UNDERSTANDING THE EFFECT OF GRANULATION AND MILL PROCESS PARAMETERS ON GRANULE CRITICAL QUALITY ATTRIBUTES

By

LALITH VENKAT GOPAL KOTAMARTHY

A thesis submitted to the

School of Graduate Studies

Rutgers, The State University of New Jersey

In partial fulfillment of the requirements

For the degree of

Master of Science

Graduate Program in Chemical and Biochemical Engineering

Written under the direction of

Rohit Ramachandran

And approved by

_____

_____

_____

New Brunswick

New Jersey

January 2018

`

ABSTRACT OF THE THESIS

Understanding the Effect of Granulation and Mill Process Parameters on Granule Critical Quality Attributes

By

LALITH VENKAT GOPAL KOTAMARTHY

Thesis Director:

Rohit Ramachandran

Milling is an essential unit operation used for particle size reduction in solid oral dosage manufacturing. Milling generally follows the granulation or crystallization during API manufacturing. Granulation process is primarily required in processing of drug product in order to alleviate issues related to powder handling, flowability of the material and segregation. However, granulation may produce particles with undesirable size distributions which might lead to problems during further downstream processing. Particle size distribution needs to be controlled, as it affects the drug bioavailability and also tablet compaction. To avoid uneven granule size distribution, milling is done post granulation. There are different kinds of mills such as hammer mills, ball mills, conical screen mills etc. which can be classified on the basis of type of force applied to break the particles. This study mainly focuses on conical screen mill. Breakage of particles in

`

comil is due to the intense shear applied on the particles between impeller and the screen and also due to the impact from a rotating impeller. Particles exit the mill based on their size relative to the aperture size of the screen bores. In the current work, the effect of mill screen type and mill operating parameters such as amount of material fed to the mill and impeller speed are studied. Milled particle size distribution and other critical quality attributes such as bulk density, friability, and porosity are also studied. In addition, the effect of granulation variables such as liquid to solid ratio, granulator impeller speed and the amount of binder in the formulation are analyzed. For the current work, Caffeine is chosen as the Active Pharmaceutical Ingredient. The formulation used has 8% caffeine, 46% Lactose monohydrate and 46% MCC Avicel PH101. Polyvinylpyrrolidone (PVP K-30) is selected as the binder. Predictive regression models are developed for throughput of the mill, milled product bulk density and milled product tapped density, to enable their use in downstream process modeling.

`

Acknowledgement

This thesis would not be complete without thanking a group of people. My journey through this thesis has been an enriching and memorable one. This would not have been possible without the help of some astute minds in a great laboratory setting.

Firstly I would like to express my sincere gratitude to my thesis advisor, Professor Rohit Ramachandran, for introducing me to the world of pharmaceuticals and giving me this great opportunity to pursue this research. His unfaltering support and motivation has been very important towards my internship and research.

I would also like to thank my thesis research committee members, Dr. Nina Shapley and Dr. Ravendra Singh for their valuable time and wise inputs.

Thanks would be an understatement to one of the most hard working and brilliant person I have known, Nirupa. She has been a wonderful colleague and a great support throughout my thesis. I am really grateful for her advice during the course of my research.

I am also glad to take this opportunity to thank Wei Ming, Dr. Sarang Oka, and Dr. James Scicolone, without whose guidance and counsel my research wouldn't have been complete. I would also like to thank Suparna, Swati Kumar and Ishani Naik for their help and suggestions. I would also like to thank all the members of the Particulate Systems Lab and ERC-SOPS for fostering the feeling of exceptional team work and camaraderie.

My research and experience in Rutgers would not have been such a wonderful experience without the unrestricted love and support of my family and friends, Ramya, Prashanth, Siddarth, Dheeraj, Praneeth, Varun and Tejashree.

`

Table of Contents

Abstract ii

Acknowledgement iv

Table of Contents v

List of Figures vii

List of Tables x

CHAPTER 1: INTRODUCTION 1

1.1 Milling 1

1.2 Types of Mill 3

1.3 High Shear Wet Granulation 5

1.4 Comil 6

1.5 Objective 9

1.6 Experimental Schematic 10

1.7 Granule Characterization 10

CHAPTER 2: EFFECT OF MILL PROPERTIES 15

2.1 Materials and Formulation 15

2.2 Equipment and Experimental Procedure 15

2.3 Process Parameters and Levels 16

2.4 Effect of Impeller Speed and Batch Size on mass throughput of the mill 17

2.5 Effect of Impeller speed and Mass of Input batch fed on PSD of the milled granule 22

2.5.1 Effect of Impeller speed and Mass of Input batch fed on %fines of milled granule 22

2.5.2 Effect of Impeller speed and Mass of Input batch fed on d50 of the milled product .. 26

2.5.3 Impact of input batch size on d50 of milled product 32

2.5.4 Effect of Milling on Span 33

2.5.5 Effect of milling on Friability of milled granules 36

2.5.6 Effect of milling on Porosity of milled granules 38

2.5.7 Effect of milling on Bulk Density and Tap density of milled granules 40

2.5.8 Effect of mill screen type on % fines of milled granules 42

CHAPTER 3: EFFECT OF GRANULATION PARAMETERS AND BINDER ADDITION 46

`

3.1 Equipment and Experimental Procedure 46
3.2 Effect of Liquid to Solid ratio of input granules on milling 47
3.3 Effect of Impeller Speed of Granulator on milling 51
3.4 Effect of Binder addition to the formulation on Milled granules 56
4 CONCLUSIONS AND FUTURE WORK 63
4.1 Conclusions 63
4.2 Future Research Opportunities 64
APPENDIX: 66
REFERENCES 70

`

List of Figures

Figure 1.1 Manufacturing routes for oral solid dosage in Pharmaceutical industry, (1) Direct Compaction (2) Dry Granulation (3) Wet Granulation 7

Figure 1.2 Schematic of high shear Batch granulator 6

Figure 1.3 Schematic of a Comil [32] 8

Figure 1.4 Process Flow sheet 10

Figure 2.1 Typical mass throughput profile for milling in a comil. The weight of input batch fed for the above graph is 600 grams and the impeller speed is 3000 rpm. 18

Figure 2.2 Side view of t50 profile 21

Figure 2.3 Top view of t50 profile 21

Figure 2.4 3D representation of %fines of milled granules in terms of Weight of input batch and Impeller speed 24

Figure 2.5 Plot showing the effect of Impeller speed on % fines and final mass of material collected, Batch size 300g. 24

Figure 2.6 Plot showing the effect of Impeller speed on % fines and final mass of material collected Batch size 600g 25

Figure 2.7 Plot showing the effect of Impeller speed on % fines and final mass of material collected, Batch size 1000g 25

Figure 2.8 3D representation of d50 of milled granules in terms of Weight of input batch and Impeller speed 27

Figure 2.9 Plot showing the effect of Impeller speed on d50 and on final mass of material collected (Input batch size-300g) 28

Figure 2.10 Plot showing the effect of Impeller speed on d50 and on final mass of material collected (Input batch size-600g) 28

`

Figure 2.11 Plot showing the effect of Impeller speed on d50 and on final mass of material collected (Input batch size-1000g) 29

Figure 2.12 Log normal particle size distribution of CAF-6 before milling 31

Figure 2.13 Log normal particle size distribution of CAF-6 after 30 seconds of milling and after 5 min of milling 32

Figure 2.14 Plot showing the effect of input batch size on milled product d50 at different impeller speeds. 33

Figure 2.15 Bores of a normal screen (left hand side image), bores of a grated screen (right hand side image) 42

Figure 2.16 Plot showing the effect of input batch size on %fines of milled product for normal and grated screen types at an impeller speed of 3000 rpm 44

Figure 2.17 Plot showing the effect of input batch size on d50 of milled product for normal and grated screen types at an impeller speed of 3000 rpm. 44

Figure 2.18 Figure showing the possible particle exit routes for a normal screen (round shaped screen) and a grated screen (rasp-shaped screen) [30] 45

Figure 3.1 Comparison of Output granule d50 vs. L/S ratio of input granules, Friability of Input granules vs. L/S Ratio 50

Figure 3.2 Comparison of Input Granules Friability vs. L/S ratio of input granules, weight of milled granules vs. L/S ratio of input granules. 51

Figure 3.3 Plot showing the effect of impeller speed on milled granule d50 53

Figure 3.4 Plot showing the effect of impeller speed on mass of milled granules collected 54

Figure 3.5 Plot showing the Log normal Particle Size Distributions of granules processed with 150 rpm (CAF-6), 170 rpm (CAF-5) and 190 rpm (CAF-8) 54

`

Figure 3.6 Plot showing the Log normal particle size distribution for granules that are smaller than 1000µm, for each granulation batch. 55

Figure 3.7 Plot showing the effect of %PVP in formulation on d50 of milled granules 60

Figure 3.8 Plot showing the effect of L/S ratio on the d50 of milled granules and on the % fines of the milled granules 61

Figure 3.9 Plot showing the effect of Impeller speed on the d50 of milled granules and on the % fines of the milled granules 61

Figure 3.10 Plot showing the effect of %PVP in the formulation on the d50 of milled granules and on the % fines of the milled granules 62

