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A Study of Magnesium Stearate Behaviour in Pharmaceutical Blends and Tablets Employing Broadband Acoustic Resonance Dissolution Spectroscopy (BARDS)

Thesis presented by

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for the degree of

Doctor of Philosophy

University College Cork

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2019

To,

My beloved parents

Aruna Peddapatla and Praveen Kumar Peddapatla

This thesis is not a work of fiction. If any experiments resemble scientific theories and concepts, then it's purely intentional.

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DECLARATION

This thesis is submitted to the National University of Ireland, University College Cork by Raghu Peddapatla for examination in the degree of Doctor of Philosophy (Pharmacy – Pharmaceutics). This thesis has not been submitted for any other purpose or degree offered by this or any other university. The material presented in this thesis is entirely the author's own original work, except where duly noted and acknowledged. This thesis was authored by Raghu Peddapatla with supervision and editorial advice from my PhD supervisor, Dr. Abina Crean.

Magnesium stearate continuous feeding experiments in chapter 4 were performed with assistance from Dr. Caroline Blackshields and Dr. Michael Cronin, School of Pharmacy, UCC. BARDS analysis of formulations in Chapter 5 and Chapter 6 were performed with assistance from Dr. Rizwan Ahmed and Dr. Dara Fitzpatrick, School of Chemistry, UCC.

Signature: **Date**

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Oral presentations

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- Raghu V. G. Peddapatla, Rizwan Ahmed, Caroline A. Blackshields, Sean McSweeney, Maria De Sousa Gallagher, Dara Fitzpatrick, Abina M. Crean., Broadband Acoustic Resonance Dissolution Spectroscopy (BARDS) -a novel at-line Process Analytical Technology (PAT) to accesses uniformity of pharmaceutical blends/tablets. *EUPAT 8*, on 3rd and 4th October 2016, Cork, Ireland.

Posters

- Raghu V. G. Peddapatla, Rizwan Ahmed, Caroline A. Blackshields, Sean McSweeney, J. Kruse, Maria De Sousa Gallagher, Dara Fitzpatrick, Abina M. Crean., Broadband Acoustic Resonance Dissolution Spectroscopy (BARDS) -a novel at-line Process Analytical Technology (PAT) to accesses uniformity of pharmaceutical blends/tablets. *PMTC Knowledge day* on August 31st 2017 organised by PMTC at University of Limerick, Limerick, Ireland

- Caroline Blackshields, Raghu Peddapatla, Abina Crean. Magnesium stearate variability and its impact on continuous feeding tablet functionality. *PMTC Knowledge day* on August 31st 2017 organised by PMTC at University of Limerick, Limerick, Ireland

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- Raghu V. G. Peddapatla, Caroline A. Blackshields, Michael F. Cronin and Abina Crean (2016) Behaviour of Magnesium Stearate in Continuous Feeding *American Institute of Chemical Engineers Annual Meeting*, from 13th – 18th November, 2016, San Francisco, USA

- Raghu V. G. Peddapatla, Caroline A. Blackshields, Michael F. Cronin, Maria De Sousa Gallagher, Abina M. Crean., (2016) Characterising magnesium stearate variability-understanding its impact on continuous feeding at *10th World meeting on pharmaceutics, biopharmaceutics, and pharmaceutical technology* on April 7th 2016 organised by APV, Germany at SECC, Glasgow, UK

- Raghu V. G. Peddapatla, Graham E. O'Mahony, Maria De Sousa Gallagher, Abina M. Crean., (2015) Characterisation of magnesium stearate from different suppliers. *PMTC Knowledge day* on August 28th 2015 organised by PMTC at University of Limerick, Limerick, Ireland.

ABSTRACT

Magnesium Stearate (MgSt) is the most commonly used lubricant in pharmaceutical industries. Effects of MgSt on the final product have been extensively studied in batch processing. In recent times pharmaceutical companies have been increasingly interested in continuous processing, where the relative effects of material properties and process parameters on blend behaviour during continuous processing has gained significant attention. It is important to assess the behaviour of materials and it is a challenging feat to monitor behaviour of very cohesive materials like MgSt in continuous processing. The main aims of this thesis were, to investigate the role of MgSt supplier variability during continuous feeding through a loss in weight feeder (LIW) and to investigate the capability of Broadband Acoustic Resonance Dissolution Spectroscopy (BARDS) to discriminate between blends and tablets with variable MgSt distribution.

Initially, the variability among four different grades of MgSt samples from two different suppliers was studied. The variability among the samples was evident (chapter-3) and the effect of this variability on continuous feeding performance of MgSt samples was studied (Chapter-4). Bulk density of the samples dictated the feed factor achieved for the MgSt samples, when fed through K-Tron MT12 feeder (Chapter-4). Higher variability in the feed rate RSD was noticed for the MgSt samples, when fed at lower feed rate of 0.15 kg/hr and for samples (Ligamed MF-2-V and Ligamed MF-2-V-BI) with similar properties. Post feeding characterisation of MgSt samples was performed to identify any effect of feeding on particulate properties. A reduction in particle size due to feeding of the samples was noted and

these samples when included in tablet blends, showed a delayed drug release, which was more prominent in tablets with fed MgSt of Alfa Aesar and Ligamed MF-2-V samples. Ligamed MF-3-V was least effected by feeding and when fed samples were included in formulations a very slight delay in drug release was noted compared to other tablets with other MgSt samples (Chapter-4).

A novel technology, BARDS was employed for the first time to analyse the excipients, tablet blends and tablets (Chapter-5 and Chapter-6). Analysis of unlubricated and lubricated blends using BARDS, clearly discriminated between the blends, resulting inan extended acoustic response for lubricated blends. K-Tron MT12 feeder, was used to feed the unlubricated and lubricated blends at three different feed rates (0.2238 kg/hr, 0.5594 kg/hr and 1.006 kg/hr), anticipating lubricated blend with varied degrees of blend lubrication. When analysed using BARDS, unlubricated blend fed at increasing feed rates showed similar acoustic response, whereas lubricated blend showed extended acoustic response, which was dependent on the feed rate (Chapter-5). Gas elimination rate constant was used to determine the degree of lubrication within blends. The degree of overlubrication was further confirmed by the standard wetting techniques and tabletability of the blends (Chapter-5).

Tablets were produced from unlubricated and lubricated blends at a compression pressure range of 30 MPa to 234 MPa. The influence of compression pressure and tablet properties, on the BARDS acoustic response was investigated in Chapter-6. The yield pressures calculated from the Heckel analysis was 98 MPa and 102 MPa for unlubricated and lubricated tablets. A significant change in the BARDS acoustic

response was noticed for tablets produced above and below yield pressure for both blends. Lubricated tablets produced at higher compression pressures, showed delamination, which was identified by BARDS. Slow gas elimination rate constant was observed for lubricated tablets compared to unlubricated tablets.

ABBREVIATIONS

API	Active Pharmaceutical Ingredient
BARDS	Broadband Acoustic Resonance Dissolution Spectroscopy
BD	Bulk density
BET	Brunauer, Emmett and Teller
CAS	Coarse auger screw
CCS	Coarse concave screw
CI	Carr’s index
CMA	Critical material attribute
CMT	Continuous mixing technology
CSlS	Coarse slotted screen
CSqS	Coarse square screen
D10	Diameter at which 10% of a sample's mass is comprised of smaller particles
D50	Diameter at which 50% of a sample's mass is comprised of smaller particles (median particle size)
D90	Diameter at which 90% of a sample's mass is comprised of smaller particles
DC	Direct compression
DI	Deionized
DSC	Differential scanning calorimeter
DVS	Dynamic vapour sorption
EDX	Energy dispersive X-ray

f_a	Fractional gas volume
FAS	Fine auger screw
FCS	Fine concave screw
FDA	Food and drug administration
ffc	Flow index
FF	Feed factor
f_{min}	Frequency minima
FPS	Frames per second
FSlS	Fine slotted screen
FSqS	Fine square screen
g	Gram
h	Hour
H	Hausner ratio
ICH	International Conference for Harmonisation
kg	Kilogram
kHz	kilo hertz
kN	Kilo Newton
l	Litre
LIBS	Laser induced breakdown spectroscopy
LIW	Loss in weight
MA	Material attribute
MCC	Microcrystalline cellulose

MgSt	Magnesium stearate
min	Minute
ml	Millilitre
mm	Millimetre
µm	micron/micrometer
MPa	Megapascal
N	Newton
N/A	Not applicable
NIR	Near infrared
PAT	Process analytical technology
PCMM	Portable Continuous Miniature and Modular
PFT	Powder flow tester
PSD	Particle size distribution
PXRD	Powder X-ray diffraction
QbD	Quality by design
RH	Relative humidity
RPM	Revolutions per minute
RSD	Relative standard deviation
s	Second
SP	Set point
SSA	Specific surface area
SD	Standard deviation

SEM	Scanning electron microscopy
SIMS	Secondary ion mass spectrometry
SRS	Strain rate sensitivity
TD	Tapped density g/cm3
TGA	Thermogravimetric analysis
TS	Tensile strength
% w/w	% weight/weight
Δt	Time to reach frequency minima
ΔT	Time to reach steady state from frequency minima

Chapter -1

General Introduction

1. General Introduction

Innovative technological solutions which enable the production of highly engineered drug products are needed in establishing robust pharmaceutical manufacturing (Rantanen and Khinast, 2015). Batch processing has been used for decades in the manufacturing of pharmaceutical dosage forms. In recent times pharmaceutical companies have become increasingly interested in continuous processing and production for pharmaceutical solid dosage forms.

In this transition between batch and continuous processing, Quality by Design (QbD) requires a better understanding the effects of variability of excipients on the performance and processing of drug products. Evaluating critical material attributes (CMAs) is envisioned to help in understanding their impact on the processing parameters and final quality of the product. This thesis mainly focuses on studying (a) the impact of variability of a lubricant, magnesium stearate (MgSt), (b) the behaviour of the lubricant during a continuous feeding process and (c) the capability of Broadband Acoustic Resonance Dissolution Spectroscopy (BARDS) to detect differences in the degree of MgSt lubrication in blends and tablets.

This introductory chapter provides an overview of pharmaceutical tablets, their manufacturing process (direct compression), principles of tablet compression, MgSt variability and its CMAs, continuous processing and BARDS.

1.1 Pharmaceutical Tablets

Pharmaceutical tablets are solid dosage forms containing active pharmaceutical ingredients (API) with excipients. Tablets are most commonly manufactured by a compression method (Guillory, 2009). Tablets are the most widely used oral dosage forms (Haritha, 2017; Shabana, 2016). They vary in size, shape, weight, hardness, thickness, disintegration and dissolution characteristics, depending on their intended use, formulation and manufacturing mode. Conventional tablets are used in oral administration of drugs and other tablets, such as sublingual, buccal, or vaginal tablets, are prepared to have features most applicable to their particular route of administration. Figure 1.1 shows different types of tablets and their site of action. The main advantages and disadvantages of pharmaceutical tablets are listed below.

Advantages

- Easy and convenient to use (relatively good patient compliance)
- Economical to manufacture and distribute (De Villiers, 2004)
- High absorption capability following administration (i.e. due to a large surface area for absorption in small intestine) with different absorption pathways (i.e., passive, carrier mediated)
- Delayed release can be achieved through different types of tablet coatings
- Tablets are highly stable when compared to other dosage forms (De Villiers, 2004).

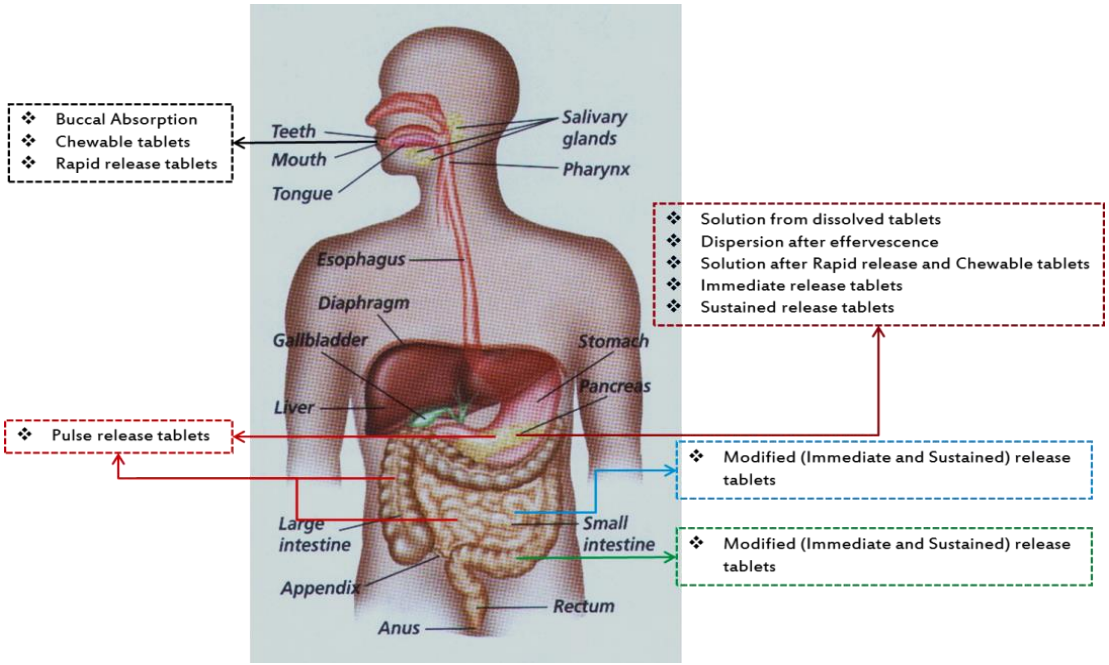


Figure 1.1 Different types of tablets and their site of action (Annotated diagram, Tortora and Derrickson, 2011).

Disadvantages

- Drug absorption from dosage forms in the gastrointestinal tract may be delayed due to presence of food
- Onset of action is slower compared to that of intravenous administration
- Percentage bioavailability can be reduced compared to that of intravenous administration, where it is 100% bioavailability
- Dosage forms with low density and highly amorphous in nature are difficult to compress
- Administration of drugs is not easy in case of children if the drug dose is large
- Chemical and physical properties of the drug make it difficult to overcome compression problems such as capping, lamination, picking and sticking (De Villiers, 2004)

1.1.1 Theory of tablet compression

Consolidation and compression of a solid particulate, solid-gas system, due to applied force is known as compaction (Metin, 1994). Compression involves the reduction in bulk volume as a result of a reduced gaseous phase. As the applied force on the powder increases, the further rearrangement of the particles is inhibited and particle deformation occurs (Patel et al., 2006). During the gaseous phase reduction process, the particles are moved to the closer proximity resulting in bond formation between the particles. At higher compression forces, the mechanical strength of the tablets depends on the consolidation (particle-particle interaction) (Marshall, 1986; Metin, 1994). The various steps involved in powder compaction are shown in Figure 1.2.

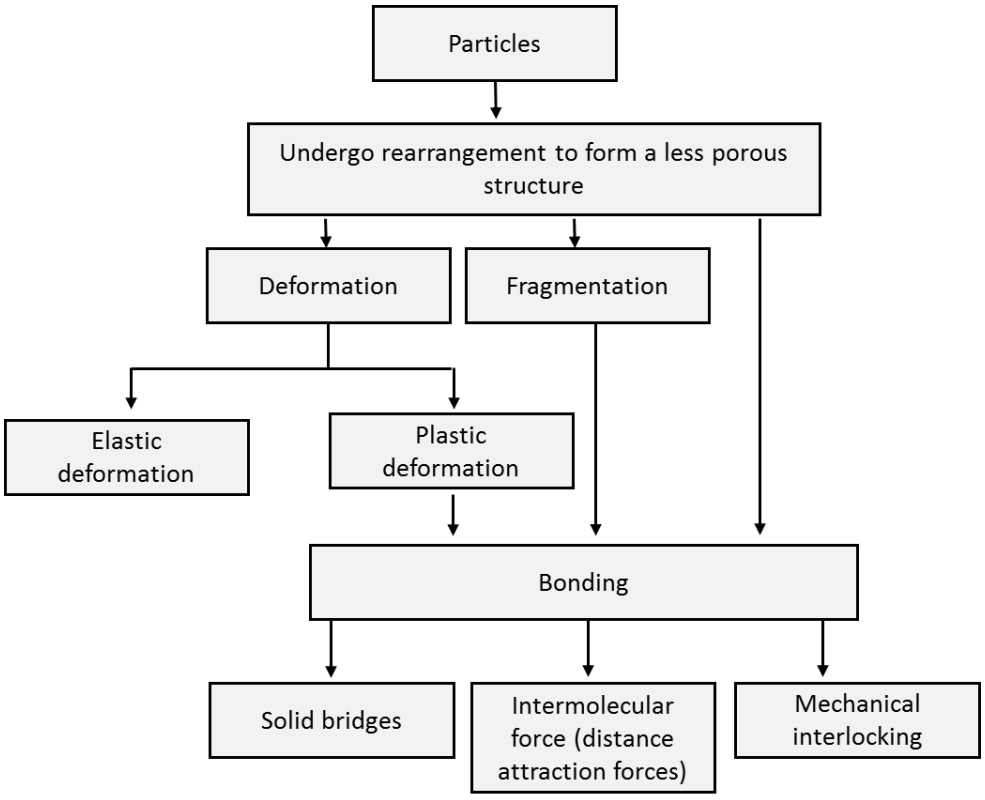


Figure 1.2 Steps involved in compaction process

1.1.1.1 Mechanism of tablet compression and/or compact formation

Upon increase in compression pressure, the further volume reduction of the powder is accomplished by deformation or fragmentation and by forming bonds between the particles (Hiestand et al., 1977; Metin, 1994). Figure 1.3 shows the different deformation mechanisms of powder material under applied compression force.

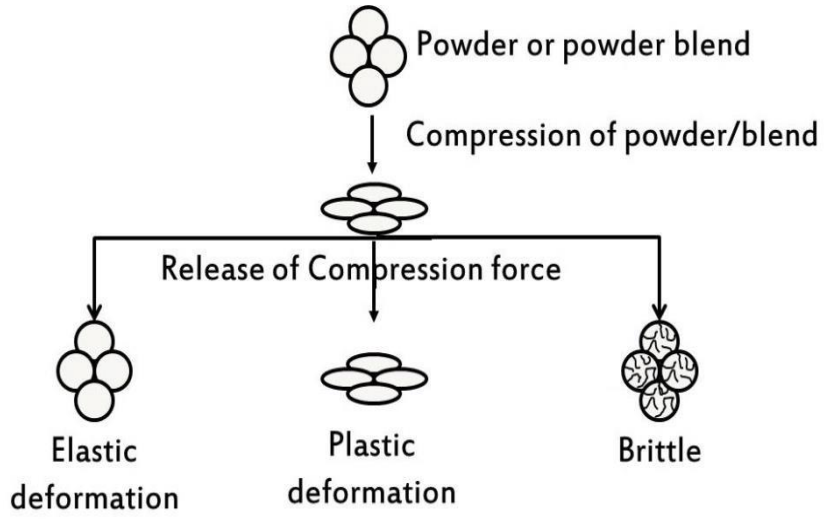


Figure 1.3 Elastic, plastic and brittle deformation mechanisms of powder under applied compression force

Elastic deformation

If the applied pressure (or stress) is released before the deformation reaches the critical value, the particles deform elastically. This type of deformation is reversible and the particles in the compact regain their original shapes when the applied stress is removed as shown in Figure 1.3. An example of such material is starch.

Plastic deformation

If the compression force increased beyond the critical stress value, the particles yield and deform plastically. This type of deformation is irreversible and a permanent change in the shape of the particles will occur (Figure 1.3). An example of such material is microcrystalline cellulose

Many pharmaceutical materials possess a combination of both elastic and plastic properties and are known as viscoelastic materials. Viscoelastic deformation is dependent on both the stress applied and the duration of compression (Aulton and Taylor, 2007). Such materials, whose deformation behaviour is highly dependent on applied stress time and press speed are said to exhibit strain rate sensitivity (SRS) (Katz and Buckner, 2013). Materials such as, maize starch, corn starch, pre-gelatinized corn starch, microcrystalline cellulose and lactose exhibits varying sensitivities to changes in strain rate (Katz and Buckner, 2013; Patel et al., 2006).

Fragmentation

Under the influence of applied stress, after the elastic limit of the material is exceeded, a material will deform plastically or destructively undergo fragmentation forming smaller particles producing newer surfaces for bonding (Figure 1.3) (Patel et al., 2006). The stress value at which the particles start to fragment is called fracture strength. Examples of brittle materials are lactose, sucrose and ascorbic acid.

1.1.1.2 Bonding or Consolidation

Pharmaceutical powders consolidate by reducing the pores or void spaces upon applied compression force, resulting in formation of interparticulate bonds. The type and the intensity of the bonding between the particles during consolidation dictates the mechanical strength of the tablet (Nyström et al., 1993). Consolidation of materials occurs mainly by particle rearrangement, plastic deformation and fragmentation.

Consolidation of materials occurs by different mechanisms such as cold welding, fusion bonding, mechanical bonding, intermolecular force bonding and liquid surface film bonding. When the surface of the particles approaches each other in close proximities, their free surface energies results in strong attractive force leading to formation of bonds by cold welding. During the compression process, there will be a certain amount of frictional heat generated in the powder bed, which results in the melting of the surface area of powder particles. When the melt is solidified, they form a fusion bonding between the particles (Marshall, 1986). During particle deformation, mechanical bonds are formed due to interactions between the particles boundaries. Under compression force, the particles come into close vicinities so that the van der Waal forces interact to consolidate the particles, forming an intermolecular bond (Celik, 2011).

