and future directions

7 General conclusions and future directions

7.1 General conclusions

This study examined the influence of surface coating on flowability and tabletting behaviours of a model fine ibuprofen powder (D_{50}=25μm), as well as the relationship between de-agglomeration and dissolution of the powders and the corresponding tablets.

A low-melting-point, cohesive ibuprofen powder was coated successfully with a traditional lubricant magnesium stearate by 'mechanofusion' to achieve improved powder flowability. ToF-SIMS and XPS results demonstrated that flow improvement was highly dependent on the coating properties. Robust tablets were made with the mixture of the dry-coated powders, PVP and superdisintegrant. In dissolution testing, a surprising finding is that such hydrophobic magnesium stearate coating did not delay the ibuprofen dissolution rate of both the coated powder and formed tablets.

The effect of coating materials (magnesium stearate, l-leucine, silica-R972 and sodium stearate fumarate) on the flowability and dissolution of mechanofusion dry-coated fine ibuprofen powders was investigated. The flowability of mechanofusion ibuprofen powder with magnesium stearate, leucine or silica was significantly improved. The dissolution rate of ibuprofen powders was more dependent on powder cohesion and agglomeration than on the hydrophobicity of the coating material. The multi-exponential dissolution modelling used in the study explained the underlying mechanism for the improved dissolution behaviour, indicating that coating increased the powder dispersibility of the cohesive powder and thus increased the surface area for dissolution.

The feasibility of developing a single-step platform via the mechanofusion process to produce a powder mixture of active and inactive excipients for direct compression was explored. Such co-processing of ibuprofen powder with different coating materials (magnesium stearate, l-leucine and silica) with PVP and superdisintegrant showed the significant improvement of powder

flowability. Robust tablets of surficient tensile strength were able to be made with such co-processed powders.

The l-leucine-mechanofused powder provided a balance between appropriate disintegration rate and tablet tensile strength. The particle size of l-leucine had a significant impact on the flowability and the tabletability of resulting mechanofusion dry-coated ibuprofen powder. SEM micrographs and the data from ToF-SIMS evidenced that l-leucine particle size has a significant influence on coating properties. The l-leucine particles in the size range of 10 to 110 μm provided a higher level of surface coating coverage of ibuprofen particles resulting in a greater improvement in flowability than the larger l-leucine particles with a size of 260 μm.

In conclusion, mechanofusion is an effective and efficient approach to process ibuprofen powders and all excipient powders in one single step. The resulting processed powders showed satisfactory flowability which indicated mechanofusion has promising potential to facilitate direct compression for industrial production. Unexpectedly, coating of hydrophobic guest particles promoted the dissolution of ibuprofen powders and its corresponding tablets. Multi-exponential modelling revealed such improvements in dissolution performance were attributed to the reduction in agglomerate strength after surface coating.

7.2 Future directions

In our studies, we have proved the mechanofusion process provided sufficient shear and energy to coat pharmaceutical lubricants on the cohesive ibuprofen powders. However, coating lubricants by other dry coating processes such as comilling and high-shear mixing have not been examined. The feasibility and capability of other processes to coat lubricants on cohesive particles are unknown and deserve future examination.

A non-brittle drug, ibuprofen, has been used as a model drug. Other types of pharmaceutical APIs have not been examined such as brittle drug particles (i.e. paracetamol). The size and shape of ibuprofen particles have no apparent change after coating; however, brittle drug particles could be

broken during the high-shear coating processes. Such particle breakage may create broader size distributions and increase the risk of particle segregation during powder mixing. Moreover, coating on different particles may have distinctive effect on compaction behavior. In the present studies, coating with lubricants significantly reduced the tensile strength of formed ibuprofen tablets due to decreased inter-particle bonding. For the brittle drug particles, such effects on tablet tensile strength could be less substantial because new and clean surfaces may be created during the compaction. This area of research deserves further investigation.

Two types of coating materials have been investigated: namely nano-sized silica glidants and boundary lubricants. It is interesting to find both types of coating materials achieved substantial improved powder flow and fluidization for cohesive ibuprofen powders; albeit, their mechanisms of action are different. The mechanisms of reduced inter-particle forces between lubricant-coated particles are likely attributed to decreased surface free energy by modifying surface chemistry, and this is supported by IGC data[1]. But the mechanisms of silica-coating are far more complex. A few theories have been proposed such as contact distance separation and ball-bearing effects[2,3]; however, the true mechanisms are unknown and future studies are warranted to provide fundamental understanding.

All experiments performed in this thesis are laboratory scale. Further work will also include the evaluation of scale-up capability of dry-coating processes in a commercial manufacturing setting.

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