`

List of Tables

Table1.1 Mills classified on the basis of milled particle size [21-23] 5

Table 2.1 Formulation components and percentages 15

Table 2.2 Batch Granulation settings 16

Table 2.3 Process Parameter levels for effect of mill parameters study 16

Table 2.4 Mass throughput profile of mill at different impeller speeds and batch sizes 19

Table 2.5 mfinal and τ values for the milling runs in Table 2.1 20

0-6 Table 2.6 % fines of the milled granules 23

Table 2.7 PSD of granules after milling 27

Table 2.8 PSD of CAF-6 before milling, after 30 seconds of milling and after 5 min of milling at an impeller speed of 3000 rpm and input batch size of 600 31

Table 2.9 Span for a sample before and after milling at various mill conditions 34

Table 2.10 Anova table for effect of milling on span 35

Table 2.11 Friability for a sample before and after milling at various mill conditions conditions 37

Table 2.12 Anova table for effect of milling on Friability 38

Table 2.13 Porosity values before and after milling 38

Table 2.14 Anova table for effect of milling on Porosity 40

Table 2.15 Bulk Density and Tapped Density values used for the regression model 41

Table 2.16 Mill Parameters and Milled granule properties for normal screen runs 43

Table 2.17 Mill Parameters and Milled granule properties for Grated screen runs 43

Table 3.1 Mill parameters employed 47

Table 3.2 Granulation parameters employed, mill parameters employed and PSD of the input feed granules, for the study of effect of L/S ratio of input granule on milled granules 48

`

Table 3.3 PSD of the milled granules and the amount of granules milled, for the effect of L/S ratio of input granule experiments 49

Table 3.4 Friability, Porosity, Bulk Density and Hausner ratio, before and after milling, for the effect of L/S ratio of input granule experiments 49

Table 3.5 Granulation parameters employed, mill parameters employed and PSD of the input feed granules, for the effect of Impeller Speed of Granulator experiments 52

Table 3.6 PSD of the milled granules and the amount of granules milled, for the effect of Impeller Speed of Granulator experiments 52

Table 3.7 Friability, Porosity, Bulk Density and Hausner ratio, before and after milling, for the effect of L/S ratio of input granule experiments 53

Table 3.8 Mass of granules below 1000g for each granulation batch 55

Table 3.9 Granulation parameters used for effect of binder addition experiments 57

Table 3.10 Formulation employed, mill parameters employed and PSD of the input feed granules, for the effect of Binder Addition experiments 58

Table 3.11 PSD of the milled granules and the amount of granules milled, for the effect of Binder Addition experiments 58

Table 3.12 Friability, Porosity, Bulk Density and Hausner ratio, before and after milling, for the effect of Binder Addition experiments 59

A 1.1 Table with regression parameters for m_{final} 66

A 1.2 Table with regression parameters for τ 67

A 1.3 Table with regression parameters for t_{50} 67

A 1.4 Granulation parameters to study the effect of mill parameters on span, friability, porosity, bulk and tap density 67

`

A 1.5 Mill parameters to study the effect of mill parameters on span, friability, porosity, bulk and tap density 68

A 1.6 Table with regression parameters for bulk density 68

A 1.7 Table with regression parameters for tap density 69

CHAPTER 1: INTRODUCTION

1.1 Milling

In the pharmaceutical industry, majority of the drugs produced are oral solids. Production of these oral solids i.e., tablets and capsules encompass different unit operations like feeding, blending, granulation, size reduction, coating, mixing with glidants and finally tableting/encapsulation. The various unit operations can be arranged in different configurations, by adding or eliminating a few operations to make disparate processing routes.

These processing routes can be broadly divided into direct compaction, dry granulation, and wet granulation routes [1]. Milling is a unit operation common to all the routes. In the direct compaction route, mills are used as material delumping process units, while in the granulation routes, mills are used for particle size reduction. In the wet granulation route, mills reduce the size of oversize granules from the granulation and drying unit. Mills break compacted ribbons from a roller compaction process into granulated product in the dry granulation route. In addition, milling is also employed after API synthesis/Filtration [2, 3].

In this study, the main focus on mill is as a particle size reduction tool. Granulation process is primarily required in drug product manufacturing in order to alleviate issues related to powder handling. Granulation allows improvement in flowability of the material and also minimizes segregation. However, granulation may produce particles with undesirable size distributions. This may downplay the positive effect of minimizing segregation and also affect further downstream processing during tablet compaction. An excess amount of fines leads to poor granule flow and weight variability, while excessive large particles may lead to tablets with

pitted surfaces and tablets with poor strength [4]. In addition, the particle size distribution also impacts drug bioavailability [5]. Hence, an understanding of the effect of milling design and operation is critical.

Formulations that cannot be directly compressed and those that are sensitive to heat and moisture are dry-granulated. Roller compaction is a popular dry granulation process that produces ribbons by compressing the pre-blended powder between counter rotating rolls. For further downstream processing these ribbons are comminuted into granules, which are subsequently used for tableting or capsule filling.

Another important use of milling is to improve the dissolution of poorly soluble drugs and thereby to improve the bioavailability [6, 7]. This is done by milling the API into ultrafine particles to increase the surface area, thereby improving the dissolution.

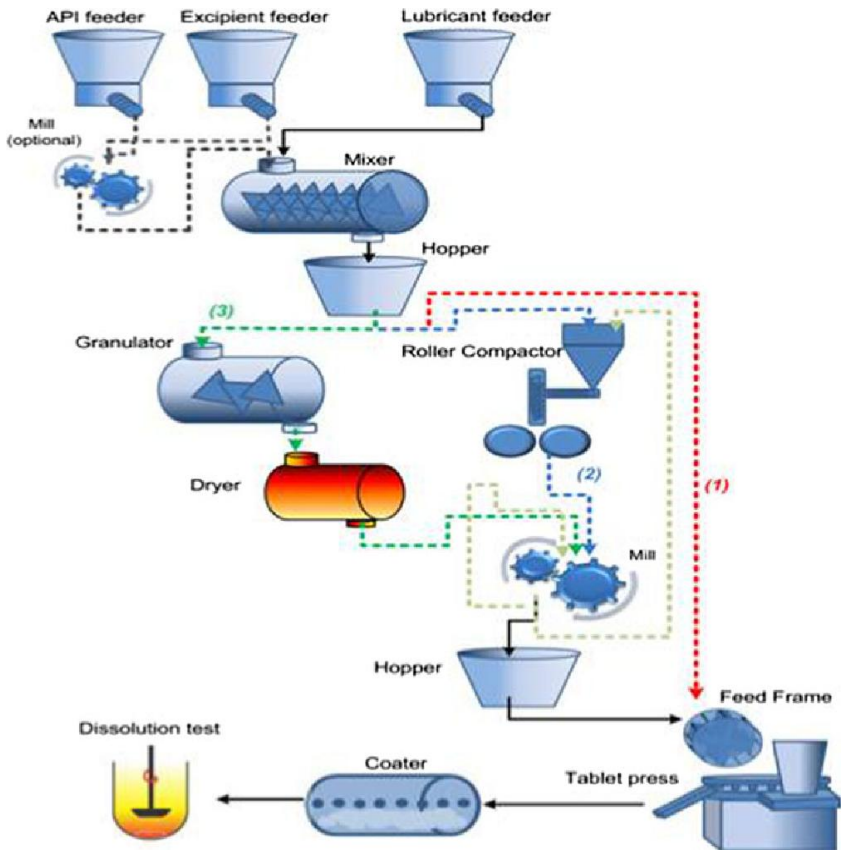


Figure 1.1 Manufacturing routes for oral solid dosage in Pharmaceutical industry, (1) Direct Compaction (2) Dry Granulation (3) Wet Granulation [8].

1.2 Types of Mill

Classification of milling equipment is generally done on the basis of type of force applied to break the impact, attrition and shear-compression [9]. The choice of equipment depends on the properties of the feed material (hardness, elasticity etc.) and the finished product specifications, like particle size, particle shape etc [10].

Impact Mill: The main mode of breakage in an impact mill is the high force collisions induced by mechanical impact. Examples of impact mill include the hammer mill and the pin mill. Hammer mills are capable of significant size reduction and can reduce the size of particle up to 10µm. The force imparted by the hammers, the feed rate, and the screen opening size are the most important critical parameters that control the degree of particle size reduction. Particle size distributions of granules produced by Impact mills generally have a relatively narrower size distribution, with fewer fines because of self-classification of screens. Pin mills operate similar to hammer mills, but typically with faster tip speeds and lower mechanical tolerances between rotating and stationary pins [11].

Attrition Mill: In an attrition mill, the size reduction of particles occurs due to intense agitation of particles inside the mill [12]. The most common kind of attrition mill, used for pharmaceutical purposes, is the air jet mill also called as Fluid energy mill. They are especially useful for API used in a low dose formulation or for poorly soluble drugs, as they decrease the size of particles from the range of 20-100µm to lower than 10µm [6]. In an air jet mill or fluid energy mill, the induction of fluid energy results in inter-particle collisions and subsequent size reduction. Fluid is injected as a high-pressure jet through nozzles leading to development of zones of turbulence

into which material is fed. Turbulence ensures a high frequency of particle–particle collisions which results in considerable decrease in size of particles. The extent of size reduction is controlled by nozzle pressure and feed rate. Spiral jet mills, loop jet mills, and fluidized bed jet mills are examples of fluid energy mills. Classification mill fitted to a fluidized bed jet mill produces much narrower PSDs than the other types of jet mills [13-16].