Compaction Triangle

The relationships between compaction pressure, tablet tensile strength and tablet solid fraction are critical to characterise the compaction process of blends. The interaction between these three parameters reflects the relationship between compressibility, tabletability and compactibility as shown in Figure 1.4 and Table 1.1.

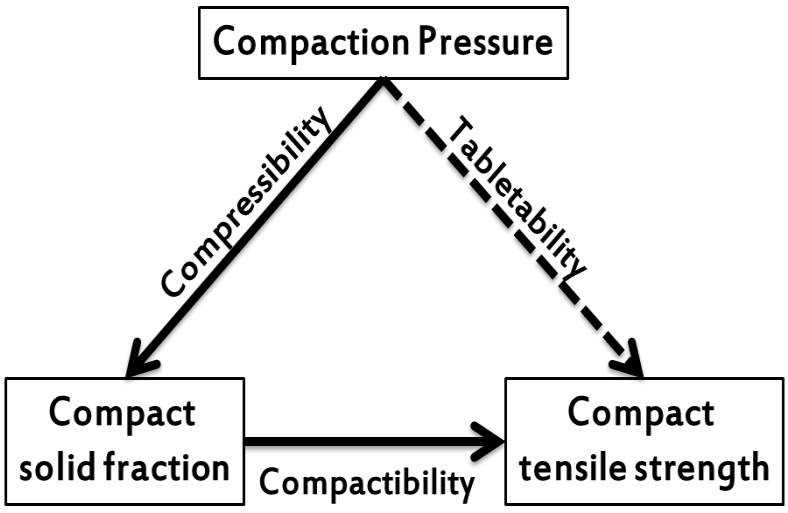


Figure 1.4 Relationships between compaction pressure, solid fraction and tensile strength for a given powder (Tye et al., 2005).

Table 1.1 Definition and relationship between the parameters assessed for compressibility, tabletability and compactibility.

Terminology	Definition	Parameters assessed	References
Compressibility	Ability of powdered material to undergo a reduction in volume upon increase in compression pressure	Tablet porosity or solid fraction Vs. Compression pressure	(Joiris et al., 1998; Patel et al., 2006; Tye et al., 2005)
Tabletability	Ability of a powdered material to be transformed into a tablet of specific strength under applied compression pressure	Tablet tensile strength Vs. Compression pressure	(Joiris et al., 1998; Patel et al., 2006; Tye et al., 2005)
Compactibility	Ability of a powdered material to produce a tablet with sufficient strength under the effect of densification	Tablet tensile strength Vs. Tablet porosity or solid fraction	(Joiris et al., 1998; Patel et al., 2006; Tye et al., 2005)

The relationship between compaction pressure – solid fraction – tensile strength represents the direct cause-effect relationship, whereas the relationship between compression pressure and tablet tensile strength is more indirect (Joiris et al., 1998; Sun and Grant, 2000; Tye et al., 2005). Compactibility is the most important among the three properties, because it reflects the relationship between the two out puts of compression pressure; tablet tensile strength and tablet solid fraction (Tye et al., 2005).

Heckel Model

The Heckel model is used to study the relationship between relative density and applied pressure (Ilkka and Paronen, 1993),

$$\ln[1/1 - D] = KP + A \qquad \text{Equation 1}$$

where D is the relative density of the tablets (g/cm^3), *K* is the slope of a straight line in the Heckel equation, *P* is the compression pressure (MPa), and *A* is a constant. The yield pressure (P_y) is calculated by taking the reciprocal of *K*.

Heckel plots can also be used to differentiate the physical significance of a compression event into three parts as shown in Figure 1.5.

- Region I - Particle rearrangement under low pressures
- Region II - Plastic deformation (or fragmentation or brittle fracture) at medium to high pressure
- Region III – Strain or work hardening at very high pressure.

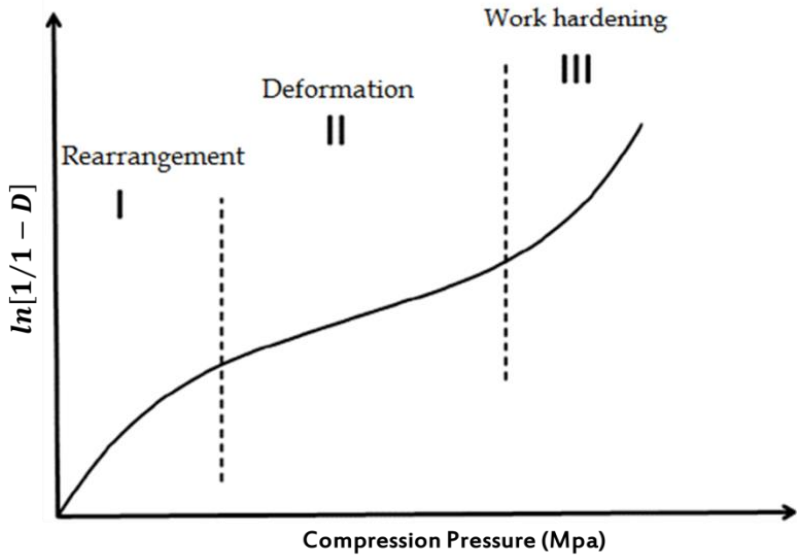


Figure 1.5 Schematic representation of Heckel Plot (Patel et al., 2006)

Compressibility reflects the ability of a material to undergo volume reduction under pressure. A unique feature of the Heckel plot resides in its ability to differentiate between plastic deformation and brittle fracture, by calculating the yield pressure (P_y) from the compaction profile of a specific formulation. If the materials undergo plastic deformation they possess a greater slope than those that undergo brittle fracture, implying the former has a lower yield pressure (Guillory, 2009).

1.1.2 Tablet manufacturing method

The manufacture of tablets is a complex, multi-stage process during which the starting materials change their physical characteristics several times before the final tablet is produced.

1.1.2.1 Direct compression

Direct compression (DC) is the easiest and least complex method to produce tablets, allowing the manufacturer to simply blend the powders in a blender and discharge into the tablet press (hopper) directly followed by compression into tablets (Figure 1.6a). DC is the preferred choice of tablet manufacture in terms of its simplicity, cost and time effectiveness, and elimination of heat and moisture effects (Garg et al., 2015; Jarvinen et al., 2013; Mangal et al., 2015). Excipient selection is critical for DC, as blends should possess excellent flow to ensure a uniform blend and compactibility, which limits its application to only 20% of APIs (Li et al., 2017; Mirani et al., 2011; Vanhoorne et al., 2014). It is the preferred choice of manufacture for tablets containing thermo-labile and moisture sensitive drugs (Jivraj et al., 2000).

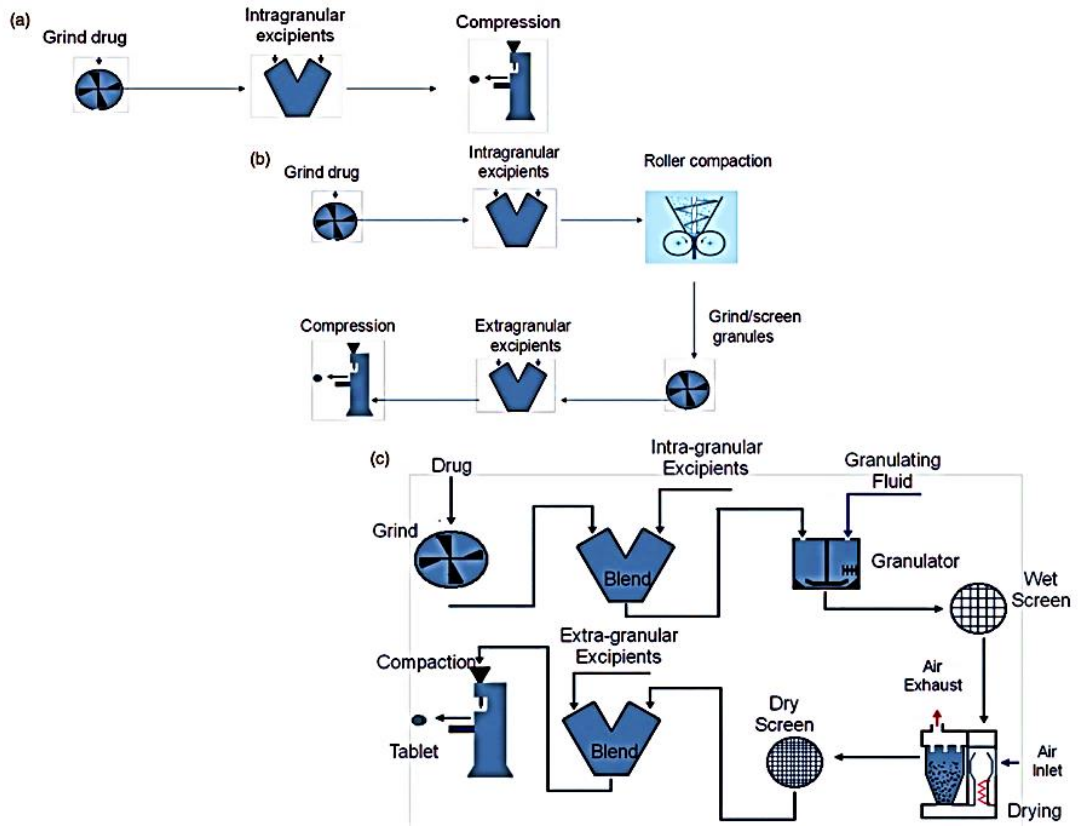


Figure 1.6. Schematic representation of different manufacturing routes for tablets; (a) Direct compression (b) Dry granulation and (c) Wet granulation (Leane et al., 2015).

1.1.2.2 Excipients in direct compressible blend

An excipient is an inert substance that is formulated (blended and compacted) alongside the API (Katdare, 2006). There are a number of reasons why excipients are added to API in dosage forms. Some of these include to increase stability, as bulking agents or fillers or diluents for formulations that have small amounts of API, to facilitate the drug absorption (Borbás et al., 2016), or as solubility enhancers. They may constitute anywhere from 1 to 99% of the total formulation mass (Dave et al., 2015). The international Pharmaceutical Excipients Council (IPEC) has defined a pharmaceutical excipient as follows,

'Any substance other than the active drug or prodrug which has been appropriately evaluated for safety and is included in drug delivery system to either:

- *Aid processing of the system during manufacture, or*
- *Protect, support or enhance stability, bioavailability or patient acceptability, or assist in product identification, or*
- *Enhance any other attribute of the overall safety and effectiveness of the drug product during storage use.'*

Excipients used in DC should possess high bulk density, good flow and good compression properties without affecting the final tablet quality (Jivraj et al., 2000). The PSD of the excipient should be consistent from batch to batch to avoid segregation in blends (Gohel and Jogani, 2005). Particle size of the excipients should be equivalent to the API (Jivraj et al., 2000). Many excipients possess multi-functional properties based on the concentration they are used within the formulation. For example, MCC can be used as anti-adherent at 5-20% w/w, as a disintegrant at 5-15% w/w and as a diluent at 20-90% w/w concentrations (Jivraj et al., 2000).

Some examples of common excipients used in DC are MCC and pregelatinized starch, dibasic calcium phosphate dehydrate, lactose, mannitol and maltose and co-processed excipients such as silicified MCC (98% MCC and 2% colloidal silicon dioxide) (Jivraj et al., 2000).

1.2 Tablet lubrication

Lubrication is one of the key aspects in effective manufacturing of a tablet or capsule dosage form. Lubricants are chemically inert, odourless, and tasteless and act by reducing the friction between the manufacturing equipment and the powder blend to ensure the continuation of pharmaceutical processes such as, blending, roller compaction, tablet manufacturing and capsule filling (Wang et al., 2010). Widely used lubricants in pharmaceutical processes are metallic salts of fatty acids, hydrocarbons & fatty alcohols, fatty acid esters, alkyl sulphate, inorganic materials and polymers. List of commonly used lubricants in pharmaceutical tablet formulations are listed in Table 1.2

Table 1.2 Types of lubricants used in tablet formulations

Category	Examples	Optimum Concentration (%w/w)	References
Metallic salts of fatty acids	MgSt, aluminium stearate, calcium stearate, sodium stearate and zinc stearate	0.25-1	(Wang et al., 2010)
Fatty acids, hydrocarbons and fatty alcohols	Stearic acid	2.5	(Phadke and Collier, 1994)
Fatty acid esters	Sodium stearyl fumerate, sodium lauryl sulphate, dodecanoic acid, sucrose mono laurate	0.12–3	(Wang et al., 2010)
Alkyl sulphate	Magnesium lauryl sulphate, sodium lauryl sulphate	0.5	(Wang et al., 2010)
Inorganic materials	Talc	0.5-5	(Delacourte et al., 1993)

Lubrication efficiency is defined as the capability of lubricant to lubricate the die walls and assist in the ejection of the compressed tablet from the die (Gupta et al., 2009a). It is mainly affected by processing factors such as internal lubrication and external lubrication (Wang et al., 2010). If the lubricant is added and blended with all other ingredients in powder form in a blender, this is called internal lubrication. In internal lubrication, the choice of lubricant is solely dependent on the process. Errors in the lubrication process may affect the tablet properties such as a reduction in breaking force and delay in drug dissolution. To avoid these negative effects on tablet quality, external lubrication systems were developed (Jahn and Steffens, 2005). During external lubrication, only punches and die are lubricated, which is beneficial when the tablet properties are sensitive to lubricant (Jahn and Steffens, 2005; Lindberg, 1970).

1.2.1 Magnesium stearate

MgSt is the most commonly used lubricant, present in more than 2500 pharmaceutical products and a widely used pharmaceutical excipient (Gupta et al., 2009a; Rao et al., 2005). Its chemical name is octadecanoic acid and it exists in form of white powder. It has a chemical formula $Mg(C_{18}H_{35})_2$, which consists of two equivalents of stearate (the anion of stearic acid) and one magnesium cation. The chemical structure of MgSt is shown in Figure 1.7. Commercially available MgSt grades also consists of a large percentage of magnesium palmitate, which may vary from supplier to supplier (Miller et al., 1985).

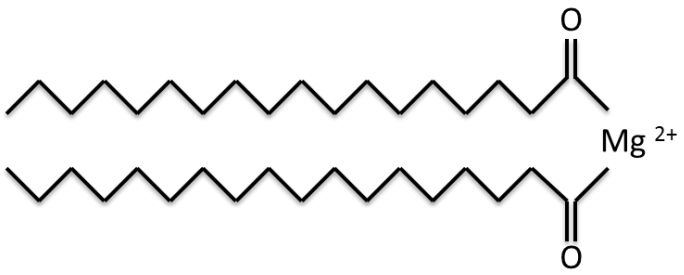


Figure 1.7 Magnesium stearate chemical structure

MgSt is the derivative of bovine or vegetable sources, which constitutes chiefly stearic and palmitic acids (organic fatty acids). Most pharmaceutical companies have transitioned from the use of bovine derived MgSt to vegetable derived MgSt, due to the risks associated with life threatening diseases such as bovine spongiform encephalopathy (BSE) and foot and mouth disease (Gupta et al., 2009a; Hamad et al., 2008). Commonly used sources of MgSt are produced from vegetable sources; palm oil and cotton seed oil after hydrogenation. A fatty acid splitting process takes place in which glycerine and fatty acids are separated. Fatty acids are further refined to yield tallow acid. At this stage, MgSt can be prepared by fusion of tallow acid with magnesium hydroxide or saponification of tallow acid with sodium hydroxide to form sodium tallowate solution. Magnesium sulphate is added to sodium tallowate solution with pH adjustment, dilution with water, wash and dry (Narang et al., 2009). MgSt exists in mono, di and trihydrate forms (Swaminathan and Kildsig, 2001).

The ideal lubricant should be odourless, tasteless, colourless, water soluble, inert and unreactive with other formulation ingredients. MgSt possesses most of these properties with some limitations. Magnesium oxide is a known reactive impurity of

MgSt, which reacts with ibuprofen to form a salt (Kararli et al., 1989). Due to its hydrophobic nature, the negative effects of MgSt on particle bonding, tablet tensile strength, tablet dissolution and disintegration has been widely reported (Li and Wu, 2014; Miller et al., 1985).

1.2.1.1 MgSt variability and its effect on final product quality

Though MgSt is used in low concentrations and inert within a formulation, it plays a major role in dosage form performance. Batch to batch, and source to source variability of MgSt has been reported to impact the tablet quality (Barra and Somma, 1996; Dave et al., 2015). Khan et al., 2008 examined the differences, raw material characteristics and the performance MgSt derived from bovine and vegetable source, in which they reported some minor differences in chemical composition. It was also reported that a dry granulated blend containing MgSt from a bovine source showed higher ejection force than the blend containing MgSt from a vegetable origin (Hamad et al., 2008). Predominately, minute quantities (0.25% to 2-5% w/w) of lubricating agents are added to the pharmaceutical blend to ensure the compression process runs smoothly (Li and Wu, 2014). Concentration and process parameters of the lubricant play a major role in product performance. Many reports show that MgSt when over blended has capacity to form a film over the other excipients of the blend due to its hydrophobic nature (Li and Wu, 2014; Miller et al., 1985). This behaviour affects the product performance by increasing the drug release time (dissolution, disintegration), decreasing tablet hardness and compactibility with MCC, starch and lactose (Lakio et al., 2013; Morin and Briens,

2013; Uzunović and Vranić, 2007). These undesirable effects of MgSt are mainly attributed to its large surface area and hydrophobicity (Rao et al., 2005).

A study by Vezin et al. investigated the effect of lubrication on tablet tensile strength by studying the lubricant mixing time, pre-compression and compression forces when 0.5% w/w MgSt was blended with MCC (Vezin et al., 1983). Tablet properties such as tablet ejection force were reported to be decreased by over blending and tablet hardness was decreased with increase in intensity of blending due to the film formation by the lubricant, which decreased the interparticulate bonding (Johansson and Nicklasson, 1986; Lerk et al., 1977; Mitrevej and Augsburger, 1982; Shah and Mlodozeniec, 1977). Bolhuis et al. determined the effect of MgSt on crushing strength of tablets, when mixed with a MCC/lactose blend, based on the type, size, rotation of the mixer used (Bolhuis et al., 1987). Kikuta et al. proposed the adverse effects of MgSt on tablet hardness, ejection force and disintegration time when over blended (Kikuta and Kitamori, 1994).

1.2.2 Tools to identify MgSt distribution in blends and tablets

Numerous attempts have been made to detect lubricant films in the blends and tablets through indirect techniques. Energy dispersive X-ray microanalysis (EDX) has been applied to detect distribution of MgSt on surfaces (Hussain et al., 1988). Roblot et al. investigated the distribution of MgSt using scanning electron microscopy (SEM) and microanalysis on the surface of lubricated particles. This study results showed the presence of MgSt within the cavities of particles and the surface regularisation due to lubricant (Roblot-Treupel and Puisieux, 1986). The effect of MgSt on potato starch particles was investigated by Abe and Ostuka (Abe

and Otsuka, 2012). They used NIR spectroscopy and identified differences between the distribution of MgSt within a blend, which is blended for 0 and 180 min blending. Hussain et al. used secondary ion mass spectrometry (SIMS) to evaluate the distribution of MgSt and its effect on sodium chloride tablets (Hussain et al., 1990). In this study, they observed that a Na^+/Mg^+ ratio of 521.11 for the uncoated excipient was reduced to 0.94, 1.25 and 13.36 after 2 min. mixing with 0.5% w/w concentration of two commercial and a high purity sample of MgSt. A study by St-Onge et al. quantitatively determined the distribution of MgSt using laser induced breakdown spectroscopy (LIBS), in which when a sample was subjected to laser, a portion of the sample melts producing luminous microplasma (St-Onge et al., 2005). The light emission from the microplasma was analysed through optical emission spectroscopy.

Raman spectroscopy is capable of directly measuring the hydrophobic $–CH_2$ groups present in MgSt, thereby it enables the detection of MgSt concentration of 0.5% w/w in tablet blends and 3% w/w in tablets (Aguirre-Mendez and Romanach, 2007). A study by Henson and Zhang showed that Raman mapping was utilized to analyse the tablets containing low dose (0.5% w/w) API, including the spatial distribution of API and excipients (Henson and Zhang, 2006). Vajna et al.,used Raman imaging (x100 magnification) and captured the distribution of MgSt in imipramine tablets (Vajna et al., 2010). A study by Widjaja and Seah showed that Raman microscopy can be used in combination with band-target entropy minimisation method (advanced multivariate analysis) to map very low concentrations of MgSt in acetaminophen tablets (Widjaja and Seah, 2008). In a study by Zhang et al. no

spectral information of MgSt (2% w/w) in placebo tablets was seen during image analysis following Raman imaging (Zhang et al., 2005).

1.3 Continuous processing

Tablets are the most frequently consumed dosage form, with more than 80% in terms of consumption (Jarvinen et al., 2013). To meet such a high demand pharmaceutical companies are transitioning from batch processing to continuous processing in which pharmaceutical products are manufactured in closed, compact units with a high degree of automation, less manual interference and more operator safety. Continuous processes are highly established in food and chemical industries where the production rates are high (Leuenberger, 2001). Knowledge transfer from those industries to pharmaceutical manufacturing processes would be a major obstacle because in continuous processing the batch size is not well defined and the system is not in equilibrium from the start of the process (Ervasti et al., 2015; Leuenberger, 2001).