Shear-Compression Mill: The conical screen mill is popular type of shear compression mill as it has can be used for delumping as well as granule breakage. It has been found to be suitable for milling a wide range of products [17, 18]. In a comil, breakage is due to the intense shear applied on the material, in the gap between the impeller and the screen. This leads to creation of inter particulate and particle-screen wall frictional contacts and subsequent reduction in size [1]. The micronized particles escape through the screen. The size of the screen, type of screen, shape of the impeller, and the speed of the impeller are the important mill parameters that control the critical quality attributes of milled granules. Another type of shear compression mill is an oscillating granulator [19]. An oscillating granulator is generally used for roll compacted ribbons which are mechanically passed through an assembly of wire mesh screen and oscillating rotors. The particle size of the milled granules is controlled by screen size, speed of the rotor and rotational angle of rotors [20]. They generally produce coarser granules compared to comil. There are many roller compactors available commercially with an oscillating granulator incorporated after the rolls. This is easy to use as it allows continuous processing from powder blend to granules. For example, Gerteis roller compactors employ one oscillating granulator under the compaction zone after the rolls, whereas Alexanderwerk employs two granulators for better control over the particle size.

Mechanism		**Impact**		**Attrition**	**Impact &Attrition**	**Shear-Compression**	
Particle Description	Size(µm)	Pin Mills	Hammer Mills	Jet Mills	Ball Mills	Conical screen mill	Oscillating Granulator
Medium fine	500-1000	Yes	Yes	No	No	Yes	Yes
Fine	150-500	Yes	Yes	No	No	Yes	Yes
Very Fine	50-150	Yes	Yes	No	No	Yes	Yes
Super Fine	10-50	Yes	Yes	Yes	Yes	No	No
Ultra Fine	<10	No	No	Yes	Yes	No	No
Colloidal	<1	No	No	No	No	No	No

Table1.1 Mills classified on the basis of milled particle size [21-23]

1.3 High Shear Wet Granulation

High shear wet granulation is the most common wet granulation technique in batch manufacturing. The key components of a high shear wet granulator are a vessel /container which houses an impeller, an inlet for the liquid binder and a chopper. High shear wet granulation goes through three different stages, dry mixing, water addition and wet massing. Initially dry powders are added into the vessel and these powders are mixed for a certain amount of time, called the dry mixing time, by the impeller at a predetermined speed. After the dry mixing, liquid binder is let into the vessel, in the form of dripping or spraying, for a certain amount of time at a predetermined rate. This phase is called water addition; during this phase the liquid binder gets mixed into the powder and the granule nucleation and growth occur. During the wet massing, the addition of liquid binder is halted and the chopper rotates at a very high speed to break down the extra large granules into spheres.

High shear wet granulation is easily scalable because of extensive study. Batch granulation regime maps have been developed [24] and have been extensively used since then for further

investigations on batch granulation. It also works well with highly cohesive powders. The granule properties depend on the material properties of the powders added, amount of the powders added and process parameters such as liquid addition, impeller speed etc. Liquid to solid ratio, wet-massing time and Impeller speed are the main parameters which affect the particle size distribution of the granules [25, 26].

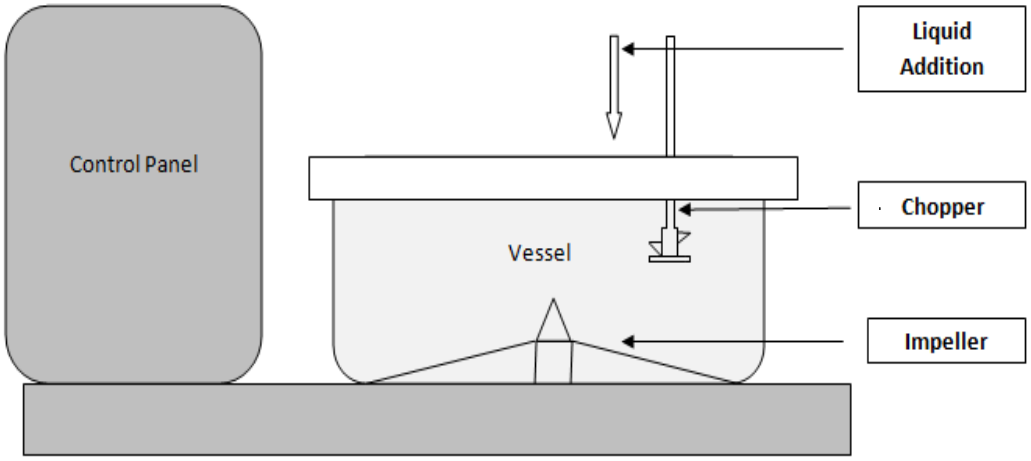


Figure 1.2 Schematic of high shear Batch granulator

1.4 Comil

As mentioned earlier, comil is a very popular mill which can be used for both delumping and size reduction. In this work, we mainly focus on size reduction. Size reduction in a comil is due to the shear action between the impeller and screen and impact energy imparted by the impeller. Comil can be run on batch as well as continuous mode [1]. For a batch mode of operation, the granules that need to be milled are added into a conical shaped vessel with holes drilled into it, called a screen. Mill contains an impeller, which can rotate at very high speeds, along its central

axis. When the mill is turned on, the impeller collides with the granules at high speed imparting kinetic energy into them. This results in particle-impeller collision, particle-particle collision and particle wall collision due to which the particles become weak and start to fracture. This is the impact breakage that occurs in Comil. As discussed earlier, the major type of breakage that occurs in a comil is due to shear compression and this is due to grinding of particles between the fast moving impeller of the walls of the comil and between particles. This creates a lot of shear which leads to rupture of particles. After the breakage, the particles exit the comil through the holes of the mill screen, if the size of the particles is small enough relative to the size of the screen.

The mill was studied at length over the past few years [27-29]. Size of the screen was reported to be the most important parameter affecting the particle size of the milled granules [27]. Others have reported that mill variables have to be studied together as there is a statistical interdependence between its parameters [28]. It was investigated that the type of the screen plays a crucial role in the amounts of fines generated. It was reported that usage of grater screen leads to lower residence time compared to round holed screens thereby lowering the amounts of fines generated [29]. Similarly, it was also reported[4] that a careful combination of grater screen and impeller type has to be employed for minimization of fines. The main focus of this study was to understand the fines generation in milling of compacted ribbons.

[30] A study on the effect of material properties and mill settings on PSD in a conical screen mill concluded that the screen size was the main parameter affecting the particle size. A smaller hole size leads to increased residence time thereby resulting in finer particle size. To investigate the effect of material properties, different amounts of Hydroxypropyl Cellulose (HPC) and different

grades of Lactose were used. Post impact behavior of the particles was explained by the theory of crack branching [31].

This theory primarily divides the breakage pattern of agglomerates by single impact into two main types: (1) the localized damage only, with shattering of particles into fine debris at the impact zone; (2) both localized damage and fragmentation, i.e., local disintegration resulting in large fragments, due to crack propagation from the impact region.

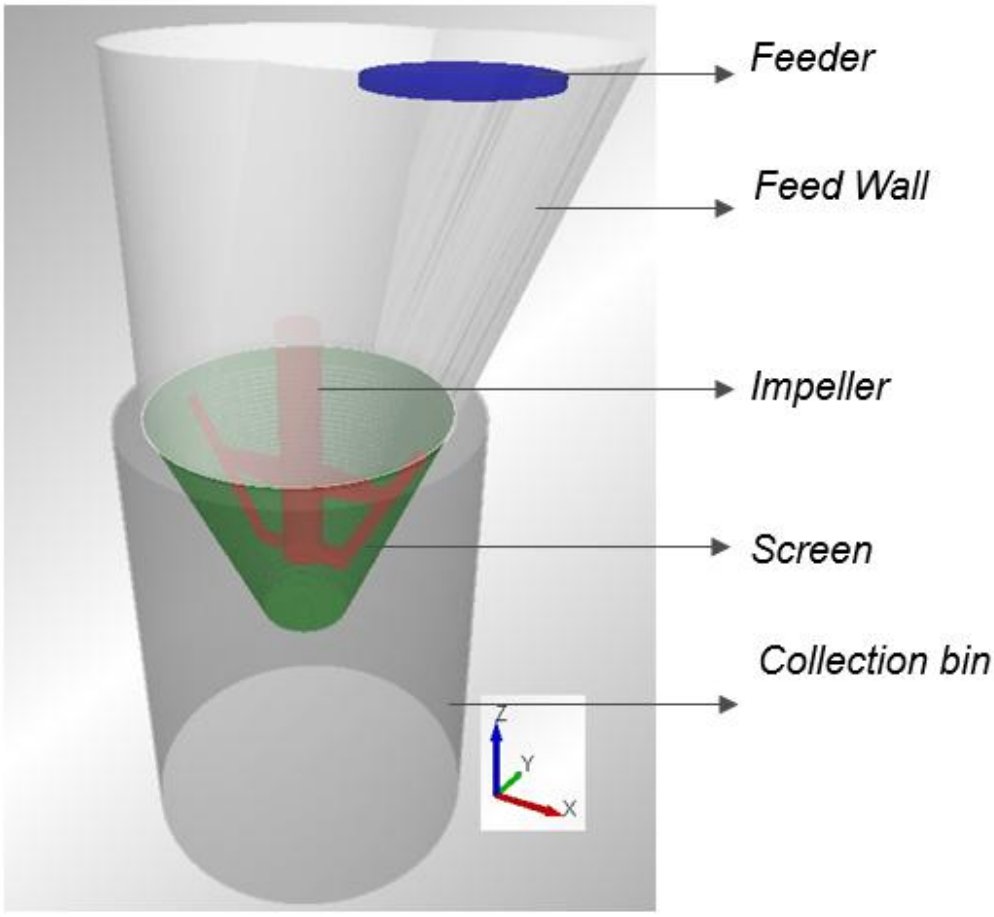


Figure 1.3 Schematic of a Comil [46]

1.5 Objective

The mill has been studied in depth over the past few years, but one of the aspects that was only vaguely understood is the effect of mass of input batch on the milled granules. The present work aims to gain insight on the effect of mass of input batch in tandem with the effect of impeller speed of the mill on the milled granules. The effect of screen type is also being investigated in this work. The effect of granulation parameters also hasn't been studied in depth before; this current work aims to characterize the effect of granulation parameters by analyzing the effect of granulation impeller speed and L/S ratio on the milled granules. Most of the research on milling focuses on PSD of milled granules as the quantification metric to assert the performance of the mill. An effort has been made towards characterizing other critical quality attributes of granules such as bulk density, tap density, friability and porosity along with PSD. For the current work, Caffeine has been chosen as the Active Pharmaceutical Ingredient. The formulation used has 8% caffeine, 46% Lactose monohydrate and 46% MCC Avicel PH101. Polyvinylpyrrolidone (PVP K-30) is selected as the binder. Predictive regression models are developed for throughput of the mill, milled product bulk density and milled product tapped density, to enable their use in downstream process modeling.

1.6 Experimental Schematic

The process flow of the experiments conducted is represented below,

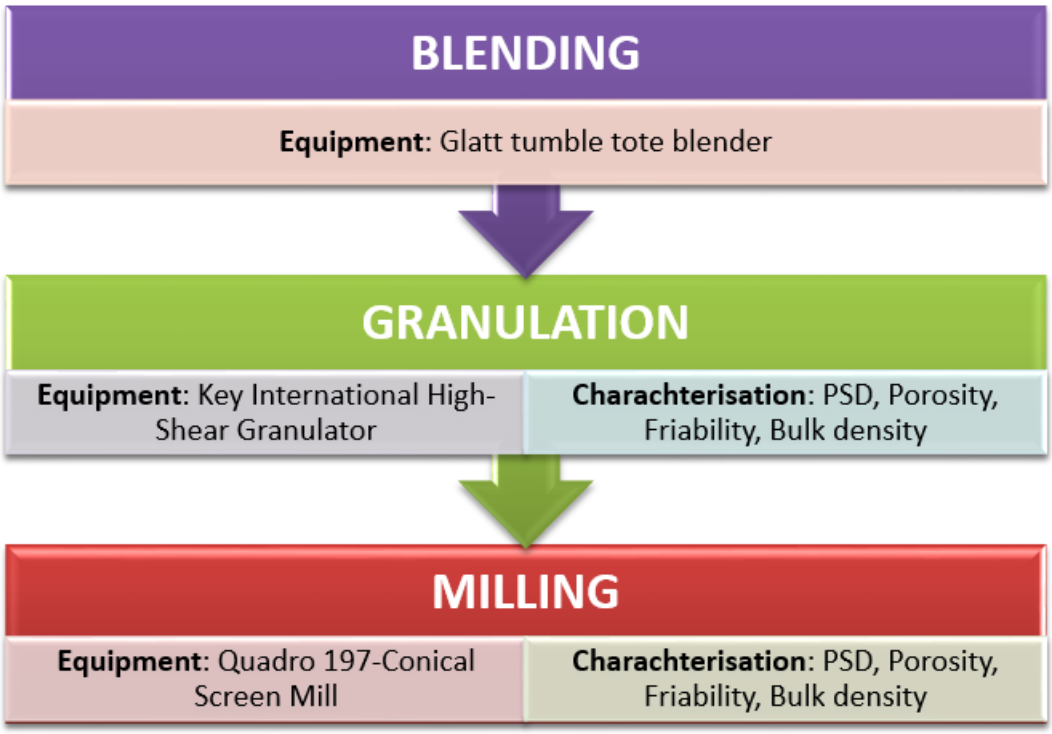


Figure 1.4 Process Flow sheet

1.7 Granule Characterization

Post milled granules are further processed to manufacture tablets or for capsule filling. For this purpose, it is very important to characterize the granules for Tablet making. During the processing of tablets, the flowability of granules affects the content uniformity of the tablets, i.e. if the granules are poorly flowing it might result in segregation thereby leading to non uniformity of tablets. The granules PSD is also important as it affects the important qualities of tablets such as content-uniformity, weight variability, dissolution profile, mechanical properties etc. [1]

***Particle Size Distribution**:* One of the most important objectives of milling is to achieve the desired range of particle size. Therefore, milling process is generally assessed by its ability to achieve the required particle size distribution. Sieve analysis and laser diffraction are the most common techniques to measure particle size of granules [33].

For the purpose of this study, sieve analysis was chosen, as the granules formed were large and out of the measuring range of Laser Diffraction. The sieve analysis was conducted using Endecotts Octagon 2000 Sieve shaker. For the analysis of granulated product, the sieves were divided into sets, coarse and fine, depending on the aperture size of the screen. The amplitude setting on sieve shaker varies from 0 to 9; the maximum setting corresponding to 3.4 mm. Each analysis was performed for 15 min at amplitude of 7 (2.38 mm). The coarse analysis consists of sieve screen sizes ranging from 4000 µm(#5), 2800 µm(#7), 2000 µm(#10), 1400 µm(#14), 1000 µm(#18) and 850 µm(#20), pan_1 (<850 µm). The fine analysis consisted of sieve screen sizes ranging from 710 µm(#25), 500 µm(#35), 355 µm(#45), 250 µm(#60), 150 µm(#100), 90 µm(#170), 63 µm(#230), pan_2 (<63 µm).

For milled product, only one analysis was carried out using the sieve screen sizes from 850 µm(#20), 710 µm(#25), 500 µm(#35), 355 µm(#45), 250 µm(#60), 150 µm(#100), 90 µm(#170), 63 µm(#230), pan_2 (<63 µm). This analysis was carried out for 20 min using amplitude of 8 (2.72 mm).

The granule mass collected on each mesh was recorded and used to develop a granule size distribution based on mass. This weighted distribution was used to identify d50, d90, d10, span and %fines of the powders.

d50 is defined as the particle size under which there are 50%, weight or volume based, of the milled granules. Similarly *d90* and *d10* are particle sizes under there are 90% and 10% of milled product respectively.

Bulk Density: The ratio of mass of untapped powder to its volume is known as the bulk density. This volume includes the volume of voids present between the particles. Hence, the bulk density depends on both the density of powder particles and the spatial arrangement of particles in the powder bed. The bulk density of a powder was determined by measuring the volume of a known weight of powder sample in a graduated cylinder [34].

Tap Density: The tapped density is an increased bulk density attained after mechanically tapping a container containing the powder sample. Tapped density was measured using Quantachrome tapped density analyzer. After observing the initial powder volume and weight, for bulk density measurement, the measuring cylinder was mechanically tapped to 10, 500 and 1250 taps; volume readings corresponding to each 0f these tapped volumes, V_{10}, V_{500}, $V_{1250,}$ were noted down,. The tapping was stopped if the difference between V_{500} and V_{1250} was less than or equal to 2 ml. If the difference was greater than 2 ml the tapping was continued in the increments of 1250 taps until the difference between 2 successive volumes was less than or equal 2 ml [34].

Hausner Ratio: The interactions between particles influence the bulk properties and flow of powders. A comparison between bulk and tapped densities is often used as an indicator of the ability of a powder to flow. The *Hausner Ratio* is the measure of the propensity of a powder to be compressed. When the powders are freely flowing, there are fewer interactions between particles and the bulk and tapped density values will be close to each other. On the contrary, a

poorly flowing powder has significant inter-particle interactions which results in a considerable difference between bulk and tapped density. These differences are reflected in *Hausner Ratio*.

Hausner ratio is given by the following equation,

$$Hausner\ ratio = \left(\frac{V_F}{V_0}\right)$$

V_0 is the unsettled apparent volume and V_F is the final tapped volume

Generally, a value of Hausner ratio larger than 1.25 is an indication of poor flowability [37].

Friability: Granule Friability indicates granules strength [35]. If the granules are very weak it might lead to crumbling of granules before they are tableted which can further lead to segregation of the sample. On the other hand, if the granules are too hard it affects the compactibility of granules.