A typical continuous process consists of separate feeding systems for API and excipients before the blending step. The blend is then processed into tablets via different modes: dry granulation (blend is roller compacted to form ribbons followed by powdering of ribbons before compression), wet granulation (blend is made into a dump mass by using binder solutions followed by drying and granules milling) and DC (blend is directly compacted into tablets) (Rogers et al., 2013). Figure 1.8 shows a Portable continuous miniature and modular (PCMM) system developed by a consortium of GEA, G-Con and Pfizer for continuous manufacturing of oral solid dosage forms.

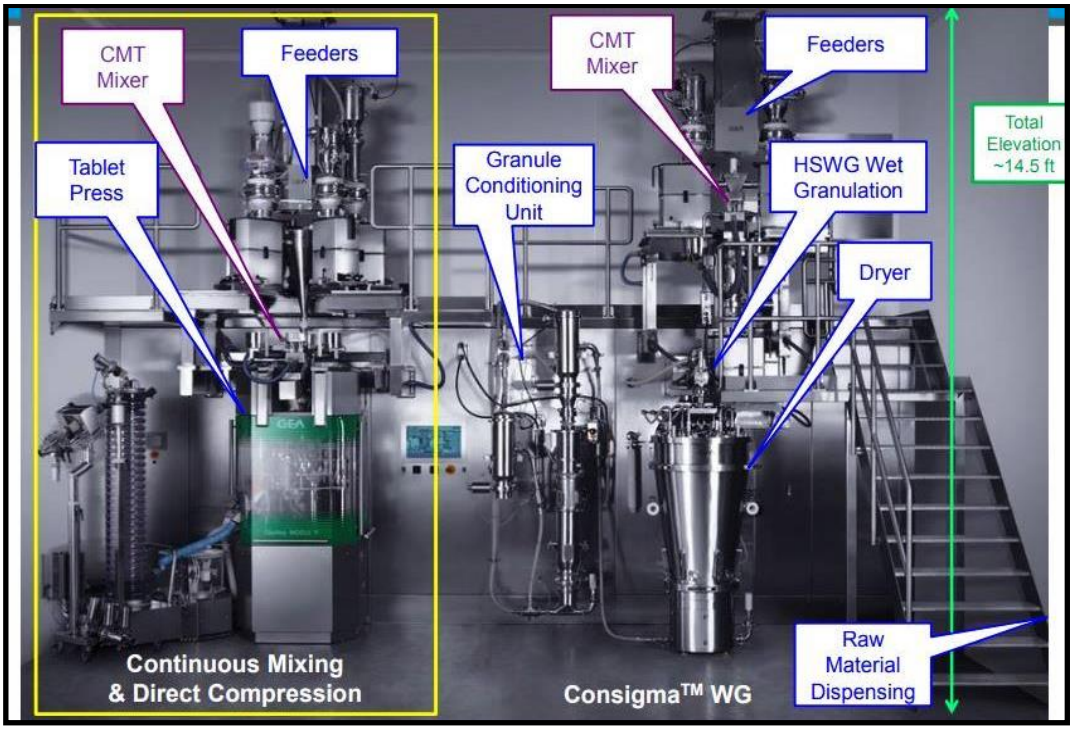


Figure 1.8 PCMM for continuous manufacturing of oral solid dosage forms (Blackwood, 2017)

Handling hydrophobic excipients like MgSt is one of the major challenges in continuous processing, as it could overcoat the powders during blending thereby compromising the tablet quality (Moreton, 2006; Pernenkil and Cooney, 2006). As a result there is a need to understand the lubricant blending behaviour in real time. Process Analytical Technology (PAT) is a system for analysing, designing and controlling manufacturing through timely measurements during the process of manufacturing dosage forms (Hinz, 2006; Järvinen et al., 2013; Vanarase et al., 2010). Pernenkil and Cooney summarised investigations on continuous blenders and feeders. In the publication a range of analytical techniques that can be used in monitoring the continuous blending systems were discussed and the need to design

an efficient feeding system with respect to cohesive powders was highlighted (Pernenkil and Cooney, 2006).

During continuous processing, process and material changes within the manufacturing system should be detected and resolved quickly before it affects the final quality of the finished product. To achieve this level of control during manufacturing, in depth material and process knowledge is essential. Therefore QbD principles are important prerequisite to ensure process control during continuous processing (Crowley and Crean, 2015). Current manufacturing models possess a fixed process were the output is variable. The objective of the continuous process is to transfer to a variable process mode to get a consistent output using QbD principles (Chen et al., 2011).

Currently, there are two approved commercial pharmaceutical products produced via continuous processes on the market. Vertex achieved FDA approval for a continuous process (based on GEA technology) in the manufacture of the cystic fibrosis drug Orkambi in July 2015. In early 2016, Johnson and Johnson in Puerto Rico got the FDA approval, for the first time a change in production method from batch to continuous manufacturing for the production of the protease inhibitor Prezista (Darunavir) used in the treatment of HIV-1 infection (Blackshields and Crean, 2018; Khinast, 2016). GSK built a $50 million continuous manufacturing plant in Singapore involving upstream technology (Palmer, 2015). Hovione entered in an agreement with Vertex to produce continuously in New Jersey as of 2017 (Khinast, 2016). Companies that provide equipment for continuous pharmaceutical drug product manufacturing include GEA, Glatt, Bohle, Continuus.

1.3.1 Continuous feeding

During continuous tablet manufacturing, feeding of raw materials and API into the downstream processing is the foremost important step. Any inconsistencies in powder feeding will be carried forward to the downstream processing resulting in drug products falling outside specification limits and batch failures. Ability to feed powders uninterruptedly, accurately and constantly is regarded as one of the initial critical process parameter in overall tablet manufacturing (Pernenkil and Cooney, 2006; Simonaho et al., 2016). Inconsistencies in feeding of API and other related excipients in a specific formulation at a desired rate will pass inconsistencies onto blending and granulation steps resulting in quality failure of the product (Engisch and Muzzio, 2015; Ervasti et al., 2015). Therefore, continuous manufacturing requires a high degree of process control via in-process testing and improved process understanding to ensure that, the drug products are produced in a controlled manner with reproducible critical quality attributes between batches. To gain an in-depth process understanding, it is essential to identify and understand the physicochemical properties of raw materials involved, which dictate the quality of the final product. During continuous processing, the feeding of powders is accomplished through loss-in-weight (LIW) feeders which control the feedrate gravimetrically (Hopkins, 2006).

Loss-in-weight feeder (LIW)

A LIW feeder consists of three different parts: a volumetric feeder, weighing platform and gravimetric controller (Figure 1.9). The volumetric feeder is located on the top of a weighing platform, which measures the mass of the material that is added into the volumetric feeder. As the material is dispensed through screws, the controller acquires the signal from weighing platform as a function of time. The instantaneous feed rate (-m_{feed}) is determined by equation 2.

$$-m_{feed} = \frac{\Delta w_{feeder}}{\Delta t} \qquad \text{Equation 2}$$

were, Δw_{feeder} is the weight measured by the platform and Δt is the time between two successive measurements.

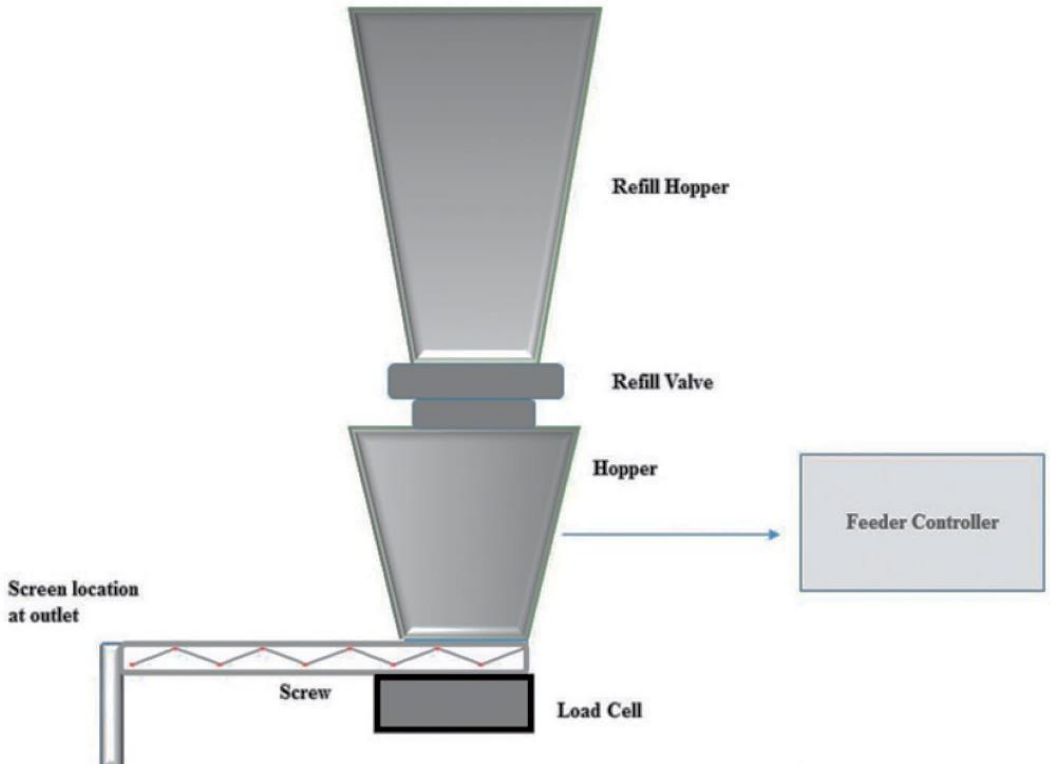


Figure 1.9 Components of loss-in-weight feeder (Blackshields and Crean, 2018).

The LIW feeder can be operated in two different modes: volumetric mode and gravimetric mode. Volumetric feeding is accomplished based on the volumetric parameters of the feeder. For example, a known motor speed is applied to a screw feeder, then theoretically a constant volume of material is discharged through feeder per unit time (Hopkins, 2006). Volumetric feeding consistency is limited due to material density variations, feed rate errors and inconsistencies in material flow (Singh et al., 2015). Whereas the gravimetric feeders have the ability to control the feed rate and optimize the flow variability based on the bulk density changes related to hopper emptying based on loss in weight principle (Engisch and Muzzio, 2012; Hopkins, 2006). The capacity of the feeder is determined by the volumetric study followed by gravimetric analysis to estimate the overall performance (Engisch and Muzzio, 2012).

LIW feeders can be equipped with range of tooling such as screws and screens. Different screws and screens are provided with the feeder to dispense the materials through LIW feeders. Different types of screws are available with different configurations (single or double and spiral or auger), and thread depths. Screens with different designs such as squared screens and slotted screens are also used to dispense cohesive materials. Optimal tooling conditions can be selected based on the powder flow properties (Figure 1.10).

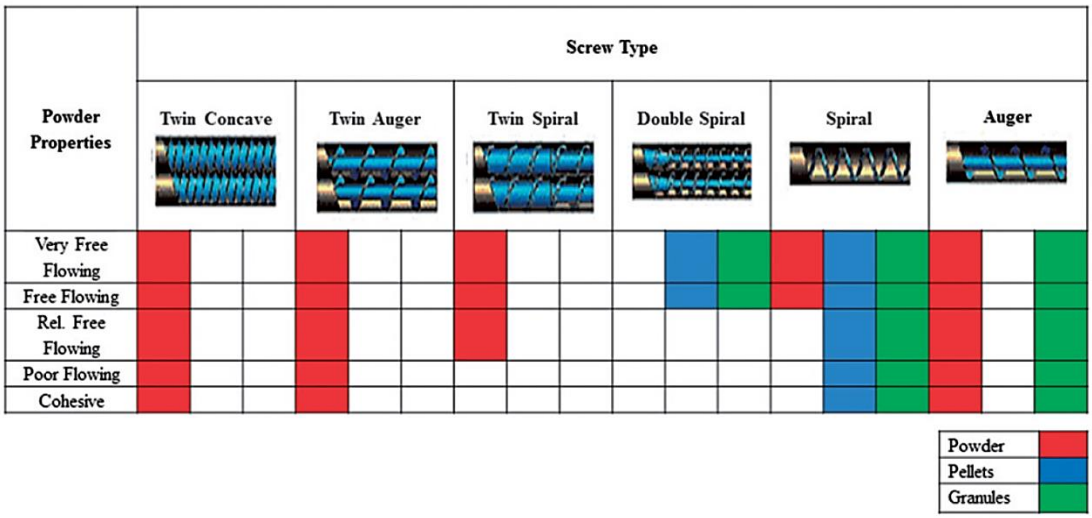


Figure 1.10 Guide to screw selection based on material flow properties (Blackshields and Crean, 2018)

Feeding of cohesive and low density materials such as MgSt is problematic during continuous manufacturing. Due to their high cohesive nature they tend to adhere to the equipment tooling (Engisch and Muzzio, 2015, 2014). The use of concave screws was found to be most suitable for these materials as these possess a 'self-cleaning' function. Cartwright et al. have addressed the importance of accurate powder feeding of low density and poor flowing API, for successful granulation performance in a twin screw extruder by comparing different types of loss in weight feeders (Cartwright et al., 2013). As MgSt is used in very low concentrations in tablet formulations, microfeeders such as K-TRON MT12 or KT20 feeders are used in its feeding. In this thesis we used a KTRON MT12 feeder (detailed in 2.2.5) to assess the feeding behaviour of different grades of MgSt and the effect of the feeding process on tablet blend compression and dissolution.

1.4 Broadband Acoustic Resonance Dissolution Spectroscopy (BARDS)

BARDS is a novel analytical technology developed by Dr. Dara Fitzpatrick in University College Cork, Ireland. BARDS technology is based on the change in acoustic phenomenon observed when material is added into a solvent under resonance (sound). Addition of solid material results in the introduction of gas/air and generation of gas/air bubbles in the solvent, changing the compressibility of the solvent system and reducing the velocity of resonance/sound in the solvent. As the material is wetted and dissolves, the gas/air released is eliminated from the surface of the solvent and the velocity of resonance/sound in the solvent increases. In the BARDS system acoustic resonances are mechanically provoked in the solvent using a stirrer bar and the change in acoustic frequency is monitored after addition of the material (Fitzpatrick et al., 2012a, 2012b).

1.4.1 Working principles of BARDS

The velocity (V) of sound in a medium whether air or liquid medium is determined by equation 3

$$V_{(sound)} = \sqrt{\frac{1}{K.\rho}} \qquad \text{Equation 3}$$

where ρ is mass density (kg m^{-3}) and *K* is compressibility (which is the inverse of bulk modulus) of the medium (Pa^{-1}). The generation of micro bubbles in a liquid decreases the density in a negligible way in comparison to a large increase in compressibility. The net effect is a significant reduction of the sound velocity in the liquid. The following relationship between the fractional bubble volume and the

sound velocity in water was derived by Frank S. Crawford, as given in equation 4 (Crawford, 1982).

$$\frac{v_w}{v} = \sqrt{1 + 1.49 \times 10^4 . f_a} \qquad \text{Equation 4}$$

where v_w and v are velocities of sound (m s^{-1}) in pure and bubble filled water respectively, and f_a is the fractional volume occupied by air bubbles. The factor 1.49×10^4 in the formula was calculated as shown in equation 5.

$$(v_w)^2 \, \rho_w \frac{1}{\gamma p} = 1.49 \times 10^4 \qquad \text{Equation 5}$$

where ρ_w is the density of water, γ is the ratio of specific heats for dry air and p is the atmospheric pressure. Equation 4 is based on the approximation presented originally by Wood *et al*. (Wood, 1955).

BARDS analysis of an induced acoustic excitation of the containing vessel is focused on the lowest variable frequency time course, i.e. fundamental resonance mode of the liquid. The fundamental resonance frequency is determined by the sound velocity in the liquid and the approximate but fixed height of the liquid level, which corresponds to one quarter of its wavelength (Crawford, 1982). The frequency response is described by equation 6.

$$freq = \frac{freq_w}{\sqrt{1+1.49\times10^4 f_a}} \qquad \text{Equation 6}$$

where $freq$ and $freq_w$ are the resonance frequencies of the bubbled filled water and fundamental resonance modes in pure water, respectively. A comprehensive outline of working principles and theory of BARDS was described by Fitzpatrick *et al*., (Fitzpatrick et al., 2012a).

1.4.2 Instrumentation and spectral information

Schematic representation of BARDS spectrometer is shown in Figure 1.11A. The BARDS spectrometer consists of a dissolution vessel equipped with a magnetic stirrer and a micro-phone set above the dissolution vessel, which receives and records the responses from the vessel. There is access at the front of the dissolution vessel and a tripper motor with a weighing boat on it to introduce the sample into the dissolution medium. The glass tumbler containing 25 mL of deionised water is placed on the stirrer plate. The stirrer motor underneath is positioned so as to allow the magnetic stirrer bar to gently tap the inner glass wall, which will act as the source of broadband acoustic excitation. This will induce various acoustic resonances in the glass, liquid and the air column above the liquid. The audio is sampled at a rate of 44.1 kHz. The resonances of the liquid vessel are recorded in a frequency band of 0-20 kHz. A frequency time course is generated as shown in Figure 1.11B.

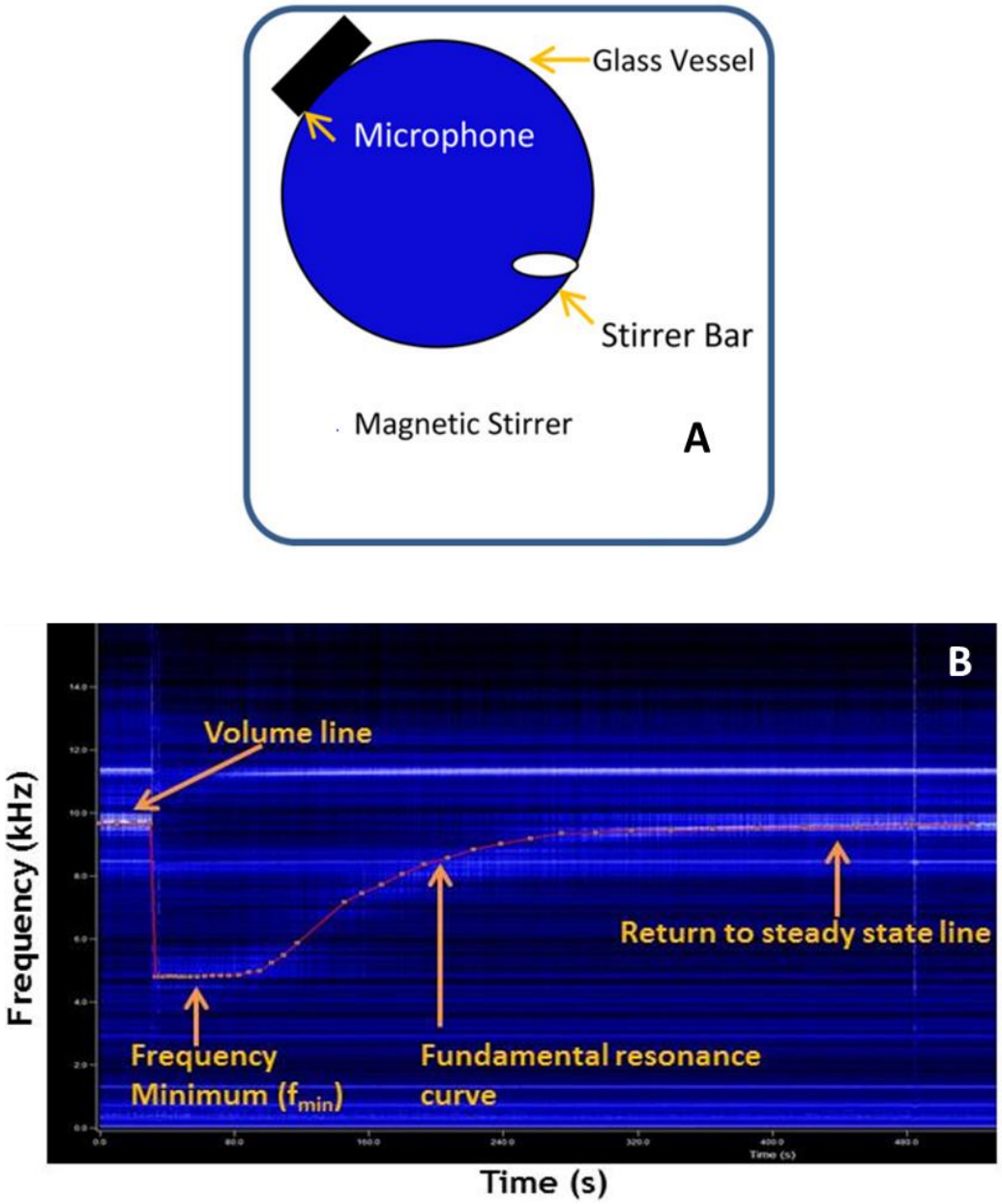


Figure 1.11 (A) Schematic diagram (top view) of the prototype BARDS spectrometer (Fitzpatrick et al., 2012). (B) Representative BARDS raw spectrum of 250 mg MCC in 25 mL water at room temperature.