Granule Friability was measured using Pharma Test Auto-Friability Tester – PTF E/ER. A special drum to load the sample is used for testing friability of granules. In this method, prior to experimentation approximately 10 g (I_{wt}) of sample is conditioned to remove the fines. For friability purposes fines defined as particles that have particle size lower than 150 µm screen size. This sample is then subjected to mechanical stress using a friabilator at 25 rpm for 10 min along with 200 glass beads (mean diameter 4mm) to falling shocks. After the glass beads were removed the weight retained on the 150 µm screen was determined (F_{wt}) [36]. Then the friability of sample was calculated as

$$Friability = \left(\frac{I_{wt} - F_{wt}}{I_{wt}}\right) * 100$$

Porosity: Porosity is an important Critical Quality Attribute measured for granules as this factor gives insight about granule structure and strength thereby affecting the tablet compression. Very low porosity values indicate dense granules, which could be difficult to compact and therefore affect compaction and dissolution. On the other hand, high porosity could lead to formation of brittle and weak granules which could break due to the stresses of any downstream processing such as milling, tableting and packaging.

Porosity was measured using Accupyc II 1340 and Geopyc 1360 (Micromeritics). True Density (ρ_t) was measured using Accupyc II 1340 in a helium gas media using 10 cm^3 chamber. Envelope Density was measured using Geopyc 1360 using a 12.7 mm chamber-piston set. A dry solid medium (DryFlow®) comprising of small and rigid spheres with high flowability displaces the void space and closely envelops the particle surface, thereby giving the envelope density (ρ_e) [37]. Porosity is calculated using the formula,

$$\text{Porosity} = (1\text{-}\frac{\rho_e}{\rho_t}) * 100\ \%$$

CHAPTER 2: EFFECT OF MILL PROPERTIES

2.1 Materials and Formulation

A general oral solid tablet or capsule consists of a multi-component mixture including the drug. The potent or the active compound in the mixture is called the API or Active Pharmaceutical Ingredient and the inactive substances are called the excipients. These excipients are added to the mixture for various reasons such as: improvement in flow properties of the material, increase in strength of the tablet, improvement in compressibility of the material etc. For these set of experiments a three component mixture in a fixed proportion was used. The details of these components and the ratio in which they were mixed are mentioned in Table 2.1

Ingredient	Weight percentage
Caffeine	8
MCC Avicel PH 101	46
Lactose Monohydrate	46

Table 2.1 Formulation components and percentages

2.2 Equipment and Experimental Procedure

The formulation, mentioned in Table 2.1, (MCC Avicel PH 101- 3kgs, Lactose Monohydrate- 3kgs, Caffeine- 521.7 g) was blended in a tote blender (Glatt tumble tote blender) for 30 minutes. Then this pre blended powders were granulated in a 2.4 L batch granulator (Key-International table-top high shear granulator) at pre-determined granulator settings (given in Table 2.2) with a batch size of 300 grams. These granules are then air dried for 48 hours before milling in a conical screen mill (Quadro 197-R) at various conditions.

Granulation Parameter	Value
Impeller Speed	150 rpm
Chopper Speed	6000 rpm
% water	55
Dry mixing time	2 minutes
Water addition time	2 minutes
Wet massing time	3 minutes

Table 2.2 Batch Granulation settings

To study the effect of mill parameters mass throughput of the mill, Particle size Distribution (d50, % fines), friability, porosity, Bulk density and Tap density are analyzed.

2.3 Process Parameters and Levels

A conical screen mill has several process/equipment properties, which can be varied to affect the efficiency and output of the mill. Parameters such as impeller speed, screen size, screen type, impeller type etc. can be varied. For this study, full-factorial DoE experimentation is carried out with Impeller speed and mass of input batch as the factors at three different levels. The details of the levels for these parameters are mentioned in Table 2.3.

Impeller Speed (rpm)	**Mass of input batch (g)**
1500	300
2250	600
3000	1000

Table 2.3 Process Parameter levels for effect of mill parameters study

The range of impeller speed for this comil (Quadro 197-R) varies from 1300-4300 rpm. These three levels of rpm were chosen based on the operating range of the comil. Also at higher impeller speed's there is a lot of dust generated, because of which 3000 rpm was chosen as the highest level. Batch size is the amount of granules that we load into the mill. As mentioned earlier there is almost no clear mention or study of this effect on the mill. Batch size can also be looked as the fill level of the mill. To study this effect we chose batch size at three different levels, 1000 grams corresponds to complete choking of the mill where as 300 grams corresponds to a level lower than the 50% full and 600 grams corresponds to about 70-75% fill level.

2.4 Effect of Impeller Speed and Batch Size on mass throughput of the mill

As mentioned earlier the novelty of this study is the effect of weight of the input batch size on end product of the mill. The interesting point is that the amount of batch size fed has an interaction effect with Impeller speed which gives a new perspective to the effect of Impeller speed. In this study, the mass throughput of the mill, at any given time, is the mass of granules that have exited the mill till that particular point of time. In a continuous operation, at steady state, the rate at which input granules are fed to the mill is equal to the rate at which granules leave the mill. In a batch operation the amount of granules in the mill continually decreases thereby leading to a decrease in the rate of mass throughput of the mill. This trend of mass throughput for a batch operation resembles a first order kinetic graph as shown in Figure 2.1.

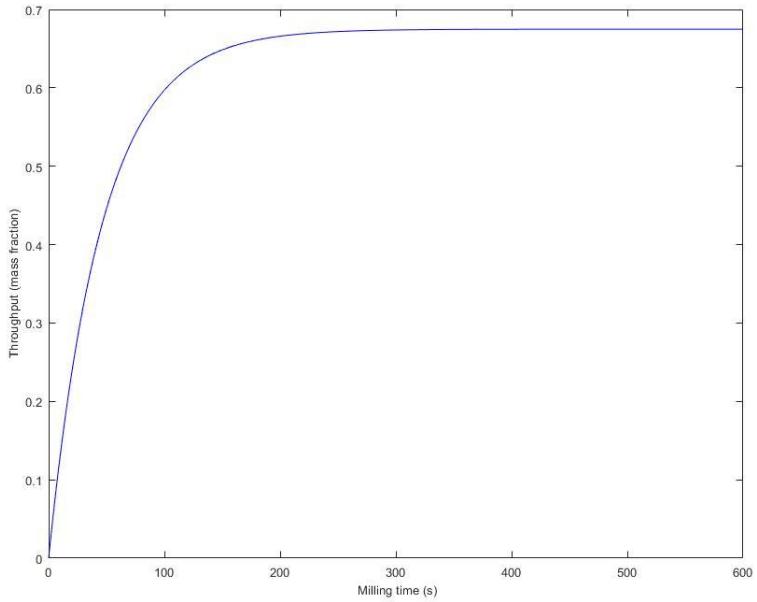


Figure 2.1 Typical mass throughput profile for milling in a comil. The weight of input batch fed for the above graph is 600 grams and the impeller speed is 3000 rpm.

Figure 2.1 shows typical data for mass throughput as a function of milling time elapsed. This data can be represented using first order kinetics model,

$$\frac{dm}{dt} = K(m_{final} - m) \qquad (1)$$

Integrating the above equation at m = 0 at t = 0 yields:

$$m = m_{final}(1 - e^{\left(\frac{-t}{\tau}\right)}) \qquad (2)$$

Where t corresponds to milling time elapsed, m is throughput mass fraction of the mill, m_{final} is throughput of the mill at t =∞ and τ = 1/K, which is time required for 63% completion of milling cycle.

Equation (2) represents the graph in figure 2.1 as the general profile of mass throughput as a function of time elapsed for the comil.

	Impeller speed (rpm)	batch size fed	% throughput at 30s	% throughput at 60s	% throughput at 90s	% throughput at 300s
1	2250	600	37.5	49.98	57.59	79.5
2	1500	1000	44	49.49	51.97	59.08
3	2250	300	31.84	43.15	50.65	76.02
4	3000	600	37.67	47.56	52.95	70.04
5	1500	300	26.81	35.16	37.47	53.96
6	3000	1000	31.14	42.38	49.45	74.75
7	1500	600	39.78	47.75	53.07	73.82
8	2250	1000	41.32	48.62	51.99	62.37
9	3000	300	29.75	45.27	54.97	82.96

Table 2.4 Mass throughput profile of mill at different impeller speeds and batch sizes

m (kg)	v(m/s)	RPM	m_{final}	τ	t_{50}
0.6	12.246	2250	0.780	56.85	58.195
1	8.164	1500	0.553	20.67	48.660
0.3	12.246	2250	0.758	70.12	75.664
0.6	16.328	3000	0.675	46.26	62.486
0.3	8.164	1500	0.522	53.93	170.761
1	16.328	3000	0.745	70.72	78.633
0.6	8.164	1500	0.708	49.46	60.602

1	12.246	2250	0.584	28.45	55.197
0.3	16.328	3000	0.841	78.26	70.620

Table 2.5 m_{final} and τ values for the milling runs in Table 2.1

In the above table t_{50} is the time taken for the mill to complete 50% of its cycle.