Acoustic spectra are characterized by specific nomenclature. The first 30 seconds of the spectrum corresponds to steady state resonances of vessel 10 kHz as shown as volume line in Figure 1.11. When the sample is tipped into the deionized water at the 30 second time point, a decrease of resonance frequencies due to a change in the velocity of sound is observed. This resonance line is called the fundamental curve (Fitzpatrick et al., 2012a). The time taken to reach the frequency minimum (f_{min}) is designated as Δt. The time for which the response holds on f_{min} is known as the lag phase. The approximate time taken for the fundamental curve to progress from f_{min} to steady state is designated as ΔT. Lag phase and ΔT are used to identify the degree of wetting of the individual powders, blends and tablets (Evans-Hurson et al., 2016; Fitzpatrick et al., 2014; Peddapatla et al., 2018; Vos et al., 2016).

Fitzpatrick et al., successfully demonstrated the differences between various chemical compounds and commercially available pharmaceutical powder blend products using BARDS (Fitzpatrick et al., 2013, 2012b). Fitzpatrick el al., demonstrated the relationship between gas dissolution, gas oversaturation, outgassing of solutions and BARDS analytical parameters were evaluated for different chemical compounds (sodium chloride, potassium chloride and sodium phosphate) (Fitzpatrick et al., 2013). Another study by Fitzpatrick et al. showed that the BARDS was able to discriminate the distinctive acoustic signature profiles of the enteric coated core spheres of varying size distributions as they dissolved in acoustic media (Fitzpatrick et al., 2014). A study by Evans Hurson et al. showed that the dissolution rate of enteric coated drug spheres depends on pH of the BARDS dissolution media (Evans-Hurson et al., 2016). A recent study by Vos *et al.,* showed

the potential of BARDS to detect the transfer of water into milk protein concentrate (MPC) powder particles with different rehydration characteristics (Vos et al., 2016). Howick et al. recently used BARDS, as a complementary technique to confirm the results seen in USP dissolution studies of a novel ghrelin receptor agonist, FHI-2571 (Howick et al., 2018). BARDS was also used in non-titrimetric determination of acid-base reactions (Ahmed et al., 2018). A study by Alfarsi et al. showed BARDS as a rapid test to determine the enteric coating thickness and integrity of controlled release formulations (Alfarsi et al., 2018).

1.5 Aims and objectives

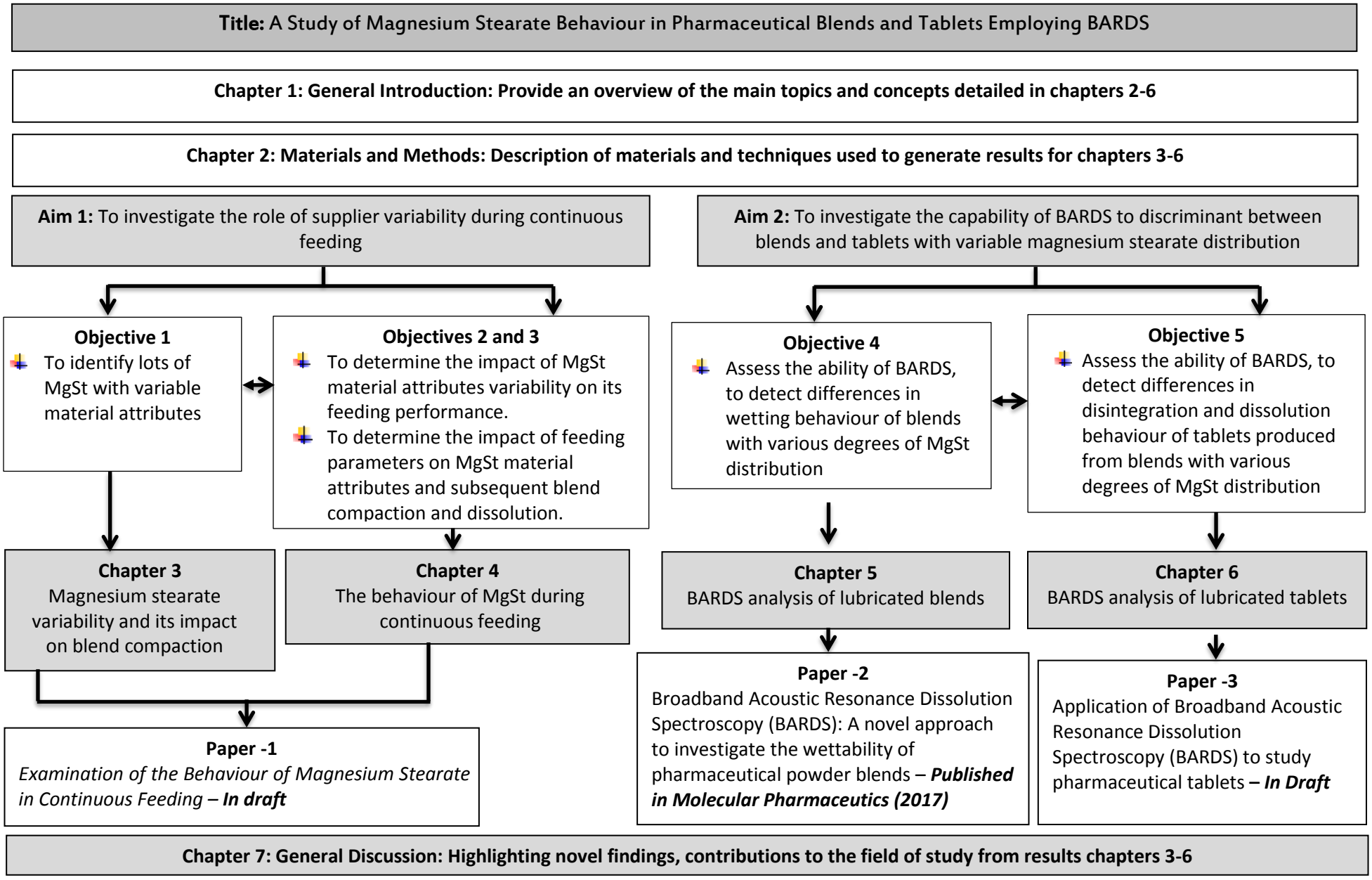
The main aims of this thesis are:

- To investigate the role of MgSt supplier variability during continuous feeding through a loss in weight feeder (LIW)
- To investigate the capability of BARDS to discriminate between blends and tablets with variable MgSt distribution.

To achieve these aims, the following objectives were established, which are further split into four different result chapters

- **Chapter 3**
  - To identify lots of MgSt with variable material attributes (MA).
- **Chapter 4**
  - To determine the impact of MgSt properties on its continuous feeding performance.
  - To determine the impact of feeding parameters on MgSt material attributes and subsequent behaviour during blend compaction and tablet dissolution.
- **Chapter 5**
  - To assess the ability of BARDS, to detect differences in wetting behaviour of blends with variable degrees of MgSt distribution
- **Chapter 6**
  - To assess the ability of BARDS, to detect differences in the behaviour of tablets produced from blends with various degrees of MgSt distribution compressed at different compression pressures.

SCHEMATIC REPRESENTATION OF THESIS



Chapter -2

Materials and Methods

2. Materials and Methods

2.1 Materials

The materials, suppliers and their application in this research are listed in Table 2.1.

Table 2.1 List of materials used in the study. N/A – Not available

Material	Grade	Supplier	Application	Batch number
Metoclopramide Hydrochloride	N/A	Kemprotec Ltd.	Active pharmaceutical ingredient	121119
Paracetamol	N/A	Mallinckrodt	Active pharmaceutical ingredient	6088905V078
MCC	Avicel PH200	FMC Biopolymer	Diluent/Binder	AC60044
MgSt	N/A	Alfa Aesar	Lubricant	10192245
MgSt	MF2V	Peter Greven	Lubricant	C527312
MgSt	MF2VBI	Peter Greven	Lubricant	C307526
MgSt	MF3V	Peter Greven	Lubricant	C526985
Tetramethylamonium hydroxide (25% in Methanol)	N/A	Sigma-Aldrich	HPLC Mobile phase	SHBC0380V
Acetonitrile	Gradient grade	Sigma-Aldrich	HPLC Mobile phase	STBH3004
Water	HPLC grade	Sigma-Aldrich	HPLC Mobile phase	BCBX4373
Glacial acetic acid	Analytical reagent grade	Fisher chemical	pH adjusting agent	1347021
Hydrochloric acid	N/A	Sigma	Dissolution media pH 1.2	N/A

2.2 Methods

2.2.1 Solid state structure analysis

2.2.1.1 Powder X-Ray Diffraction

Principle

When X-rays are diffracted through a sample, crystalline substances act as 3 dimensional diffraction gratings for X-rays with wavelengths similar to the spacing of planes in a crystal lattice. The interaction of the incident rays with sample produces a constructive interference (a diffracted ray) when conditions satisfy Bragg's Law (Ewald, 1962).

Purpose

PXRD was used to analyse the crystallinity of MgSt samples.

Analysis

PXRD patterns for all MgSt samples were obtained using a STOE STADI MP PXRD using a monochromated $K\alpha_1$ ((λ = 1.5406 Å) radiation. Samples were analysed in transmission mode, over 2 theta range 2 to 110 in steps of 0.50 at 1.7 second per step. Analysis was performed in triplicate for each sample.

2.2.1.2 Differential Scanning Calorimetry (DSC)

Principle

In DSC, the energy required to establish a zero-temperature difference between sample and reference material is measured as a function of temperature (Watson and O'Neill, 1962).

Purpose

DSC was performed on MgSt samples to characterise the endothermic transitions, melting behaviour and water present in the samples.

Calibration

Standard samples of sapphire and indium were used in the calibration of the DSC.

Sample preparation

MgSt samples of approximately 2 - 4mg weighed into T_0 aluminium pans and closed.

Analysis

DSC measurements were carried out using a DSC Q1000 (TA instrument). Sample pans were heated from -40^{o}C to 300^{o}C at 10^{o}C/min in a nitrogen atmosphere at a flow rate was 50 ml/min. Data analysis was performed using Universal Analysis 2000 software – V4.5A (TA Instrument). All measurements were performed in triplicate.

2.2.1.3 Thermogravimetric Analysis (TGA)

Principle

During TGA, the mass change of the sample is measured over time in a controlled temperature environment (Gabbott, 2008).

Purpose

TGA was performed on MgSt samples to characterise the type of hydrate and nature of water present in the samples.

Calibration

Calcium oxalate was used in TGA calibration. The resultant thermogram was

matched with the reference thermogram; (1) in the region of water of crystallisation loss at 150^{o}C, (2) carbon monoxide loss as a result of calcium oxalate decomposition at 400^{o}C and (3) further decomposition at 600^{o}C.

Analysis

TGA measurements were carried out using TGA Q500 (TA instrument) with samples of approximately 3 mg weighed into the platinum pan. Samples were heated from ambient temperature to 300^{o}C at a rate of 10^{o}C/min. Nitrogen flow rate was 60 ml/min through the furnace. Data analysis was performed using Universal Analysis 2000 software – V4.5A (TA Instrument). Measurements were performed in triplicate.

2.2.2 Particulate analysis

2.2.2.1 Scanning electron microscopy (SEM)

Principle

High energy beam of electrons are used in a raster scan pattern, which interacts with atoms at various depths within the sample that produces an image (Reimer, 2000).

Purpose

SEM was used to understand the morphology of MgSt samples.

Sample Preparation

Powder was sprinkled on to the carbon tape and excess loose particles were removed with pressurised air. Samples were coated with specific concentration of a

mixture containing gold and palladium (Au:Pd - 80:20) using a sputter coater (Q150T Turbo-Pumped Sputter Coater/Carbon Coater).

Analysis

A Jeol Scanning electron microscope (JSM) – 5510-Jeol Ltd. was used to image the particle morphology at an accelerating voltage of 5kV.

2.2.2.2 Particle Size Distribution (PSD)

Principle

Laser diffraction spectroscopy utilizes diffraction patterns of a laser beam passed through any object (e.g. fluidised powder), to measure the geometrical dimensions of the particles (Lieberman and Schwartz, 1989)**.**

Analysis

Dry powder laser diffraction analysis was performed using Mastersizer, 3000 (Malvern Instruments). Samples were subjected to pressure titrations (increase in air pressure dispersion from 1.5 bar to 3 bar) to study the degree of agglomeration and the ease of de-agglomeration. Samples were placed into the vibratory hopper and the feed rate of the sample was visually monitored until a constant mass flow was achieved. Measurements were taken at 1.5 bar, 2 bar and 3 bar dispersion pressure. The D_{10}, D_{50}, D_{90} are reported for all the samples, n=5.

2.2.2.3 Brunauer–Emmett–Teller-Specific Surface Area Analysis (BET)

Principle

Brunauer–Emmett–Teller theory elucidates the physical adsorption of gas molecules (nitrogen) on solid surface to study the specific surface area (m^2/g) of specific material (Brunauer et al., 1938; Gregg et al., 1967).

Purpose

BET was used to determine the surface area of MgSt samples.

Calibration

The total and external surface areas are measured by evaluating the amount of nitrogen adsorbed, at liquid nitrogen temperature, by carbon black at range of partial pressures of nitrogen. The test results of multipoint and single point surface area of carbon black was found to be 30±0.75 mg^2/g and 29±0.75 mg^2/g, which was in agreement with the calibration standards.

Sample preparation

Samples were degassed at 35^oC for 3 hrs using Micromeritics FlowPrep 060 (Sample Degas System) (Rao et al., 2005).

Analysis

During analysis, liquid nitrogen (N_2) was used to maintain isothermal conditions (-196^{oC}). The specific surface area for MgSt samples was determined from N_2 adsorption isotherms measured using a Micrometrics Gemini VI (Surface Area and Pore Size Analyser). Specific surface area (SSA) was calculated from BET theory (Brunauer et al., 1938). All samples were analysed in triplicates (n=3).

2.2.3 Bulk Properties Analysis

2.2.3.1 True density

Principle

Gas pycnometer work by the employing the Archimedes' principle of fluid (gas) displacement and the technique of gas expansion (Tamari, 2004). True density is measured by purging helium gas into the powder bed.

Purpose

Helium pycnometer was used to determine the true density of MgSt samples and tablet blends.

Analysis

True density of MgSt samples was measured using gas pycnometer (Accu Pyc II 1340 Gas Pycnometer) according to USP <699> Density of Solids. All samples were analysed in triplicates (n=3).

2.2.3.2 Bulk and tapped density

Bulk and tapped density was determined according to USP 35 <616> method using a 100 ml graduated cylinder. The tapped density was measured after tapping with the Tap Density Tester (Erweka). Carr's Index (CI) a measure of the powder bridge strength and stability, was calculated from equation 7. Hausner Ratio (H) a measure of the interparticulate friction, was determined from equation 8. Flowability is rated based on Carr's index and Hausner ratio (Shah et al., 2008).

$$CI = 100 \times \frac{V_B - V_T}{V_B}$$ Equation 7

$$H = \frac{\rho_T}{\rho_B}$$ Equation 8

V_B is bulk volume, V_T is tapped volume, ρ_T is tapped density and ρ_B is bulk density. All measurements were performed in triplicate.

2.2.3.3 Flowability – Brookfield Powder Flow Tester

Principle

The principal of operation of the powder flow tester (PFT) is based on an annular shear cell method, following Jenike silo design principles (Jenike, 1964). A compression lid is driven vertically downward into a powder sample contained in an annular shear cell. The powder sample has a defined volume and the weight of the sample is measured before the start of the test. A calibrated beam load cell is used to control the compaction stress applied to the powder. The annular shear cell is then rotated at a defined speed and the torque resistance of the powder in the shear cell moving against the powder in the stationary lid is measured by a calibrated reaction torque sensor. The geometries of the lid, shear cell, rotational speed of the cell, and the compressive loads applied to the powder all contribute to the calculations which determine the “flowability” of the powder.

Analysis

A Powder Flow Tester (PFT) from Brookfield (Brookfield Engineering Laboratories, Inc.) was used in the analysis of flowability of MgSt powders. The base of the trough was fitted with a perforated screen to prevent powder at the base of the cell from moving during shear. Curved blade was used to level the powder surface in the

trough for flow testing. The mass of the powder was recorded before testing, with the axial distance between the lid and the powder used to calculate changes in the volume of powder during testing. Shear cell kit was attached to the compression plate of the PFT for flow testing. Flow function was a measure of unconfined failure strength versus major principal consolidating stress. Flow index (ffc) for MgSt samples was calculated by inverse slope of flow function. Measurements were performed in triplicate.

2.2.3.4 Dynamic Moisture Sorption-Desorption

Principle

Dynamic vapour sorption (DVS) is a gravimetric technique that measures how quickly and how much of a solvent (water vapour) is absorbed by a sample and measures the change in mass of the sample (Engelund et al., 2010).

Purpose

A DVS Intrinsic (Surface Measurement Systems) was used to study the moisture sorption/desorption behaviour of MgSt samples

Calibration

The calibration was based on the principle that the vapour pressure above a saturated salt solution is constant due to its equilibrium with its surrounding environment at a particular temperature. Calibration was performed individually for the balance, relative humidity generation system and relative humidity probe using lithium chloride.

Analysis

MgSt powder samples were weighed onto a pan and placed in sample chamber. Moisture sorption-desorption studies were carried out using DVS instrument. Initially the sample was dried for 6 hours and equilibrated at 25^{o}C and 10% relative humidity (%RH). Sorption studies were carried out by exposing sample to stepwise humidity change from 0%-90%-0% RH for sorption and desorption cycles. The actual humidity values were controlled to ±0.5% the target and the mass change in samples was recorded every minute.

2.2.3.5 Contact angle

Principle

The contact angle was calculated by fitting the Young equation to the shape of the drop and calculating the slope of the tangent at the liquid–solid–vapour interface line (Pepin et al., 1999).

Calibration

Tensiometer was calibrated for the embedded camera using a metal sphere, to calculate the contact angles of the samples tested.

Sample preparation

For blends: Samples were mounted on double sided adhesive carbon tape adhered to a glass slide and excess powder was removed by tapping the slide.

For tablets: Contact angle measurements were recorded for unlubricated and lubricated tablets with similar porosities to study the wettability.

Analysis

The contact angle of powder samples was measured by the sessile drop method using a Theta-Optical Tensiometer (Biolin Scientific). A water drop of 10 µl volume was dispensed onto the sample surface and video images were captured at a rate of 1.7 frames per second (FPS). Measurements were performed in air under ambient conditions of 22 ± 2°C. All measurements reported are average ± standard deviation, where n = 9.

2.2.4 Formulation Preparation

2.2.4.1 Paracetamol Blends – evaluated in chapter - 4

MCC (50% w/w) and paracetamol (10% w/w) were passed through 450 µm sieve to remove agglomerates and pre-blended in a plastic bag for 1 minute to get an initial blend. To this blend 39.5% w/w MCC is added in a cubic blender with 3.5 litre volume and blended for 30 minutes at 30 rpm using a ERWEKA AR402 drive unit at angle of 90°. Different grades of MgSt were unfed and fed through K-TRON MT12 feeder (described in section 2.2.5) were added separately to the blend at a concentration of 0.5 % w/w and the components were further blended for a further 1 minute. A control formulation without MgSt was also prepared.

2.2.4.2 Metaclopromide HCl Blends – evaluated in chapter – 5

Formulation 1 (unlubricated) and Formulation 2 (lubricated) with a total blend size of 2 kg were blended in a stainless steel double cone blender (DKM) with a 11.9 liter volume operated with ERWEKA AR402 drive unit at angle of 90^0. The blender rotated for 30 minutes at 30 rpm with MCC (90% w/w) and metoclopramide

hydrochloride (10% w/w). MgSt (0.5% w/w) (Alfa Aesar) was added to the formulation 2 and blended for a further 1 minute at 30 rpm. Six blend samples (three samples from the top and three from the bottom of the blender) were collected using a sample thief from each blend and analysed using BARDS (as detailed in section 2.2.6.7).

2.2.5 Continuous Feeding

K-TRON MT12 feeder (Coperion K-TRON) is a loss in weight micro feeder with lower throughputs, which is mainly suitable to feed low amounts of powders. It was supplied with a range of different twin screw designs, for example coarse concave screws (CCS), coarse auger screws (CAS), fine concave screws (FCS), and fine auger screws (FAS). CCS have a self-cleaning function suitable for cohesive materials and the auger screws do not have this self-cleaning ability but have the advantage of higher feeding capacity (Blackshields and Crean, 2018; Engisch and Muzzio, 2014). The feeder was also supplied with different designs of screens, for example coarse square screen (CSqS), fine square screen (FSqS), coarse slotted screen (CSlS) and fine slotted screen (FSlS). In feeder set different screw designs can be paired with different screw designs. The function of the screen is to break up clumps of cohesive powders and can also be used to create back pressure to prevent very free flowing powders from flowing uncontrollably from the feeder (Blackshields and Crean, 2018; Engisch and Muzzio, 2014). An independent catch scale using the K-Sampler Test System was used to collect fed material which was placed directly below the outlet of the feeder to minimise vibrations and was shielded from

external draughts. The material was collected in a stainless steel tray. The feeder and balance was earthed to minimise the formation of electrostatics.

2.2.5.1 Continuous feeding – MgSt

Feeding trials were carried out on a K-Tron MT12 LIW twin screw microfeeder (Coperion K-TRON). CCS and FCS were selected for this study based on the results on a study by Engisch and Muzzio et al., (Engisch and Muzzio, 2015, 2014). For each powder, screw and discharge screen combination, the feed factor (FF) was determined through calibration. The FF is the gravimetric speed equivalent for 100% screw speed with a specific screw and screen setting. It gives an indication of the maximum feed rates that can be achieved for a powder with specific equipment set up. In each case the hopper was filled to approx. 500 g fill weight. Data was recorded every second for 30 minutes with K-Sampler software (COPERION K-TRON).

Establishing feeding conditions for MgSt

The feeding study was conducted in 2 parts. Initially a trial was performed using MgSt from Alfa Aesar as outlined in Table 2.2. The optimum combination of screw and screens (with lowest feed rate %RSD) from the results of this initial study was used in a second experimental trial to compare the feeding behaviour of three other different grades of MgSt.

Table 2.2 Feeding configurations for Alfa Aesar trial.

Exp. No.	Screw Type	Screen Type	Set Point (kg/hr)
1	FCS	FSqS	0.25
2	FCS	FSqS	0.15
3	FCS	CSqS	0.25
4	FCS	CSqS	0.15
5	FCS	No Screen	0.25
6	FCS	No Screen	0.15
7	CCS	FSqS	0.25
8	CCS	FSqS	0.15
9	CCS	CSqS	0.25
10	CCS	CSqS	0.15
11	CCS	No Screen	0.25
12	CCS	No Screen	0.15

2.2.5.2 Continuous feeding – Metoclopramide tablet formulations

This section, part of the feeding studies involved feeding metoclopramide HCl blends. Formulation 1 and formulation 2 (section 2.2.4.2) were each fed with a K-TRON MT-12 twin screw microfeeder to achieve different levels of MgSt distribution within blends in a controlled manner. The feeder set up used in this study comprised of a FCS and FSqS, with the objective of minimizing MgSt build-up on screws. The FF is the theoretical 100% feed rate that can be achieved with a given set of tooling and material and was determined through equipment calibration. The feed rates set points were set at 0.2238 kg/hr, 0.5594 kg/hr and

1.0069 kg/hr for 20%, 50% and 90% of the feed factor for formulation 1. The same feed rates were used for formulation 2 for direct comparison. The hopper was filled to the same level for all feeding runs. The feeder performance was evaluated using an independent catch scale using the K-Sampler Test System. Blend samples were collected and analyzed using BARDS (section 2.2.6.7).

2.2.6 Blend Compaction

2.2.6.1 Tablet compaction

All tablet blend formulations were compressed by DC at target compression forces of 1.5 to 11 kN, which corresponded to compression pressures of 30 to 234 MPa using 8 mm flat faced round punches on a Riva Piccola tablet press (Riva).

2.2.6.2 Tablets Characterisation

Hardness, thickness, diameter and weight of tablets were determined by using SMARTTEST 50 Autotester (Pharmatron). The tablet tensile strength σ (MPa) was calculated using equation 9

$$\sigma = \frac{2H}{\pi t D} \qquad \text{Equation 9}$$

where H is hardness (N), t is tablet overall thickness (mm) and D is tablet diameter (mm). Tablets with and without lubricant were compressed at different compression pressures were analysed using BARDS. Porosity of the tablets was calculated using equation 10

$$Porosity = \frac{Volume\ of\ tablet - Volume\ solid\ fraction\ of\ tablet}{Volume\ of\ tablet} \times 100 \qquad \text{Equation 10}$$

Tablets produced from the unlubricated and lubricated blends are referred to as unlubricated and lubricated tablets respectively.

2.2.6.3 Heckel Analysis

Compressibility of the unlubricated and lubricated blends was examined by fitting the experimental data with Heckel equation 11 (Heckel, 1961) for metoclopramide tablets studied in Chapter 6

$$\ln[1/1-D] = KP + A \qquad \text{Equation 11}$$

where *D* is the relative density of the tablets (g/cm^3), *K* is the slope of straight line in Heckel plot, *P* is the compression pressure (MPa), *A* is the constant. The yield pressure (P_y) was calculated by taking the reciprocal of the Heckel slope *K*.

2.2.6.4 Disintegration Test

The *in vitro* disintegration time was determined for each tablet using a standardised pharmacopoeial disintegration test apparatus, in accordance with USP30 <701> (Hirschfelder, 1930). Disintegration media, water was maintained at 37^{o}C ± 2 ^{o}C. Each tablet was placed in a tube of the apparatus. The tablet was observed for every 1, 3 and 5 minutes until no substantial mass remained in the apparatus. Measurements were performed in triplicate.

2.2.6.5 Dissolution Test

Tablets produced from Paracetamol Blends

The dissolution tests of paracetamol tablets formulated using different MgSt grades (unfed and fed through K-Tron MT12 feeder) was performed using USP paddle apparatus Distek 2100B dissolution tester, at a stirring speed of 50 rpm in deionised

water. Tablets with tensile strength of 2 MPa were chosen across all batches. The dissolution apparatus was maintained at 37°C throughout the experiment. Samples in the amount of 3.5 mL were withdrawn at time points between 1 to 120 min and 24 hours. Dissolution samples were collected for analysis and replaced with an equal volume of fresh dissolution media to maintain a constant total volume. These samples were filtered using a 0.45 µm filter and analysed using UV spectrophotometer at 243 nm. All dissolution tests were performed in triplicate.

Tablets produced from Metoclopramide hydrochloride blends

The dissolution test of metoclopramide hydrochloride tablets was performed using USP paddle apparatus, Distek 2100B dissolution tester, at a stirring speed of 50 rpm in 0.1 N HCl (pH 1.2). Tablets with tensile strength of 2 MPa were chosen across all batches. The dissolution apparatus was maintained at 37°C throughout the experiment. Samples in the amount of 3.5 mL were withdrawn at time points between 1 and 60 min. Dissolution samples were collected for analysis and replaced with an equal volume of fresh dissolution media to maintain a constant total volume. These samples were filtered using a 0.45 µm filter and analysed using HPLC.

Mobile phase for HPLC constituted of 30 parts acetonitrile, 70 parts water and 0.2 part of Tetramethylammoonium hydroxide (TMA) hydroxide. pH of the mobile phase is adjusted to 6.5 with acetic acid. A 10 µl sample is injected through Gemini 5µ C_{18} column (250 x 4.60 mm 5 micron) with a mobile phase pumped at a flow rate of 1 ml/min and the samples were analysed at 215 nm using UV detector. All dissolution tests were performed in triplicate.

2.2.6.6 Wetting time of compacted blends

The wetting time of the blends compacted to a porosity of 23.6% ± 1.3 was measured using the following procedure (Pabari and Ramtoola, 2012; Rajpurohit et al., 2011). Two Whatman filter papers were placed in a petri dish of 10 cm in diameter. A small volume (8 mL) of red amaranth solution was added into the petri dish. A tablet was placed carefully on the surface of the filter paper. The time required for the red solution to reach the upper surface of the tablet was noted as the wetting time. All the measurements were made in triplicate and the average value and standard deviation was determined.

2.2.6.7 BARDS

Principle

BARDS is developed on the basis of the change in acoustic phenomena observed when a solute/tablet is added into a solvent. Addition of a solute results in the introduction of air (gas) into the solvent, which changes the compressibility of the liquid system and reduces the velocity of the sound (resonance) therein. These changes in the compressibility of the liquid are recorded by the BARDS instrument as a frequency-time profile (Fitzpatrick et al., 2012a, 2012b). The BARDS spectrometer records the initial steady state resonances of the vessel containing solvent, deionised water, as a reference for 30 seconds once the stirrer is set in motion. Following addition of the sample (blend or tablet) the pitch of the resonance modes in the deionised water decreased giving rise to a frequency minimum *(f_{min})* by effecting the change in the velocity of the sound, before

gradually returning to steady state over several minutes. Details related to BARDS instrument were provided in section 1.4.2.

Purpose

BARDS was used to study the behaviour of excipients, metoclopramide and metoclopramide tablet blends and tablets in an aqueous environment.

Analysis

The target weight of blend samples and tablets analysed was 250 mg. Samples were added to a glass vial with 25 mL DI water at ambient temperature. Spectra were recorded for a total of 800-1200 seconds which is dictated by the rate of return of the fundamental frequency to steady state. All experiments were performed in duplicate for blends and tablets. An average reading and range of values is presented. The time courses of the observed acoustic profiles were measured under standardized conditions of constant volume, concentration, temperature and stirring rate.

2.2.7 Statistical Analysis

Results are presented as average ± standard deviation (SD) unless otherwise stated. Results were compared using ANOVA (Graphpad, Prism). Drug dissolution profiles were tested by comparing the percentage of drug dissolved at each time point using one-way ANOVA followed by Tukey test. Feeding results are presented as average ± %RSD (%RSD = SD/AVGx100).

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Peddapatla, R. V. G. 2019. A study of magnesium stearate behaviour in pharmaceutical blends and tablets employing Broadband Acoustic Resonance Dissolution Spectroscopy (BARDS). PhD Thesis, University College Cork.

Please note that Chapters 3 & 4 (pp. 57-115) are unavailable due to a restriction requested by the author.

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Chapter 5

Broadband Acoustic Resonance Dissolution Spectroscopy (BARDS) Analysis of Lubricated Blends

(*Results from this chapter were published in Peddapatla et al., 2018.*)

Peddapatla, R.V.G., Ahmed, M.R., Blackshields, C.A., Sousa-Gallagher, M.J., McSweeney, S., Kruse, J., Crean, A.M., Fitzpatrick, D., (2018). Broadband Acoustic Resonance Dissolution Spectroscopy (BARDS): A Novel Approach to Investigate the Wettability of Pharmaceutical Powder Blends. Mol. Pharm. 15, 31–39. https://doi.org/10.1021/acs.molpharmaceut.7b00658

5. BARDS Analysis of Lubricated Blends

5.1 Introduction

In chapter - 4, the continuous feeding behaviour of four grades of MgSt and effect of fed MgSt samples on tablet properties was studied. In this chapter, applicability of BARDS, to detect differences in the distribution of powder lubricant within pharmaceutical powder blends following continuous feeding of blends is investigated.

BARDS works on the principle of frequency change of acoustic resonances that are mechanically provoked in a solvent using a stirrer bar when a solute is added (Fitzpatrick et al., 2012a). The acoustic resonances correlate with the compressibility of the solvent system with or without solute. When a powder is introduced into a solvent it introduces gas (air) into the solvent, which changes the compressibility of the solvent. As the powder is wetted or dissolved, the associated gas is eliminated and solvent compressibility returns to a steady state. The acoustic resonance generated depends on different physical and chemical parameters of the powder that is added into the solvent. BARDS monitors the acoustic profile of solvent as a powder disperses and dissolves. It correlates the acoustic profile of the solvent to changes in the compressibility of the solvent as a result of powder dispersion and dissolution within the solvent (Fitzpatrick et al., 2012a, 2012b).

BARDS Spectrometer consists of a dissolution vessel equipped with a magnetic stirrer and a micro-phone set above the dissolution vessel, which receives and records the responses from the vessel. There is access at the front of the dissolution vessel and a tripper motor with a weighing boat on it to introduce the sample into

the dissolution medium. The glass tumbler containing 25 mL of deionised water is placed on the stirrer plate. The stirrer motor underneath is positioned so as to allow the magnetic stirrer bar to gently tap the inner glass wall, which will act as the source of broadband acoustic excitation. This will induce various acoustic resonances in the glass, liquid and the air column above the liquid. The audio is sampled at a rate of 44.1 kHz. The resonances of the liquid vessel are recorded in a frequency band of 0-20 kHz. A frequency time course is generated as shown in Figure 5.1.

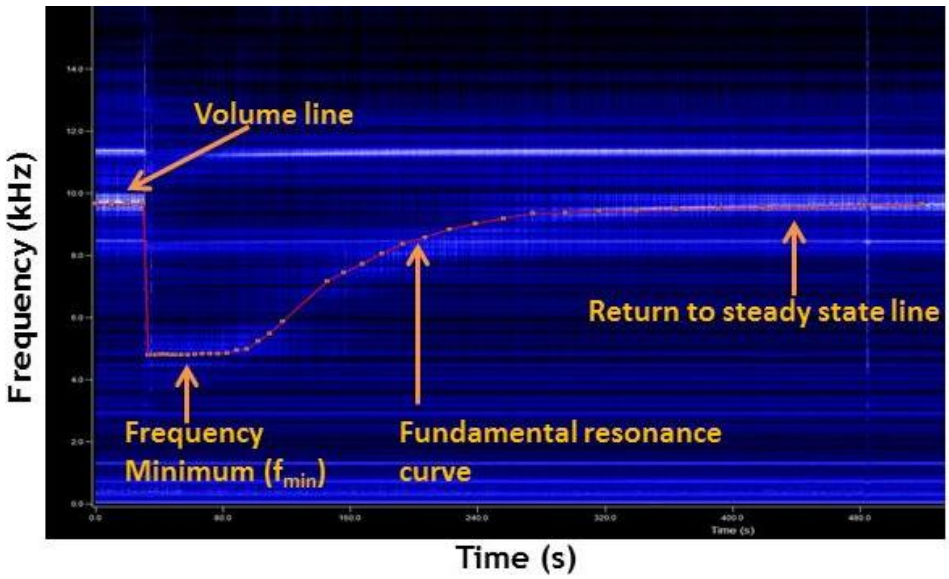


Figure 5.1 Representative BARDS raw spectrum of 250 mg MCC in 25 mL water

Acoustic spectra are characterized by specific nomenclature. The first 30 seconds of the spectrum corresponds to steady state resonances of vessel 10 kHz as shown as volume line in Figure 5.1. When the sample is tipped into the solvent at the 30 second time point, a decrease of resonance frequencies due to a change in the velocity of sound is observed. This resonance line is called the fundamental curve

(Fitzpatrick et al., 2012a). The time taken to reach the frequency minimum (f_{min}) is designated as Δt. The time for which the response maintains f_{min} is known as the lag phase. The approximate time taken for the fundamental curve to progress from f_{min} to steady state is designated as ΔT. In this study all the time points shown are specific to each phase of the acoustic response. Lag phase and ΔT were used to identify the degree of wetting of the individual powders and blends (Evans-Hurson et al., 2016; Fitzpatrick et al., 2014; Vos et al., 2016)

Fitzpatrick et al. successfully demonstrated the differences between various chemical compounds and commercially available pharmaceutical powder blend products using BARDS (Fitzpatrick et al., 2013, 2012b). Another study by Fitzpatrick et al. showed that the BARDS was able to discriminate the distinctive acoustic signature profiles of the enteric coated core spheres of varying size distributions as they dissolve in acoustic media (Fitzpatrick et al., 2014). A study by Evans Hurson et al. showed that the dissolution rate of enteric coated drug spheres depended on the pH of the BARDS dissolution media (Evans-Hurson et al., 2016). A recent study by Vos *et al.* showed the potential of BARDS to detect the transfer of water into milk protein concentrate (MPC) powder particles with different rehydration characteristics (Vos et al., 2016). The work presented in this chapter focuses on demonstrating the ability of BARDS to detect the degree of lubrication within tablet blends. The distribution of a hydrophobic lubricant, such as MgSt, in tablet blends is a critical formulation factor due to its capability to alter the wetting behaviour of MCC and API within the blend and hence drug dissolution.

5.2 Aim and objectives

The main aim of this study was to demonstrate the ability of BARDS to detect differences in lubricant distribution in powder blends. The blends compared using the BARDS technique were of equivalent composition but prepared under a range of processing conditions.

Main objectives of this chapter are:

- To analyse the functionality of BARDS technique to detect the wetting behaviour of MCC, MgSt (Alfa Aesar grade) and a model API (metoclopramide hydrochloride) as single components.
- To determine the ability of BARDS to differentiate between unlubricated and lubricated blends containing MCC, MgSt (Alfa Aesar grade) and a model API (metoclopramide hydrochloride).
- To determine the ability of BARDS to detect differences in the distribution of MgSt within blends generated using K-Tron MT12 LIW feeder.
- To compare the ability of BARDS to detect differences in the blends wetting behaviour of blends with more widely reported wetting measurement techniques such as contact angle and wetting time.

5.3 Results

5.3.1 Preliminary BARDS studies – proof of concept

The BARDS acoustic spectra of the individual blend components, 25 mg of metoclopramide 225 mg of MCC, and 250 mg of a metoclopramide HCl/MCC blend are shown in Figure 5.2. Table 5.1 details the lag times and steady state time points for the individual components and blends. All samples were added to 25 mL water following the period (30 s) of steady state resonance. The acoustic response generated for MgSt upon addition to water was a straight line without any frequency decrease (acoustic spectra shown in supplementary information, Figure – S3). The MgSt sample did not disperse in water due to its hydrophobic nature. Hence no air was introduced into the water and no change in resonance frequency was observed. There was a slight frequency decrease of 0.3 kHz for metoclopramide HCl samples and gradual return to steady state after approx. 50 s as shown in Figure 5.2. The acoustic profile after addition of metoclopramide was a V-shaped response to f_{min}, which is a good indication of trapped and adhered gases that are introduced into the solvent with a fast gas release. The frequency change was sustained only for a short period of approx. 15 s due to the high solubility and rapid dissolution of metoclopramide hydrochloride in water.

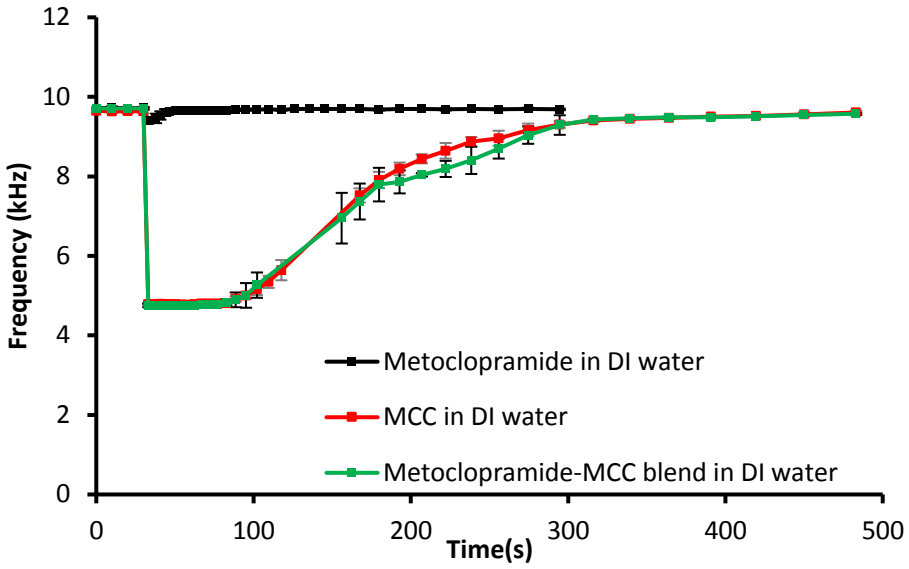


Figure 5.2 BARDS acoustic response of Metoclopramide (25mg), MCC (225 mg) and blend of metoclopramide (10% w/w) and MCC (90% w/w) (250 mg) in 25 mL deionised water (DI). Average values shown, n =3, y error bars indicate standard deviation

In contrast, the frequency of MCC and metoclopramide/MCC blend was decreased to approx. 5 kHz and sustained a lag time up to approx. 80 s after sample addition was observed. Both the spectra gradually returned to steady state (ΔT) at approx. 310 s (Table 5.1), with a slight deflection of acoustic response for metoclopramide/MCC blend in the range of 190 – 270 s (Figure 5.2). The U-shaped acoustic response of the MCC and metoclopramide/MCC blend indicates the gas oversaturation in the solvent (Fitzpatrick et al., 2012a). The greater frequency decrease observed for MCC, compared to metoclopramide, relates to the larger sample weight and hence the volume of entrained gas introduced. MCC does not dissolve in water but hydrates in water resulting in the prolonged lag time.

Figure 5.3 shows the BARDS profiles of metoclopramide/MCC lubricated and unlubricated blends after varied degrees of manual rotation. The blend frequency decreases to a f_{min} of approx. 5 kHz for all blends. The frequency is sustained at f_{min} for approx. 120 s and 145 s for the lubricated blends prepared at 5 rotations and 100 rotations respectively, which is designated as lag phase (start of f_{min} to finish of f_{min}). This differentiates the effect of lubricant presence and blending time on the lag time. In contrast the unlubricated blend lag phase was sustained for approx. 80 s. Similarly the time taken to return to steady state resonance (ΔT) was approx. 600 s for the lubricated blend rotated 5 times and approx. 800 s for 100 times rotated blend Figure 5.3 and Table 5.1. The notable shift in the lag times and the time taken to return to steady state was attributed to the increased coating of metoclopramide and MCC with hydrophobic MgSt which delayed the wetting of the blend and hence displacement of gas from powder to water phase.

This phenomenon of powder lubricants retarding the wetting and dissolution of blend components is a commonly observed effect of MgSt when over blended (Duong et al., 2017; Gupta et al., 2009a; Rao et al., 2005). The end of lag time signifies the starting point of wetting of blends, which is similar to the results obtained by Hurson *et al.,* on enteric coated drug spheres (Evans-Hurson et al., 2016). Lag time can be potentially used to indicate the coating thickness or the degree of lubrication of the blends by hydrophobic MgSt and the start of return to steady state frequency can be related to the wetting of blend and outgassing of the oversaturated gases. The results of this preliminary proof of concept study demonstrated the potential of BARDS to detect differences in the wetting of blends due to the presence of MgSt and the degree of blending of MgSt.

Table 5.1 BARDS profile lag times and time to return to steady state for metoclopramide, MCC, blend of metoclopramide – MCC, and blend of metoclopramide-MCC-MgSt prepared by manual rotation.