On regressing m_{final} and τ we get the following equations,

$$m_{final} = 3.351159m + 0.145144v - 1.43681m^2 - 0.01826mv^2 - 0.19605m^2v + 0.021326m^2v^2 - 1.15712 \quad (3)$$

with an R^2 of 0.987, adjusted R^2 of0.95 and significance F of 0.0383.

$$\tau = 223.6696m + 17.4493v - 29.9949m^2 - 0.1502v^2 - 1.95513mv^2 + 3.047324m^2v^2 - 34.3714m^2v - 98.2929 \quad (4)$$

with an R^2 of 0.9, adjusted R^2 of 0.922 and significance F of 0.2.

Therefore the final equation of output in fraction can be predicted from equation (2) by replacing m_{final} and τ from equation (3) and equation (4) respectively, into equation (2).

When t_{50} from table 2.2 is regressed we get an equation for time required for 50 percent completion of a mill cycle in terms of mass of input batch fed and impeller speed.

$$t_{50} = -556.582m - 33.2253v - 5.71665m2v2 + 5.892524mv2 + 92.89835m2v - 60.3054mv + 596.8258 \quad (5)$$

with an R^2 of 0.935 and adjusted R^2 of 0.75 and significance F of 0.183

The regression parameters for the regression of m_{final}, τ and t_{50} are mentioned in the appendix tables A 1.1, A 1.2 and A1.3 respectively.

Equation (5) is plotted with mass on x axis, velocity on y axis and time on z axis,

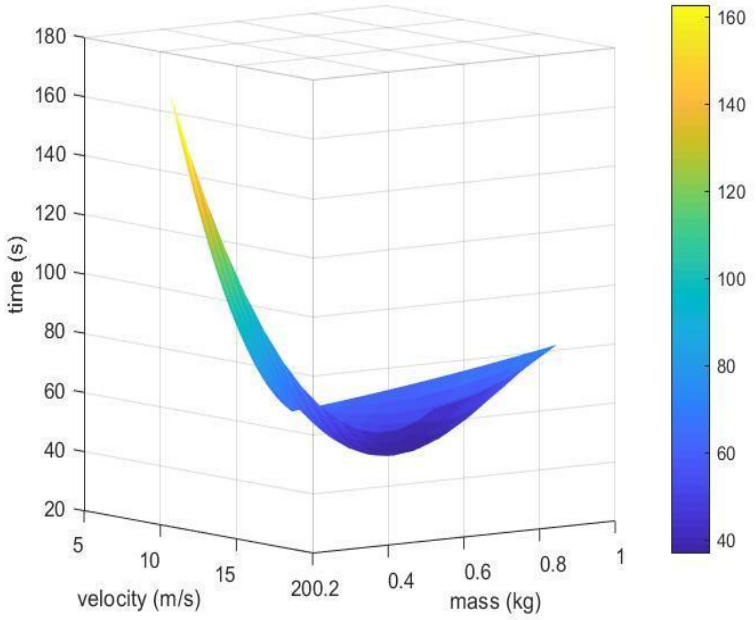


Figure 2.2 Side view of t50 profile

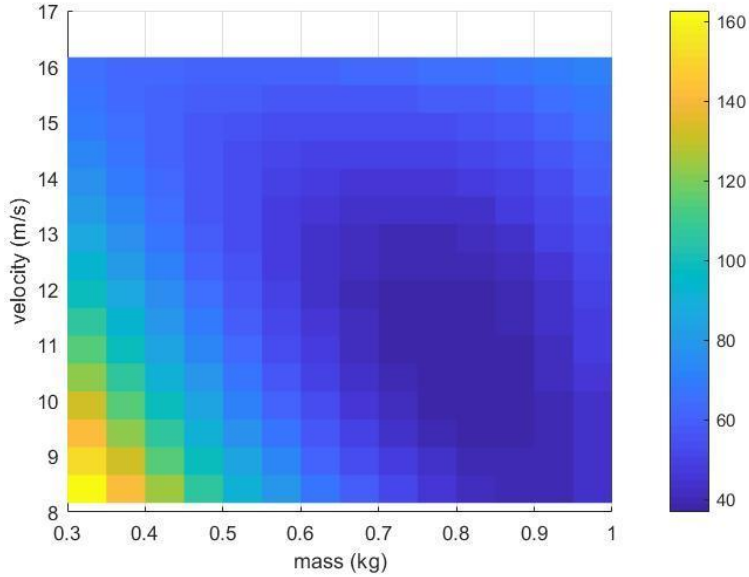


Figure 2.3 Top view of t50 profile

On observation, minima can be seen in Fig 2.3 and Fig 2.4 around 45s. This minima falls between 0.8 and 0.9 kg weight of input batch fed and between 10 to 11 m/s speed of the impeller. This corresponds to 1837 rpm to 2021 rpm. Minima of these figures describes the lowest time required to complete 50% of mill cycle within the range of these conditions, and it also tells about the conditions that should be employed to achieve that minimum time for 50% completion of mill cycle.

From the above equations it is clear that the throughput of a milling cycle is affected by both the impeller speed and the weight of the input feed.

2.5 Effect of Impeller speed and Mass of Input batch fed on PSD of the milled granule

Particle Size Distribution (PSD) is a method of representing a given set of powders in terms of particle size. Ideally a narrow weighted distribution, with maximum percentage of particles falling in the ideal size range, is preferred for granules. Milling is performed after granulation to achieve this narrow distribution. PSD is generally reported with d50, d90, d10, span and %fines. In this section, the pre-milled granule formulation is called CAF-4.

2.5.1 Effect of Impeller speed and Mass of Input batch fed on %fines of milled granule

To simplify further downstream processing neither too large nor too small granules are preferred [38]. Milling is followed by tablet compaction; large amount of fines produced during milling might lead to segregation or flow issues during tableting. Hence it is important to study

the %fines generated during milling. For the present study, particles below the size of 90µm are considered as fines. % fines was calculated as,

$$\%fines = \left(\frac{mass\ of\ particles\ below\ 90\mu m}{mass\ collected\ at\ the\ end\ of\ milling}\right) * 100$$

	Fines (g)	Impeller speed (rpm)	Mass of input batch (g)	Mass collected at the end of milling cycle (g)	% fines
1	16.39	1500	600	442.91	3.70
2	12.98	1500	1000	590.79	2.20
3	6.15	1500	300	161.87	3.80
4	31.44	2250	600	477	6.59
5	10.09	2250	300	228.07	4.42
6	26.54	2250	1000	623.72	4.26
7	22.39	3000	600	445.31	5.03
8	52.54	3000	1000	747.5	7.03
9	36.12	3000	300	248.87	14.51

Table 2.6 % fines of the milled granules

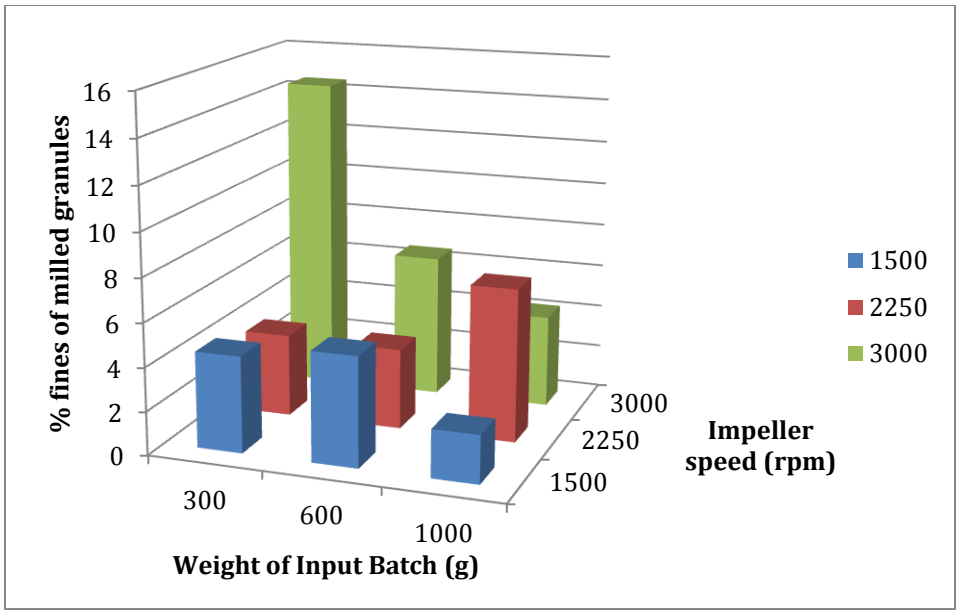


Figure 2.4 3D representations of %fines of milled granules in terms of Weight of input batch and Impeller speed

The Figure 2.4 is a graphical representation of the date in the table 2.3. In the figure 2.4, it can be observed that neither Impeller speed nor mass of input batch have the same trend on %fines of the milled granules at each level. 2D graphs of %fines of milled granules vs. Impeller speed, for each level of mass of input batch fed are shown below.