Components	Approx. Lag time (s)	Approx. Time to return to steady state (s)
Metoclopramide	Not observed	50
MCC	80	310
Metoclopramide/MCC (5 rotations)	80	310
Metoclopramide/MCC/MgSt (5 rotations)	120	600
Metoclopramide/MCC/MgSt (100 rotations)	145	800

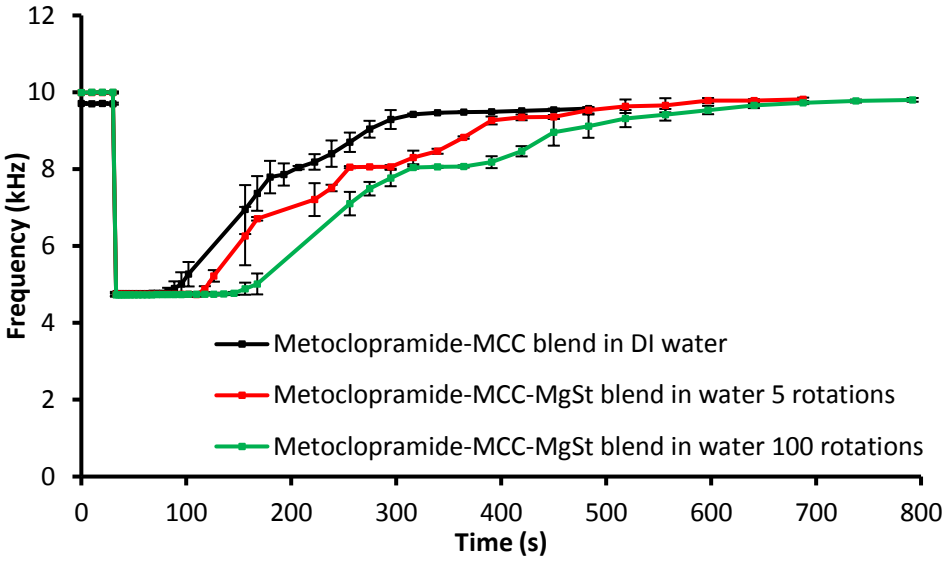


Figure 5.3 BARDS acoustic response for blends manually blended in 25 mL deionised water. Metoclopramide 10% w/w and MCC 90% w/w (250mg) after 5 rotations, metoclopramide 10% w/w, MCC 89.5% w/w and 0.5% w/w MgSt (250mg) after 5 rotations and after 100 rotations. Average values shown, n =3, y error bars indicate standard deviation.

5.3.2 Comparison of unlubricated and lubricated formulations by BARDS

Following on from the preliminary proof of concept study, the ability of BARDS to detect differences in the wetting behavior of lubricated and unlubricated blends prepared using a lab scale double cone blender and subsequently fed at different feed rates through a LIW screw feeder (K-Tron MT12) was assessed.

5.3.2.1 BARDS analysis of blends prior to feeding

Figure 5.4 shows the BARDS profiles of unlubricated and lubricated formulations, prior to feeding collected from blender immediately after blending, from six different locations. Following addition of the sample to water there was a decrease to a plateau frequency of approx. 5 kHz after 30 s. Unlubricated blend (API/MCC) showed a lag time of approx. 80s and lubricated blend (API/MCC/MgSt) showed a lag time of approx. 100 s. The lag phase indicates that the rate of gas evolution in the water phase is equal to the rate of gas loss from the water phase. The disappearance of gas from the solvent after f_{min} proceeded more slowly for lubricated blend, which resulted in notable extension in time of approx. 640 s for acoustic resonance to return to steady state, whereas for unlubricated blend it was found to be approx. 450 s. The differences between acoustic responses between the two blend formulations as shown in Figure 5.3 and Figure 5.4, is mainly due to the volume of gas introduced into the solvent after blend sample addition, the amount of gas generated, the rate of gas released from the blend and the rate of gas eliminated from the solvent during the wetting of unlubricated and lubricated formulations. All these parameters were examined in depth by determining the changes in gas volumes using equation 6.

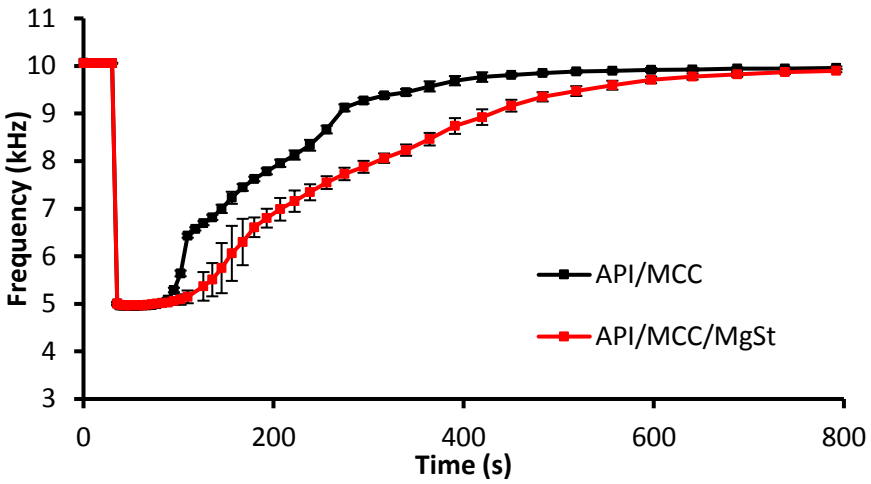


Figure 5.4 BARDS acoustic response for blends prepared using lab scale blender in 25 mL deionised water. Unlubricated blend (metoclopramide 10% w/w and MCC 90% w/w) (250mg) and lubricated blend (metoclopramide 10% w/w, MCC 89.5% w/w and 0.5% w/w MgSt) (250mg). Samples analysed were collected from 6 different locations in the blender and analysed in duplicate. Average values shown, n =12, y error bars indicate standard deviation.

Equation 6 was applied to BARDS frequency data to analyze the fractional gas volume (fa) occupied by compressible gas following the introduction of powder samples and during the wetting of the formulations. Both formulations quickly immersed when added into the water and reached a constant gas volume which lasted for a lag phase of approx. 45 s and 65 s for unlubricated and lubricated formulations respectively, Figure 5.5A. The curves represent an evolution and gas release from the water surface. No difference in the gas evolution following the addition of sample into the water was noted between the formulations. However, the release of gas from the water following sample addition was extended in the lubricated blend data.

Figure 5.5A is plotted in a logarithmic scale as shown in Figure 5.5B. The gas or air elimination rate constant (k) for the compressible gas in solution was assumed to be a first order process and was determined from the descending slope of the log plots shown in Figure 5.5B

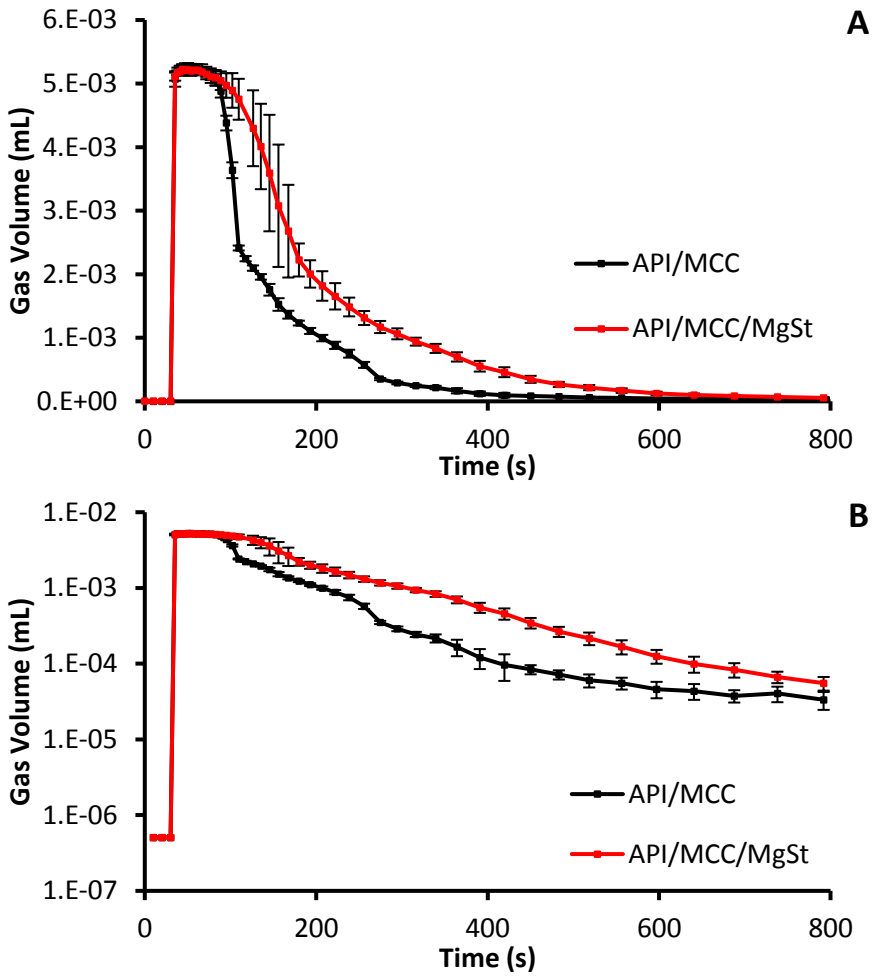


Figure 5.5 Gas volume plots for blends prepared using lab scale blender in 25 mL deionised water. (A) Plot of calculated gas volume versus time and (B) Plot of log of calculated gas volume versus time for unlubricated (API/MCC) and lubricated blends (API/MCC/MgSt). Samples analysed were collected from 6 different locations in the blender and analysed in duplicate. Average values shown, n =12, y error bars indicate standard deviation.

Table 5.2 shows the gas elimination rate constants (*k)* and the time range for which this constant is calculated. The gas elimination rate constants calculated for all samples of unlubricated blend were consistent ($k \approx 1 \times 10^{-5}$ s^{-1}), whereas the presence of MgSt in lubricated formulation resulted in a reduction in gas elimination constant ($k \approx 7 – 8 \times 10^{-6}$ s^{-1}), and greater variability between samples.

This result is generally in agreement with the previous study on milk protein powder concentrates (Vos et al., 2016). The slow gas generation of lubricated blends strongly inhibits hydration of the powder. In order to validate this hypothesis, these blends were fed through K-Tron MT12 loss in weight feeder, to obtain blends of varying degrees of lubrication to determine the influence of increased distribution of MgSt in blends on the BARDS acoustic response. These blends were also analysed for tabletability, wetting time and contact angle measurements which are more recognized methods to determine degree of lubrication on blend hydration (Pabari and Ramtoola, 2012; Rajpurohit et al., 2011).

Table 5.2 Calculated gas volume elimination rate constant (*k*) and time ranges used for the calculation of the rate constant for samples of unlubricated and lubricated blend formulations. Samples were taken from various locations in the lab scale blender.

Blend Location	**Unlubricated blend**		**Lubricated blend**	
	Time range (s)	***k* (s^{-1})**	**Time range (s)**	***k* (s^{-1})**
Top – 1	95-390	1.E-05	109-556	8.E-06
Top – 2	95-390	1.E-05	167-556	7.E-06
Top – 3	95-390	1.E-05	109-556	8.E-06
Bottom – 1	95-390	1.E-05	109-556	8.E-06
Bottom – 2	95-390	1.E-05	156-556	7.E-06
Bottom – 3	95-390	1.E-05	126-556	8.E-06

5.3.2.2 Feeding of blends through K-Tron MT12 feeder

Unlubricated and lubricated blends were each fed through a K-TRON MT-12 twin screw micro-feeder to achieve different levels of MgSt distribution within blends in a controlled manner. The feeder set up used in this study comprised of a FCS and FSqS, with the objective of minimizing MgSt build-up on screws, feeding rate of blends and promote over-lubrication of blends. The FF is the theoretical 100% feed rate that can be achieved with a given set of tooling and material and was determined through equipment calibration. The FF determined for both blends was 1.11 kg/hr for unlubricated blend and 2.41 kg/hr for lubricated blend. The feed rate set points were set for 20% (0.2238 kg/hr), 50% (0.5594 kg/hr) and 90% (1.006kg/hr) of the feed factor for the unlubricated blend. The same feed rates were used for lubricated blend for direct comparison. Figure 5.6 shows image of

two blends at three different feed rates. Figure 5.6A shows feeding behaviour of unlubricated blend and lubricated blend through FCS. It was visually evident that some of the powder adhered to the feeder outlet while feeding lubricated blend, this is may be due to the electrostatic properties of MgSt. Figure 5.6B shows the post feeding assessment of screws, in which unlubricated blend is adhered within screws and no such behaviour is noticed with lubricated blend.

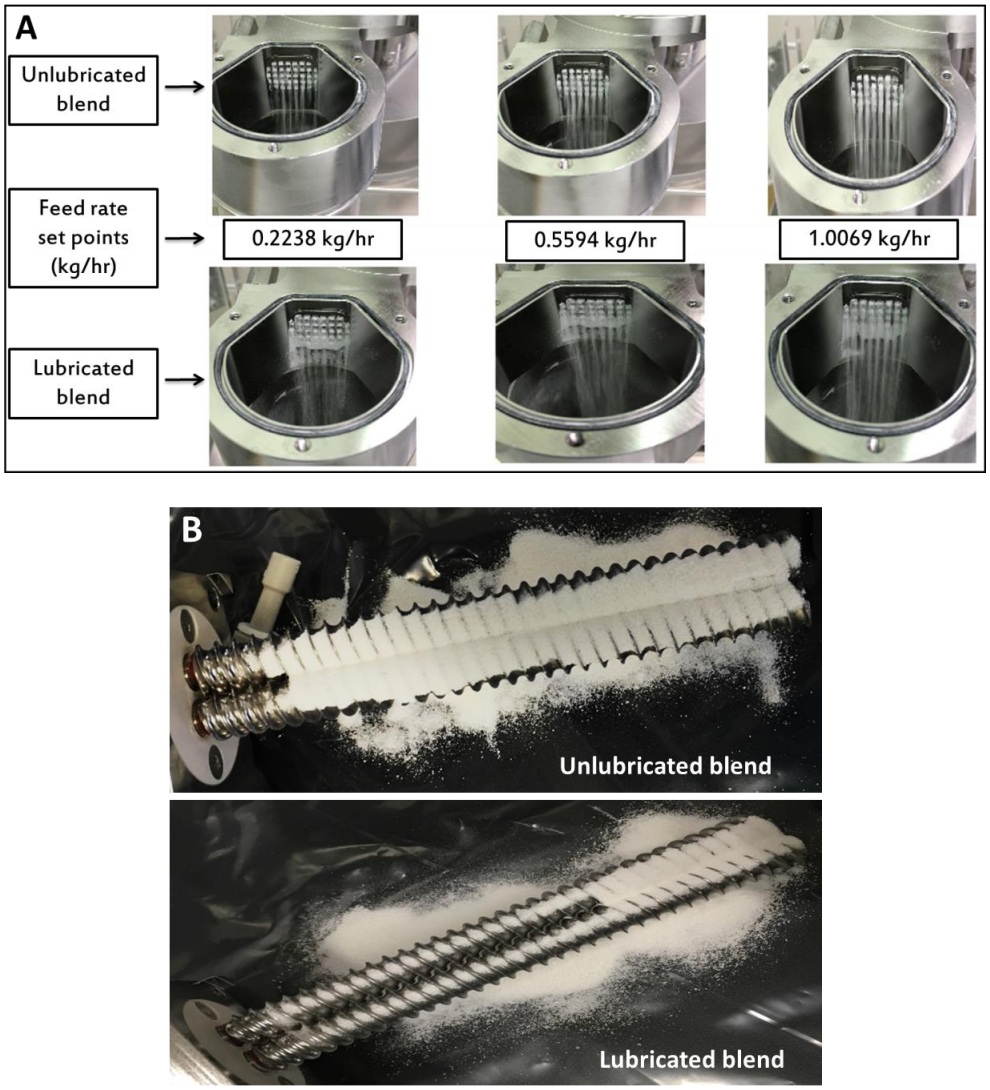


Figure 5.6 Feeding of unlubricated and lubricated blend (A) Image of blends during feeding at three different feed rates and (B) Post feeding assessment of screws.

Figure 5.7 shows the performance data of K-TRON MT12 feeder for unlubricated and lubricated blends. As the feed rate increased, the feeder performance (% RSD weight) decreased for both blends. The lubricated blend demonstrated lower %RSD compared to unlubricated blend at three feed rates. For both blend formulations, lowest feed rate of 0.2238 kg/hr showed highest %RSD. Drive command (%) of the feeder is the value that indicates how much of the controller output is used or required to deliver indicated actual mass flow value (feed rate set point). Drive command during feeding of unlubricated blend at three different feed rates was found to be approx. 20, 50 and 90%. The drive command halved (10%, 25% and 45%) during the feeding of lubricated blend. This may be due to the effect of lubricant on screws. The ability of MgSt to reduce the shear stress in contact with metal objects was observed in the Brookfield flow results of chapter 3. These blends fed through the feeder are further compacted into tablets and tabletability was analysed to see the effect of lubricant in these blends on tablets due to feeding.

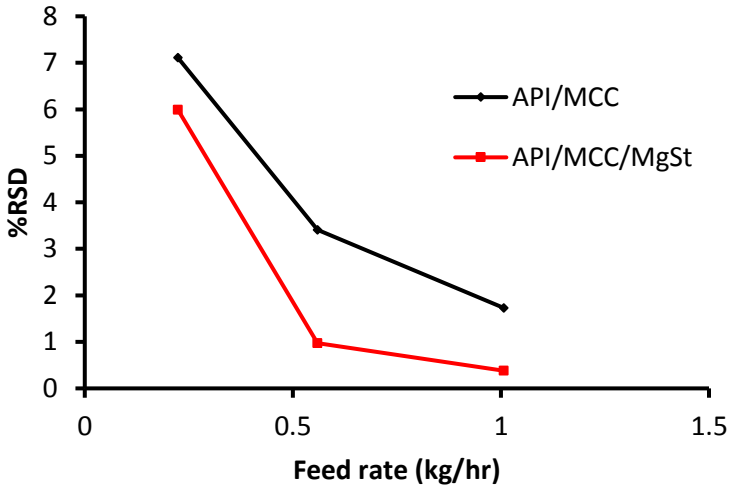


Figure 5.7 Feeding performance of unlubricated blend (API/MCC) and lubricated blends (API/MCC/MgSt) at different feed rates through K-Tron MT12 feeder.

5.3.2.3 Tabletability of blends fed through K-Tron MT12 feeder

Tabletability profiles of unlubricated and lubricated blends fed through MT-12 feeder are shown in Figure 5.8. Tabletability is represented by a plot of tensile strength versus compaction pressure. As the compression pressure increased tablet tensile strength increased. The unlubricated blend fed at three different feed rates did not show any significant effect on tabletability. However, lubricated blend was more affected by feeding. As the feed rate was increased, the tabletability decreased resulting in a reduction in tablet hardness (Figure 5.8). This data demonstrates that the feeding affected the distribution of MgSt in the lubricated blend which resulted in a lower tensile strength of the tablets from this blend as the feed rate increased. This behaviour indicates overlubrication.

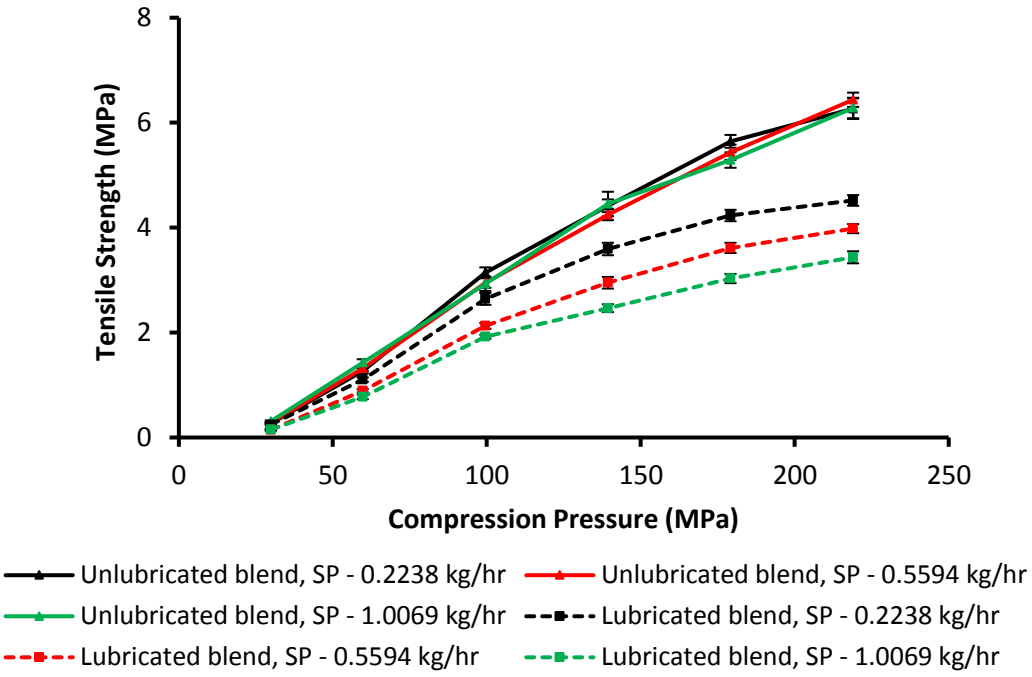


Figure 5.8 Tabletability profiles of unlubricated and lubricated blend fed at different feed rates and compacted at a range of compression pressures. Average values shown, n=20 at each compression pressure, y error bars indicate standard deviation. (Feed rate SP = Set point).

5.3.2.4 BARDS analysis of blends following to feeding

The overlubrication of the lubricated blends was confirmed by analysing the tabletability of the fed blends (Figure 5.8). The subsequent objective was to demonstrate differences in the wetting behaviour of lubricated blends with equivalent lubricant composition but different degrees of lubricant distribution obtained using a feeding system. The hypothesis of this chapter was that the BARDS technique could detect differences in blend wetting behaviour related to the degree of lubrication.

The unlubricated blend was unaffected by feed rate when analysed by BARDS as shown in Figure 5.9A. The lag phase lasted for approx. 90 s and the acoustic response reached steady state after approx. 420s as shown in Figure 5.9A. In contrast, lubricated blend formulation showed a slight extension in the lag phase as the feed rate increased and all the lubricated blends returned to steady state after approx. 790 s. as shown in Figure 5.9B. The extension in lag phase was attributed to increased coating of the MCC and drug particles with MgSt due to increased feeding rate and hence prolonged wetting as discussed previously.

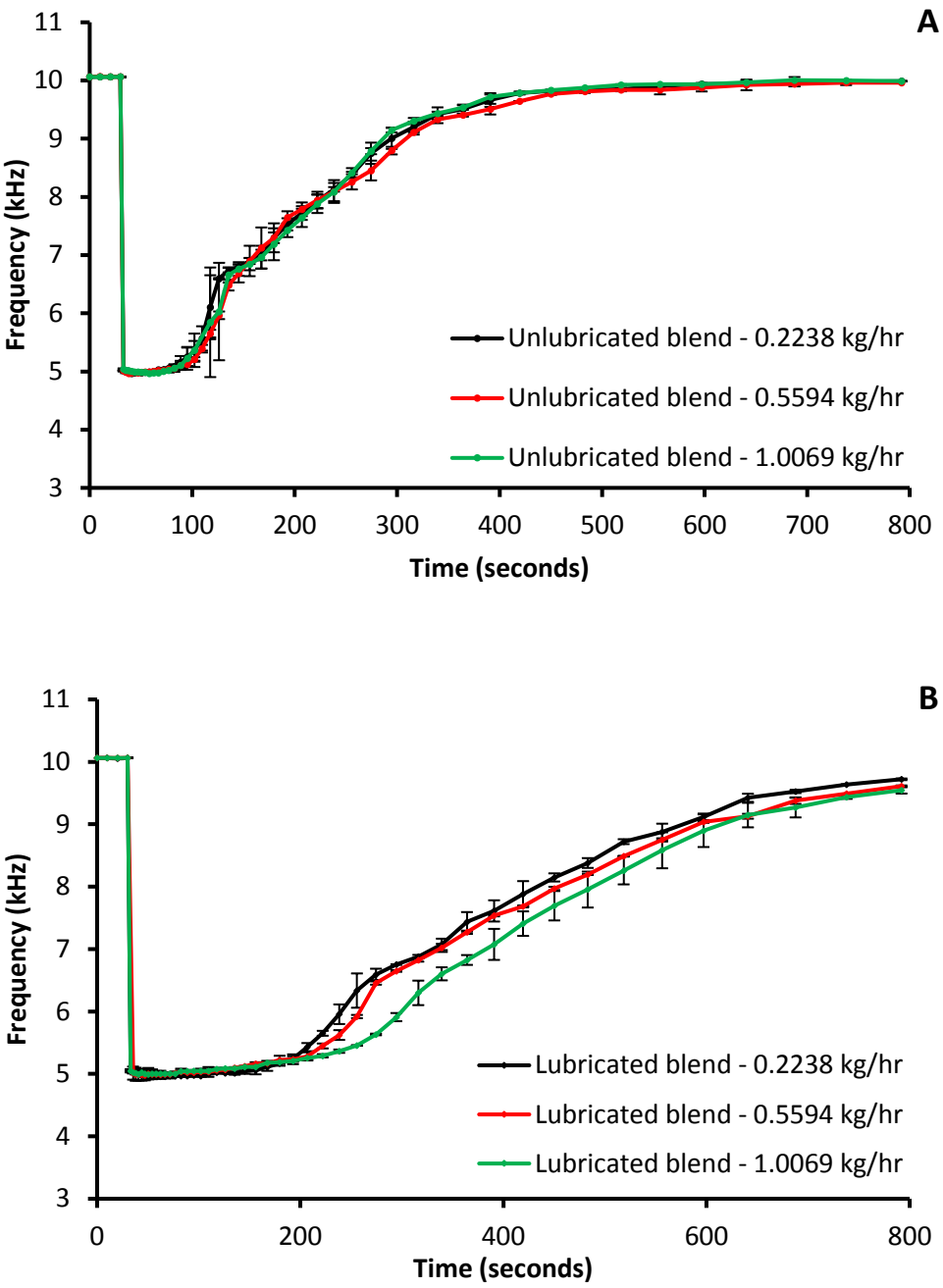


Figure 5.9 BARDS acoustic response for blend samples in 25 mL deionised water. Blends were prepared using lab scale blender and fed at different rates through a screw feeder. (A) Unlubricated blend and (B) Lubricated blend. Average values shown, n =2, y error bars indicate max and min values.

The unlubricated blend when fed at different feed rates, showed constant gas volumes over the time period of approx. 60s, with a relatively rapid gas elimination rate constant thereafter ($k \approx 1.17 - 1.21 \times 10^{-5}\ s^{-1}$), Figure 5.10A and Table 5.3. Lubricated blends show an increase in gas volume during the gas elimination stage with increase in formulation feed rate, Figure 5.10C. Slower gas elimination rate constants were observed for the lubricated blend ($k \approx 5.99 - 6.74 \times 10^{-6}\ s^{-1}$), Table 5.3.

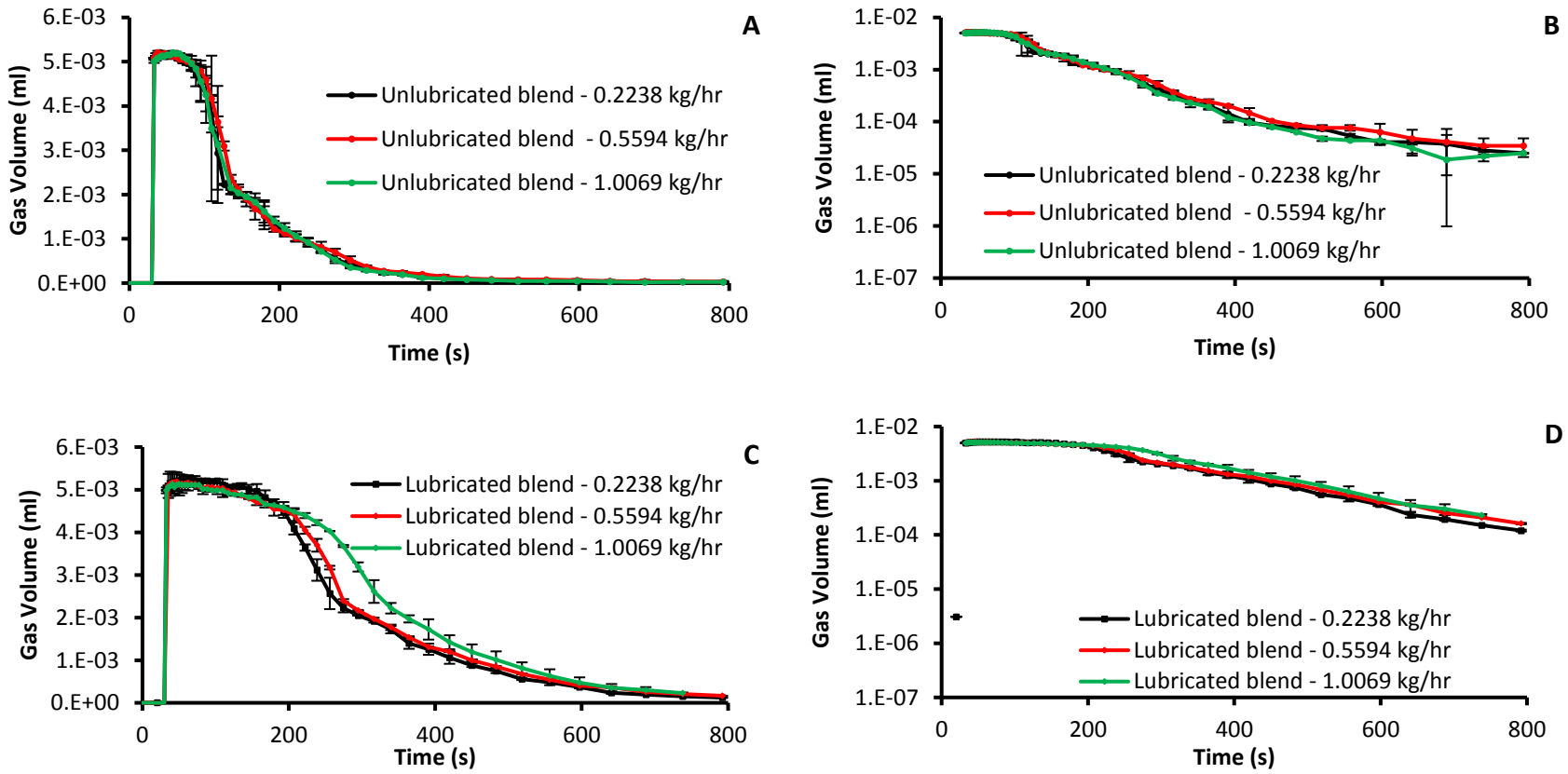


Figure 5.10 Gas volume plots for blends in 25 mL deionised water. Blends were prepared using lab scale blender- and fed at three different rates through a screw feeder. (A) Unlubricated blend plot of calculated gas volume versus time, (B) Unlubricated blend plot of log of calculated gas volume versus time, (C) Lubricated blend plot of calculated gas volume versus time, and (D) Unlubricated blend plot of log of calculated gas volume versus time. Average values shown, n =2, y error bars indicate max and min values.

Table 5.3 Lag time, time to return to steady state, calculated gas volume elimination rate constant (k) and time ranges used for calculation of the constant for samples of unlubricated and lubricated blends.

Feed rate (kg/hr)	Unlubricated blend				Lubricated blend			
	Approx. Lag time (s)	Time to return to steady state (s)	*k* (s^{-1})	Time range (s)	Approx. Lag time (s)	Time to return to steady state (s)	*k* (s^{-1})	Time range (s)
0.2238	90	420	1.17E-05	95-419	210	790	5.99E-06	207-792
0.5594	90	420	1.19E-05	95-419	220	790	6.02E-06	222-792
1.0069	90	420	1.21E-05	95-419	240	790	6.74E-06	255-792

5.3.2.5 Contact angle and wetting time of formulations before and after feeding

Contact angle is a commonly employed technique used to investigate the wetting of powders. When the surface of compacted powder is exposed to a liquid drop, the rate of change of the contact angle is monitored and recorded until the it reaches equilibrium (Ji et al., 2016). In this study, the major diluent used in preparing blends was MCC, which swells upon contact with water (Hattori and Otsuka, 2014). The contact angle reported is the initial angle of contact between compacted powder and water droplet, after the droplet is stabilized. Compacts with similar porosity were prepared for contact angle measurements. Contact angle results are shown in Figure 5.11. It was anticipated that presence of lubricant and degree of distribution of MgSt within tablet blend would delay the wetting of compacts. The compact from unlubricated blend showed a contact angle of approx. 10^0, and the compact from lubricated blend showed a 4 fold increase in the contact angle, which was attributed to the presence of MgSt. The feed rate did not show any effect on the contact angle measurements for compacts of the unlubricated blend as anticipated. However, for compacts of lubricated blend as the feed rate increased the average

contact angle increased but it was not statistically significant, possibly due to variability in measurements. The contact angle method detected differences in wetting behaviour between lubricated and unlubricated blends, however due to inherent test variability the technique was unable to detect differences between lubricated blends fed at different feed rates.

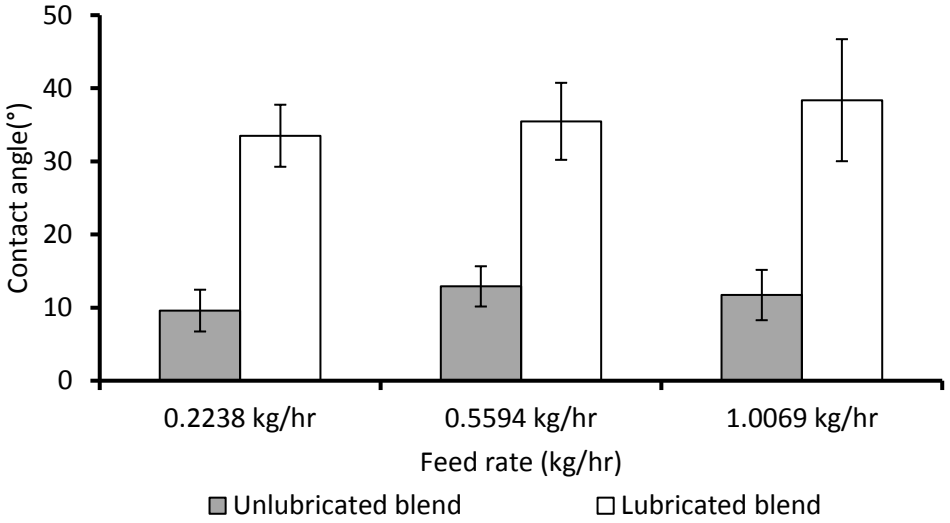


Figure 5.11 Contact angle (^{0}) of deionized water on unlubricated and lubricated blend compacts with similar porosity. Average values shown, n =3, y error bars indicate standard deviation.

The wetting time method is an alternative method that can used to determine the wetting behaviour of powders. Figure 5.12 shows the differences in the wetting time for the unlubricated and lubricated blend compacts of equivalent porosities. An increase in the feed rate was expected to result in an increased degree of lubrication for lubricated blend compacts. However increased feed rate did not show significant differences in wetting times (54.6s ± 0.5 and 52s ± 2.6) between the blends fed at 0.2238 kg/hr and 0.5594 kg/hr respectively. However, lubricated

blend formulation fed at 1.0069 kg/hr, showed an increased wetting time of 74.3 s ± 10.96 s. These results support the attribution of differences in BARDS profiles to differences in blend wetting behavior.

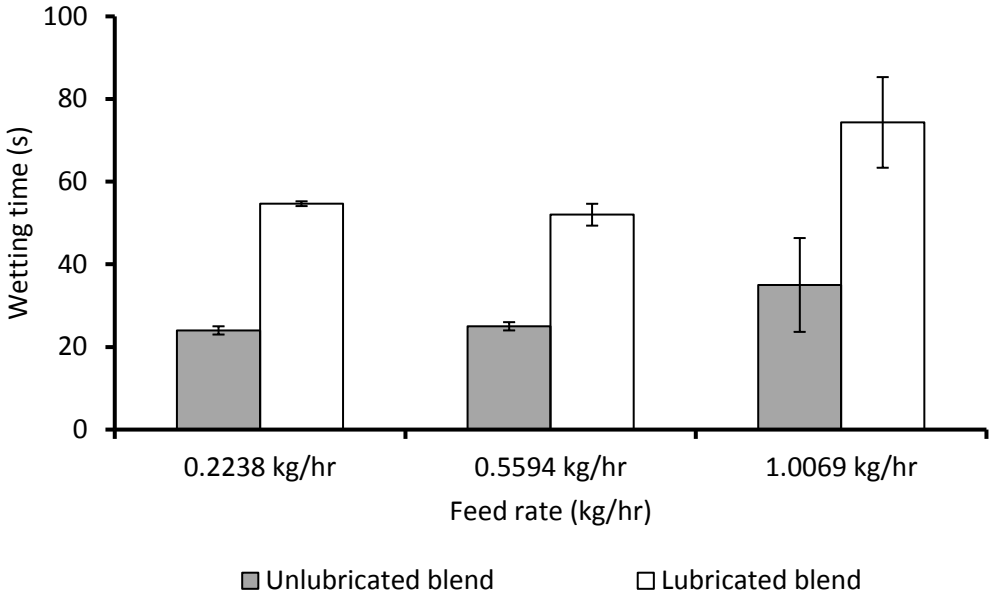


Figure 5.12 Wetting time of blend compacts with aqueous amaranth solution of unlubricated and lubricated blend compacts with similar porosity. Average values shown, n =3, y error bars indicate standard deviation.

Compared to both techniques assessed, the BARDS method was easier to perform and analysed the blends in their powdered form without the need for compaction prior to analysis.

5.4 Discussion

MgSt is one of the most commonly used lubricants in tablet manufacturing and due to its hydrophobic nature, if not properly monitored during blending has the potential to overcoat powders in the blend thereby compromising the tablet quality (Moreton, 2006; Pernenkil and Cooney, 2006). This chapter demonstrated the capability of BARDS to identify differences in wetting behaviour of blends due to different degrees of MgSt distribution, at a fixed MgSt concentration (Figure 5.4). BARDS analysis generated reproducible, qualitative data that could be related to powder wetting in a timeframe suitable for its use as an at-line process analytical technology (PAT) tool. Other PAT tools like near infrared and Raman spectroscopy, have been successfully used to measure the MgSt homogeneity within blends (Lakio et al., 2013), in-line and at-line (Liew et al., 2010; Nakagawa et al., 2013), with the objective of identifying differences in subsequent blend behaviour including hydration. Compared to these techniques, the BARDS method proposed studies blend wetting behaviour by immersion of powder in the liquid system of interest. Previous BARDS hydration studies focused mainly on single component milk protein powders (Vos et al., 2016) here we demonstrated the applicability of BARDS in multi-component pharmaceutical powder blends for the first time and specifically to the study of blend lubrication.

Individual components and blends yield significantly different acoustic profiles specific to the amount of sample and composition of blend as shown in Figure 5.2 and Figure 5.3. Compound solubility has an effect on the acoustic response (Fitzpatrick et al., 2012a). The results demonstrated that a soluble API

(metoclopramide hydrochloride) sustained a short V- shaped frequency change for only very short duration compared to insoluble MCC, which wets but does not dissolve in water. Preliminary testing of blends prepared manually showed notable shift in the acoustic response for blends rotated 100 times compared to blends prepared with 5 rotations. This was further demonstrated by preparing lab scale blends in a controlled manner.

Blends were prepared using V-cone blender, with and without MgSt. Lubricated blends showed extended acoustic response compared to unlubricated blends as shown in Figure 5.4. Equation 6 was used to convert this BARDS frequency data, to generate fractional gas volume (f_a) occupied by the compressible gas during wetting or dissolution of the powders. From this the log plots of gas volume were plotted to calculate the gas elimination rate constants to allow the quantitative comparison of the wetting behavior of powders, which signifies the degree of lubrication caused by MgSt. Unlubricated blend showed faster gas elimination rate constant compared to lubricated blend Table 5.2. These blends were fed through K-Tron MT-12 feeder to get varied distribution of MgSt within lubricated blend. Lubricated blend showed less %RSD compared to unlubricated blend. It was established that the blends were over lubricated as there was a decrease in tensile strength in tablets compacted from lubricated blend, as they were fed at higher feed rates (Figure 5.8). As expected no change in acoustic response was seen for unlubricated blends as the feed rate increased. However in lubricated blends extended acoustic response was seen as the feed rate increased (Figure 5.9).

Results generated in this chapter by BARDS were also compared to more standard wetting techniques of contact angle and wetting time. However, there are some limitations to these techniques. For both methods the powder was compacted prior to analysis in order to achieve reproducible results. The nature of this formulation, in particular the hydrophilic and swelling behavior of MCC, undermines the reproducibility and accuracy of the contact angle technique. However despite these limitations, the contact angle results demonstrated a significant change in the measurements between lubricated and unlubricated formulations. BARDS offers some key advantages compared to traditional techniques; powder can be directly analysed without packing or compacting and the acoustic profile is generated by dispersion of the blend in water, akin to disintegration and dissolution experiments. BARDS experiments require only 25 mL of solvent with 10-300 mg of sample, which greatly minimizes the quantities of powder required in comparison to comparable wetting tests (Alghunaim et al., 2016).

The results from this chapter highlights the ability of BARDS as a novel technique to identify over or under lubricated blends and could potentially assist in predicting dissolution behavior of specific batches. BARDS can also be used to identify batch to batch variability (Fitzpatrick et al., 2012b). BARDS can also be used to rapidly monitor the degree of lubrication and wetting behavior of pharmaceutical blends demonstrating its potential as an at-line PAT screening tool during development and routine pharmaceutical production for enhanced quality control and finished product quality.

5.5 Conclusions

Results from this chapter demonstrate the ability of the BARDS to detect differences in the wetting behavior of commonly used tablet excipients MCC, MgSt and a model API (metoclopramide hydrochloride) as single component and multi-component powder blends. BARDS was capable of detecting the differences in the wetting behaviour of lubricated and unlubricated blends and was compared with the wetting measurement techniques of contact angle and wetting time. The BARDS technique was also shown to be capable of detecting differences in the wetting behavior of lubricated blends, of equivalent composition, following different blending processes and feeding rates. The results of this study highlight the ability of the BARDS technique as a relatively rapid, at-line technique for in-process analysis of pharmaceutical blend lubrication and potentially the wetting behaviour of pharmaceutical powders and blends.

The next chapter focuses in demonstrating behaviour of tablets in BARDS media, formulated at range of compression forces.