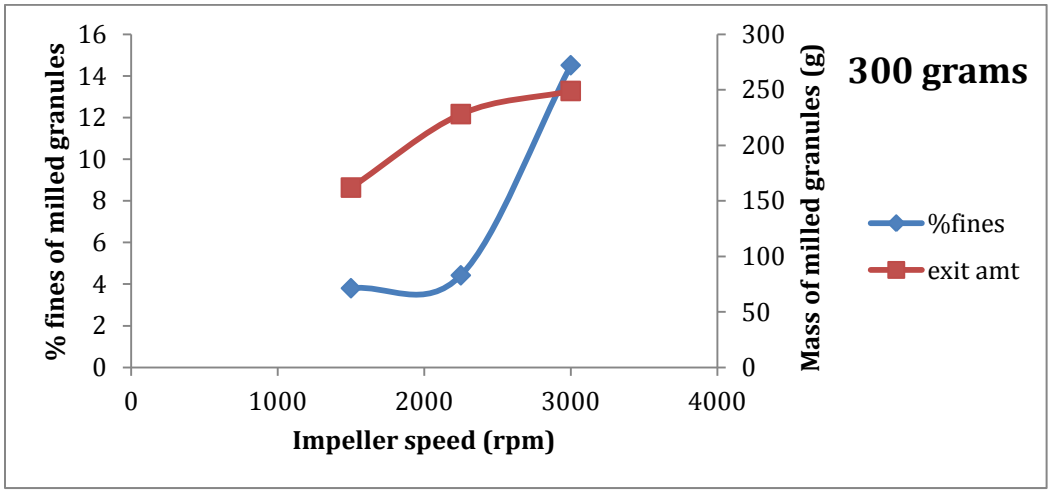


Figure 2.5 Plot showing the effect of Impeller speed on % fines and final mass of material collected, Batch size 300g.

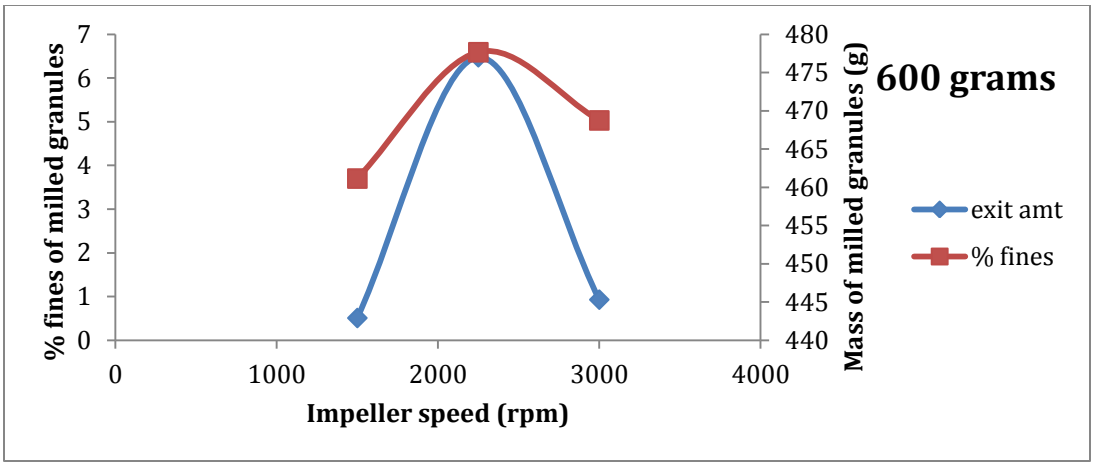


Figure 2.6: Plot showing the effect of Impeller speed on % fines and final mass of material collected Batch size 600g

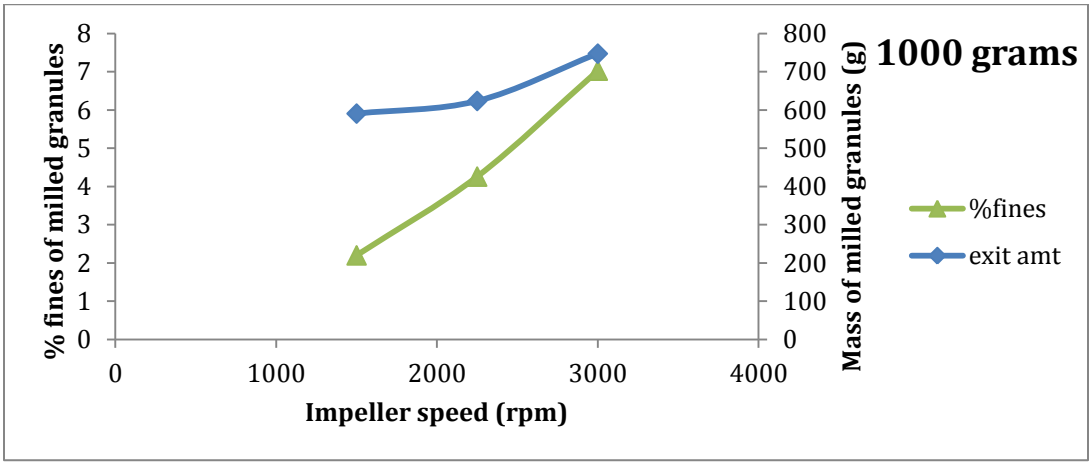


Figure 2.7 Plot showing the effect of Impeller speed on % fines and final mass of material collected, Batch size 1000g

Form the Figure 2.5, 2.6 and 2.7 it can be seen that the amount of fines and the final mass of granules collected are directly correlated, i.e. for the same amount of input batch fed, as the mass of exited granules increases the percentage of fines generated also increase. For Input batch of 300 grams, a quadratic relation between % fines generated and impeller speed can be observed, as mentioned in Schenck and Plank et al [29]. This can be attributed to the fact that

for 300 grams input batch size, there is more space for the particles present in the mill to move around. Because of this space the possibility of high velocity collisions between the particle and particle, particle and screen and particle and impeller increases. Therefore in this situation the effect of impart force imparted by the impeller is much higher compared to the other input batch sizes. The huge increase in %fines for 3000 rpm is because of the much higher force imparted due to the impeller, compared to 1500 and 2250 rpm.

2.5.2 Effect of Impeller speed and Mass of Input batch fed on d50 of the milled product

d50 is defined as the particle size under which there are 50%, weight or volume based, of the milled granules. Similarly *d90* and *d10* are particle sizes under there are 90% and 10% of milled product respectively.

In the present study d50, d10 and d90 values are weight based.

	Impeller speed (rpm)	**batch size(g)**	**d50(µm)**	**d90(µm)**	**d10(µm)**	**span**
1	2250	600	440	675	115	1.27
2	1500	1000	565	750	320	0.76
3	2250	300	420	655	15	1.52
4	3000	600	515	710	190	1.01
5	1500	300	490	795	180	1.26
6	3000	1000	405	660	110	1.36
7	1500	600	500	700	185	1.03

8	2250	1000	475	700	125	1.21
9	3000	300	400	645	120	1.31

Table 2.7 PSD of granules after milling

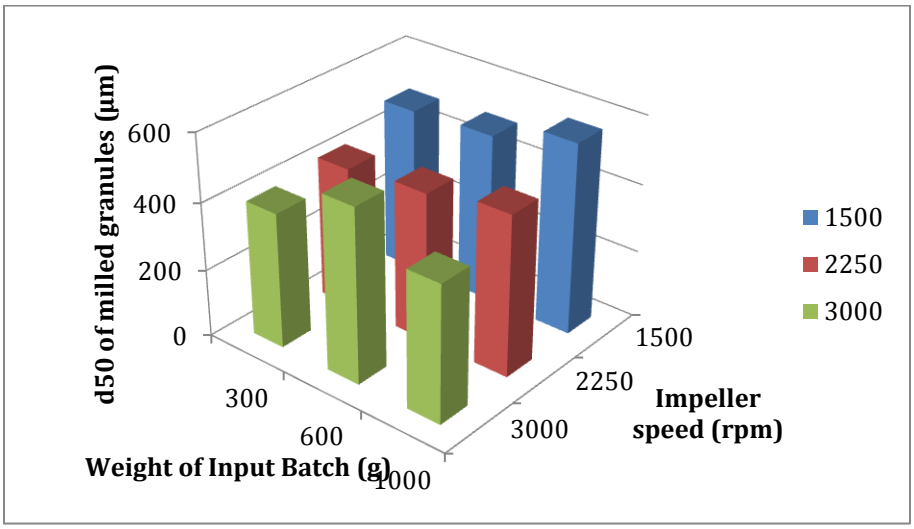


Figure 2.8 3D representation of d50 of milled granules in terms of Weight of input batch and Impeller speed

Though d50, d90 and d10 are measured, many studies generally describe a PSD by d50 as it is considered as the median particle diameter. Figure 2.8 is a graphical representation of the d50 data in the table 2.4. Similar to the 3D graph of %fines the plot in the Figure 2.8 also does not have the same trend of Impeller speed or weight of input batch on milled product d50 for all the levels of impeller speed or mass of input batch. To get a clear understanding of the effect of Impeller speed and weight of input batch fed on milled product d50, 2D graphs of milled product d50 vs. Impeller speed, for each level of mass of input batch fed are shown below.