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Please note that Chapters 6 & 7 (pp. 144-179) are unavailable due to a restriction requested by the author.

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Supplementary Information

Table S1 - Tukey's multiple comparison tests for dissolution profiles of paracetamol tablets prepared without lubricant and tablets with different MgSt samples.

Comparison	Summary
No Lubricant vs Alfa Aesar	***
No lubricant vs Ligamed MF-2-V	***
No lubricant vs Ligamed MF-2-V-BI	***
No lubricant vs Ligamed MF-3-V	***
API/MCC/AA Unfed vs Ligamed MF-2-V	ns
Alfa Aesar vs Ligamed MF-2-V-BI	ns
Alfa Aesar vs Ligamed MF-3-V	ns
Ligamed MF-2-V vs Ligamed MF-2-V-BI	ns
Ligamed MF-2-V vs Ligamed MF-3-V	ns
API/MCC/MF2VBI Unfed vs Ligamed MF-3-V	ns

*Where, * represents P≤0.05, ** represents P≤0.01, *** represents P≤0.001, **** represents P≤0.0001 and ns Not significant*

Table S2 - ANOVA – Comparison of Alfa Aesar across different feed rates.

Not compared, Repeated comparison

Alfa Aesar				Feed Rate (kg/hr)								
				Unfed			0.15kg/hr			0.25 kg/hr		
			Pressure (Bar)	1.5	2.0	3.0	1.5	2.0	3.0	1.5	2.0	3.0
D10	Feed Rate (kg/hr)	Unfed	1.5		****	***	**	****	****	ns	****	****
			2.0	****		****	**	ns	****	***	ns	****
			3.0	***	****		****	****	ns	****	****	ns
		0.15	1.5	**	**	****		****	****	ns	***	****
			2.0	****	ns	****	****		****	****	ns	****
			3.0	****	****	ns	****	****		****	****	ns
		0.25	1.5	ns	***	****	ns	****	****		****	****
			2.0	****	ns	****	***	ns	****	****		****
			3.0	****	****	ns	****	****	ns	****	****	
D50	Feed Rate (kg/hr)	Unfed	1.5		***	****	ns	****	****	ns	*	****
			2.0	***		****	ns	ns	***	ns	ns	ns
			3.0	****	****		****	**	ns	****	****	**
		0.15	1.5	ns	ns	****		**	****	ns	ns	**
			2.0	****	ns	**	**		ns	**	ns	ns
			3.0	****	***	ns	****	ns		****	****	ns
		0.25	1.5	ns	ns	****	ns	**	****		ns	**
			2.0	*	ns	****	ns	ns	****	ns		**
			3.0	****	ns	**	**	ns	ns	**	**	
D90	Feed Rate (kg/hr)	Unfed	1.5		*	****	****	****	****	***	****	****
			2.0	*		****	ns	*	****	ns	ns	***
			3.0	****	****		**	ns	ns	***	***	ns
		0.15	1.5	****		**		ns	***	ns	ns	ns
			2.0	****	*	ns	ns		ns	ns	ns	ns
			3.0	****	****	ns	***	ns		***	**	ns
		0.25	1.5	***	ns	***	ns	ns	***		ns	*
			2.0	****	ns	***	ns	ns	**	ns		ns
			3.0	****	***	ns	ns	ns	ns	*	ns	

*Where, * represents P≤0.05, ** represents P≤0.01, *** represents P≤0.001, **** represents P≤0.0001 and ns Not significant*

Table S3 - ANOVA – Comparison of Ligamed MF-2-V across different feed rates.

Not compared, Repeated comparison

Ligamed MF-2-V				Feed Rate (kg/hr)								
				Unfed			0.15kg/hr			0.25 kg/hr		
			Pressure (Bar)	1.5	2.0	3.0	1.5	2.0	3.0	1.5	2.0	3.0
D10	Feed Rate (kg/hr)	Unfed	1.5		****	****	****	****	****	ns	****	****
			2.0	****		****	*	****	****	****	**	****
			3.0	****	****		****	****	***	****	****	ns
		0.15	1.5	****	*	****		****	****	**	****	****
			2.0	****	****	****	****		****	ns	****	****
			3.0	****	****	***	****	****		****	****	*
		0.25	1.5	ns	****	****	**	ns	****		****	****
			2.0	****	**	****	****	****	****	****		****
			3.0	****	****	ns	****	****	*	****	****	
D50	Feed Rate (kg/hr)	Unfed	1.5		****	****	*	****	****	**	****	****
			2.0	****		****	*	****	****	ns	****	****
			3.0	****	****		****	**	***	****	**	*
		0.15	1.5	*	*	****		****	****	ns	****	****
			2.0	****	****	**	****		****	****	ns	****
			3.0	****	****	***	****	****		****	****	ns
		0.25	1.5	**	ns	****	ns	****	****		****	****
			2.0	****	****	**	****	ns	****	****		****
			3.0	****	****	*	****	****	ns	****	****	
D90	Feed Rate (kg/hr)	Unfed	1.5		ns	**	****	****	****	****	****	****
			2.0	ns		ns	**	****	****	*	****	****
			3.0	**	ns		ns	****	****	ns	***	****
		0.15	1.5	****	**	ns		***	****	ns	**	****
			2.0	****	****	****	***		***	***	ns	*
			3.0	****	****	****	****	***		****	****	ns
		0.25	1.5	****	*	ns	ns	***	****		**	****
			2.0	****	****	***	**	ns	****	**		**
			3.0	****	****	****	****	*	ns	****	**	

*Where, * represents P≤0.05, ** represents P≤0.01, *** represents P≤0.001, **** represents P≤0.0001 and ns Not significant*

Table S4 - ANOVA – Comparision of Ligamed MF-2-V-BI across different feed rates

Not compared, Repeated comparison

Ligamed MF-2-V-BI				Feed Rate (kg/hr)								
				Unfed			0.15kg/hr			0.25 kg/hr		
			Pressure (Bar)	1.5	2.0	3.0	1.5	2.0	3.0	1.5	2.0	3.0
D10	Feed Rate (kg/hr)	Unfed	1.5		ns	****	*	****	****	ns	****	****
			2.0	ns		****	ns	****	****	ns	****	****
			3.0	****	****		****	****	****	****	****	**
		0.15	1.5	*	ns	****		****	****	*	****	****
			2.0	****	****	****	****		****	****	ns	****
			3.0	****	****	****	****	****		****	****	ns
		0.25	1.5	ns	ns	****	*	****	****		****	****
			2.0	****	****	****	****	ns	****	****		****
			3.0	****	****	**	****	****	ns	****	****	
D50	Feed Rate (kg/hr)	Unfed	1.5		ns	****	ns	****	****	ns	****	****
			2.0	ns		****	*	****	****	ns	****	****
			3.0	****	****		****	ns	****	****	ns	****
		0.15	1.5	ns	*	****		****	****	ns	****	****
			2.0	****	****	ns	****		****	****	ns	****
			3.0	****	****	****	****	****		****	****	ns
		0.25	1.5	ns	ns	****	ns	****	****		****	****
			2.0	****	****	ns	****	ns	****	****		****
			3.0	****	****	****	****	****	ns	****	****	
D90	Feed Rate (kg/hr)	Unfed	1.5		*	ns	*	****	****	ns	****	****
			2.0	*		**	****	****	****	***	****	****
			3.0	ns	**		ns	****	****	ns	****	****
		0.15	1.5	*	****	ns		*	****	ns	ns	****
			2.0	****	****	****	*		ns	****	ns	ns
			3.0	****	****	****	****	ns		****	*	ns
		0.25	1.5	ns	***	ns	ns	****	****		**	****
			2.0	****	****	****	ns	ns	*	**		ns
			3.0	****	****	****	****	ns	ns	****	ns	

*Where, * represents P≤0.05, ** represents P≤0.01, *** represents P≤0.001, **** represents P≤0.0001 and ns Not significant*

Table S5 - ANOVA – Comparision of Ligamed MF-3-V across different feed rates.

Not compared, Repeated comparison

Ligamed MF-3-V				Feed Rate (kg/hr)								
				Unfed			0.15kg/hr			0.25 kg/hr		
			Pressure (Bar)	1.5	2.0	3.0	1.5	2.0	3.0	1.5	2.0	3.0
D10	Feed Rate (kg/hr)	Unfed	1.5		****	****	ns	****	****	ns	****	****
			2.0	****		****	****	ns	****	****	****	****
			3.0	****	****		****	****	ns	****	****	ns
		0.15	1.5	ns	****	****		****	****	ns	****	****
			2.0	****	ns	****	****		****	****	*	****
			3.0	****	****	ns	****	****		****	****	ns
		0.25	1.5	ns	****	****	ns	****	****		****	****
			2.0	****	****	****	****	*	****	****		****
			3.0	****	****	ns	****	****	ns	****	****	
D50	Feed Rate (kg/hr)	Unfed	1.5		****	****	****	****	****	****	****	****
			2.0	****		****	ns	****	****	****	****	****
			3.0	****	****		****	****	**	****	****	ns
		0.15	1.5	****	ns	****		****	****	**	****	****
			2.0	****	****	****	****		****	****	ns	****
			3.0	****	****	**	****	****		****	****	ns
		0.25	1.5	****	****	****	**	****	****		****	****
			2.0	****	****	****	****	ns	****	****		****
			3.0	****	****	ns	****	****	ns	****	****	
D90	Feed Rate (kg/hr)	Unfed	1.5		ns	****	****	****	****	****	****	****
			2.0	ns		****	****	****	****	****	****	***
			3.0	****	****		*	ns	****	**	ns	****
		0.15	1.5	****	****	*		****	****	ns	****	****
			2.0	****	****	ns	****		****	****	ns	***
			3.0	****	****	****	****	****		****	****	ns
		0.25	1.5	****	****	**	ns	****	****		****	****
			2.0	****	****	ns	****	ns	****	****		****
			3.0	****	***	****	****	***	ns	****	****	

*Where, * represents P≤0.05, ** represents P≤0.01, *** represents P≤0.001, **** represents P≤0.0001 and ns Not significant*

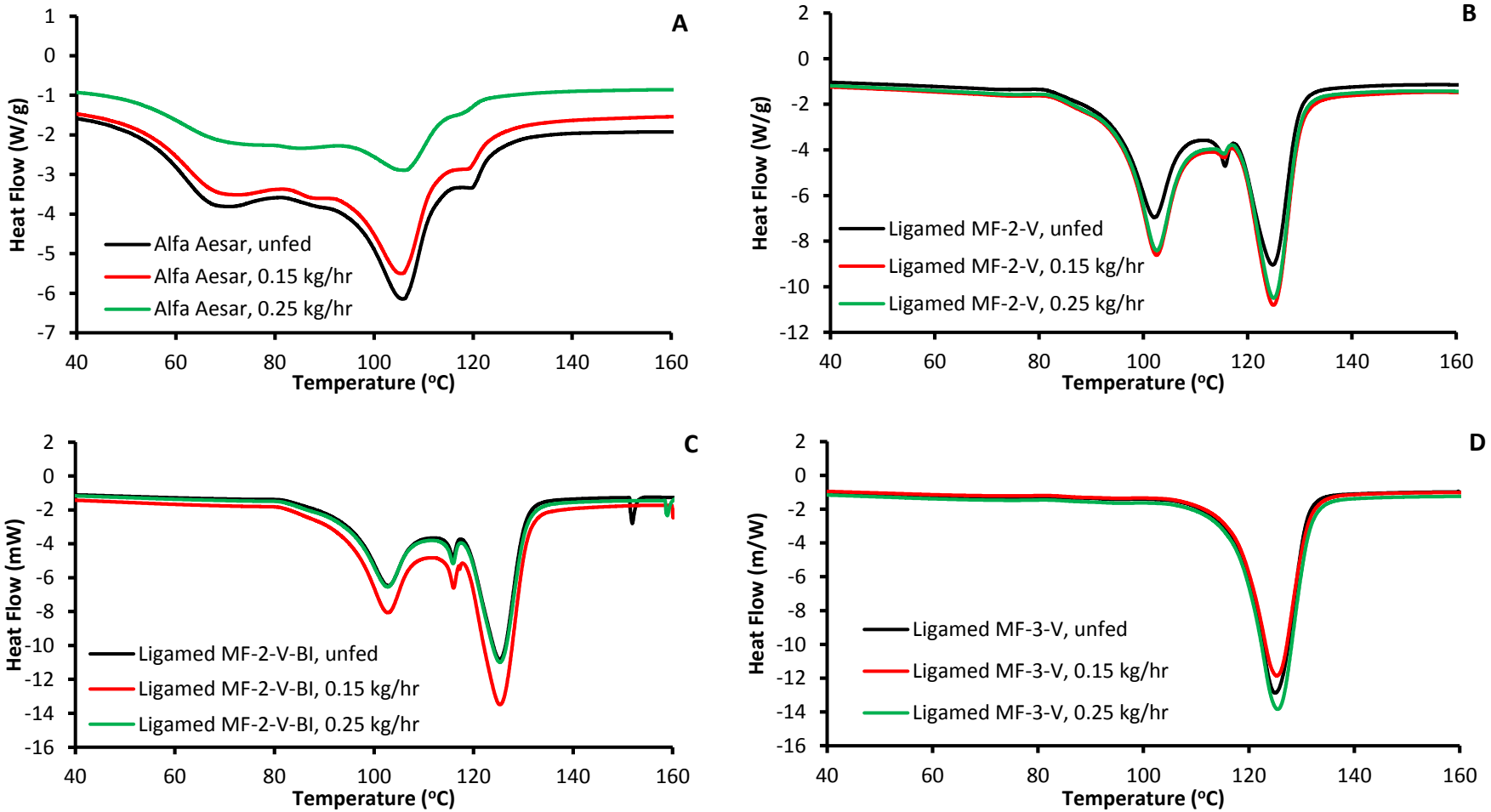


Figure S1 – DSC thermograms of unfed and fed lubricants through K-Tron MT12 feeder.

(A) Alfa Aesar, (B) Ligamed MF-2-V, (C) Ligamed MF-2-V-BI, (D) Ligamed MF-3-V.

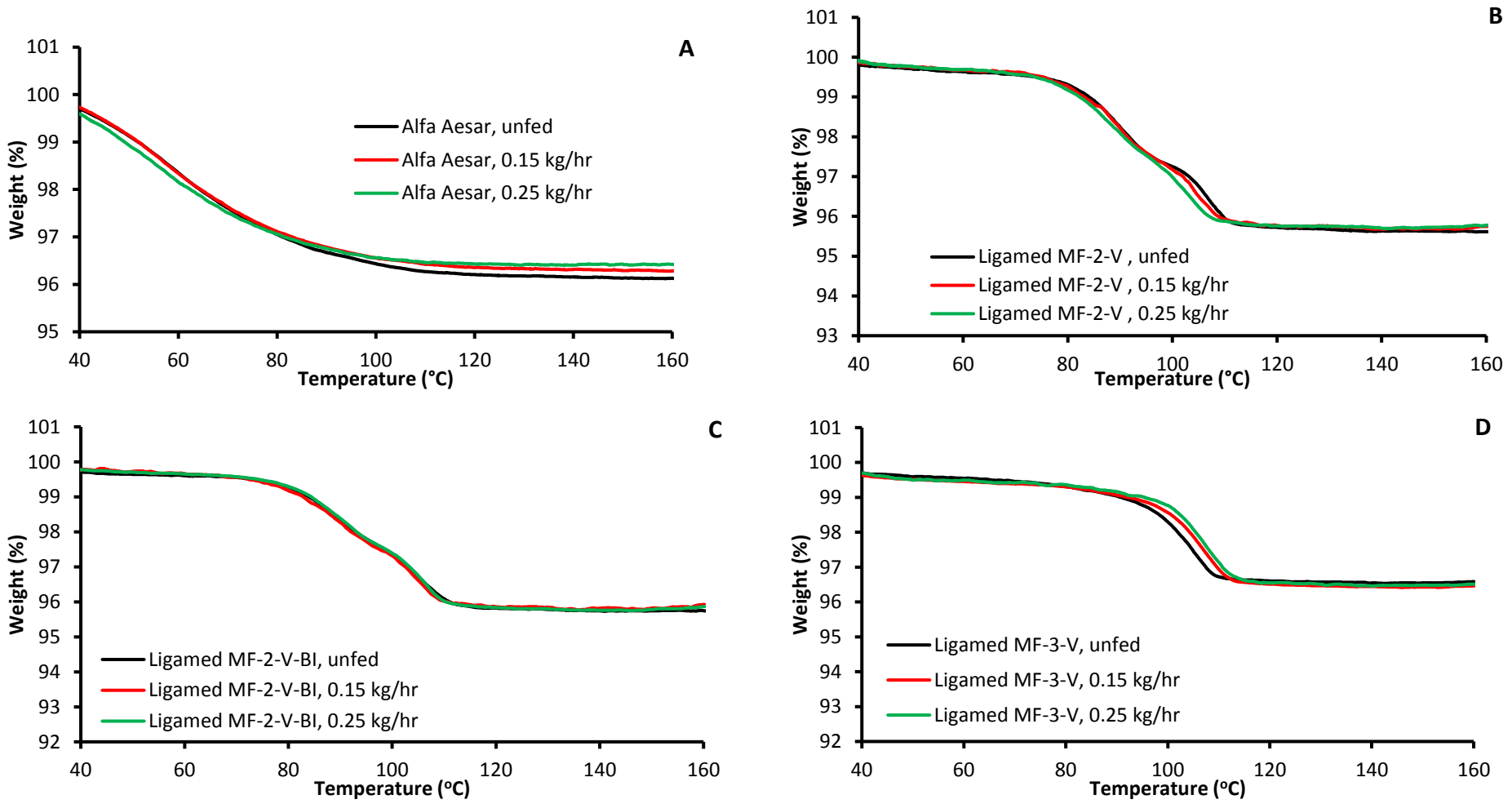


Figure S2 – TGA thermograms of unfed and fed lubricants through K-Tron MT12 feeder.

(A) Alfa Aesar, (B) Ligamed MF-2-V, (C) Ligamed MF-2-V-BI, (D) Ligamed MF-3-V.

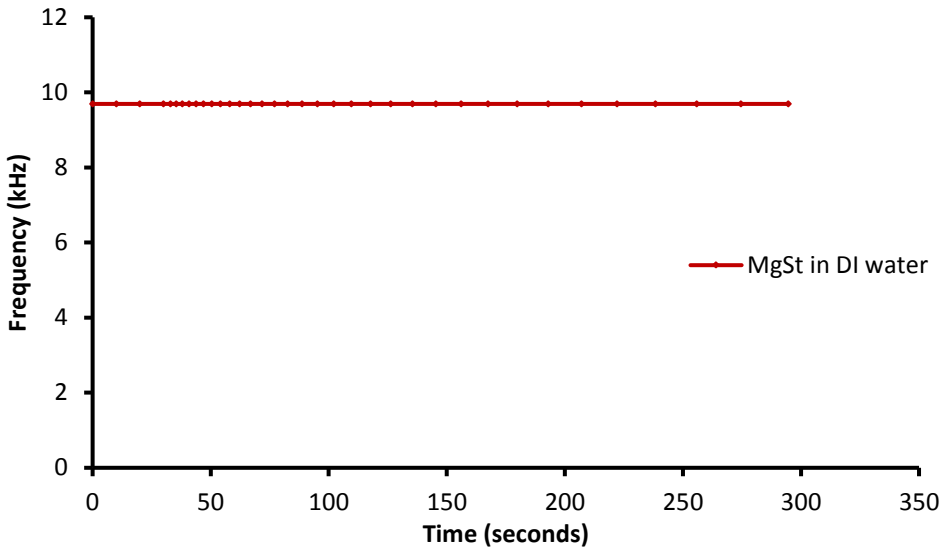


Figure S3 – BARDS acoustic response of MgSt in 25 mL of deionised water at room temperature.

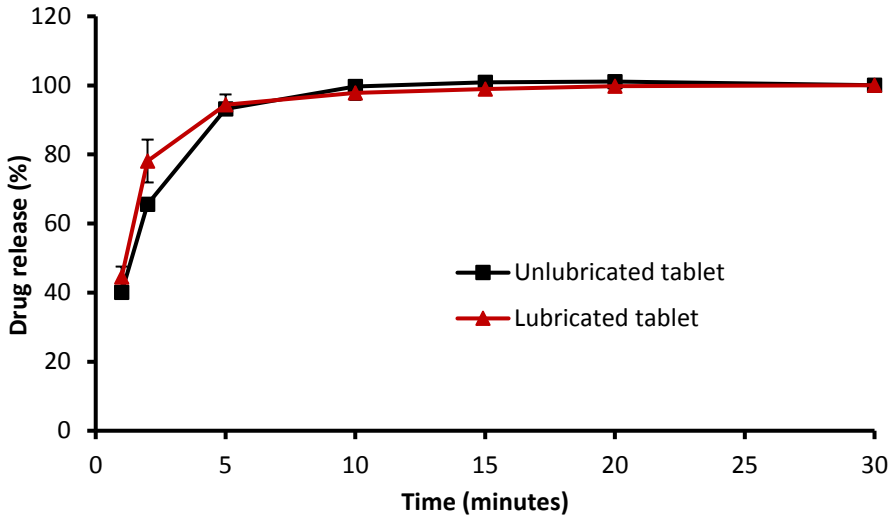


Figure S4 – Dissolution profiles of tablets from unlubricated and lubricated blends fed at three feed rates compacted produced at 3 MPa and tested in water at 37^{o}C. Average values shown n=3, y error bars indicate standard deviation.