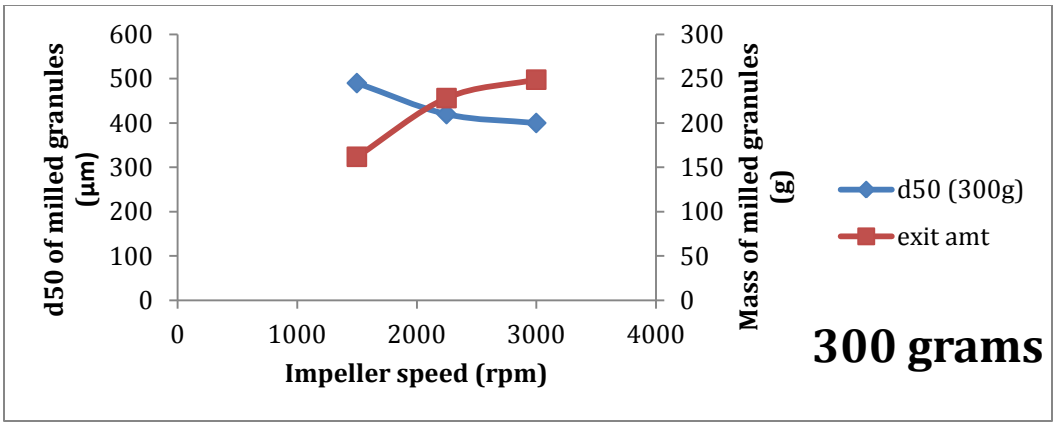


Figure 2.9 Plot showing the effect of Impeller speed on d50 and on final mass of material collected (Input batch size-300g)

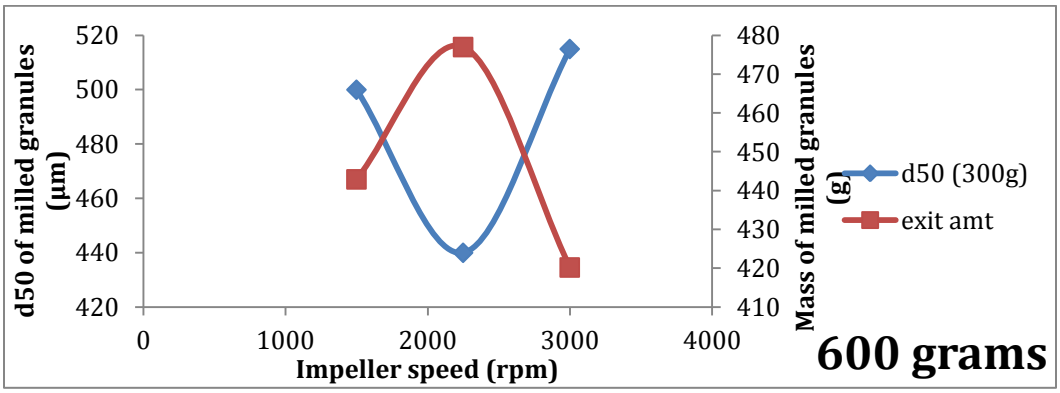


Figure 2.10 Plot showing the effect of Impeller speed on d50 and on final mass of material collected (Input batch size-600g)

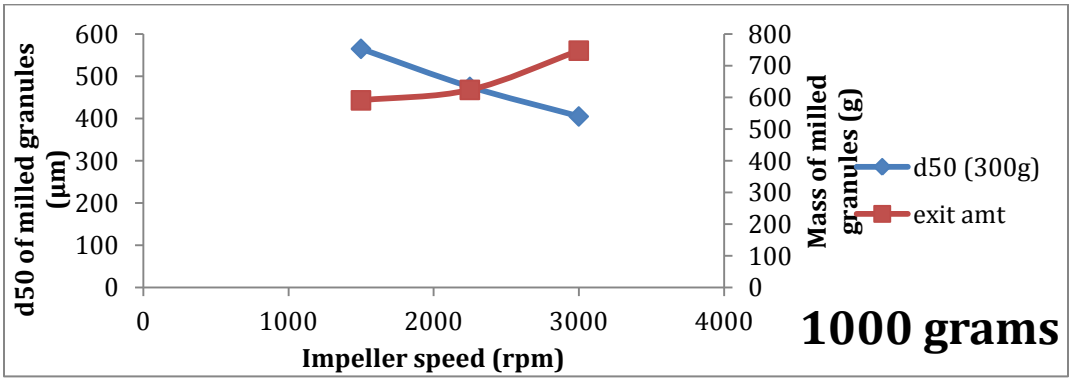


Figure 2.11 Plot showing the effect of Impeller speed on d50 and on final mass of material collected (Input batch size-1000g)

From the figure 2.9, 2.10 and 2.11 it can be seen that, for the same level of batch size, higher the total amount of material collected at end of milling cycle lower is the milled product d50, i.e.d50 of the milled product and the mass of granules collected at the end of milling cycle are inversely correlated. In section 2.5.1 it was learnt that mass of granules collected at the end of milling cycle and %fines are directly correlated. Therefore %fines and d50 of milled product are inversely correlated, i.e. lower the d50 of milled particle more are the fines generated during milling. This shows that, for the same formulation, a large degree of size reduction cannot be obtained without intense fines formation; this aligns with the work done by Verheezen et al. [30].

Earlier it was observed that both mass of input batch fed and the impeller speed affect the throughput of the mill. This can be thought of as milling being governed by two different regimes in a comil [19].

One is impact dominated which is breakage of particles due to the collision between particle and impeller and particle and particle or also because of shear between the impeller and screen [29, 30].

The other regime is called Quasi static, in this regime the mill throughput is dominated by the exit of the already existing smaller particles due to the movement of particles within the mill [19], created by the impeller. Therefore amongst the two regimes impact regime is more size reduction oriented. These regimes generally coexist and dominate during different times during the milling cycle.

As the impeller speed increases the particles stay in the mill for a longer time, despite the fact increase in impeller speeds means faster movement of particles [39, 40]. This might be because of the recirculation induced by high impeller speeds. But it is known that increase in impeller speed leads to more breakage as the particles in the mill are subjected to more collision and shear between the screen and the impeller [1, 29, and 30]. This means that quasi static regime which is dominated by exit of particles out of the mill due to their movement is favored by lower impeller speeds whereas the impact regime which is related to breakage is favored by the higher impeller speeds.

When the input batch fed in the mill is large there are more number of particles in the mill which are smaller than the screen size. For the same formulation and granulation parameters employed, though the ratio of particles above the screen size and below the screen size is still same, a smaller input batch size will have fewer particles smaller than the screen size. Therefore a larger input batch size is favored by the quasi static regime over a smaller batch size due to the presence of more number of particles smaller than the screen size, for the same formulation.

At the same time a smaller input batch size means that the particles in the mill have more possibility to achieve high velocities, at the same impeller speed, which would result in increased number of high speed collisions. For a larger batch the impact energy imparted by the impeller gets drained away in moving the huge number of particles around rather than resulting in high speed collisions of particles. Hence a smaller input batch is favored by impact regime over a large batch, for the same formulation.

For the present study, 300 grams input batch size and 3000 rpm is the most favored impact regime batch because of its low input batch size and high impeller speed. Therefore this batch results in the lowest d50 of 400 and highest % fines of 14.1. Similarly 1000 grams input batch

size and 1500 rpm is most favored by quasi static regime due to its large input batch size and low impeller speed and rightly the d50 of this batch is the highest at 565 and the % fines are lowest at 2.2. Rest of the runs, fall in between these two extremities.

	d50	d90	d10
Pre-milled	1000	2120	280
after 30 sec	290	500	110
after 5 min	515	710	190

Table 2.8 PSD of CAF-4 before milling, after 30 seconds of milling and after 5 min of milling at an impeller speed of 3000 rpm and input batch size of 600

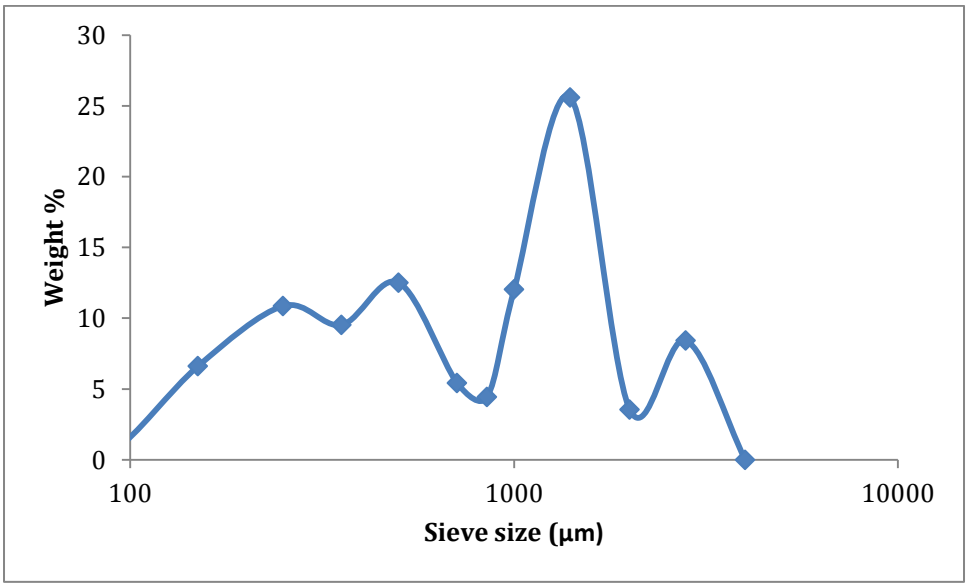


Figure 2.12 Log normal particle size distribution of CAF-4 before milling

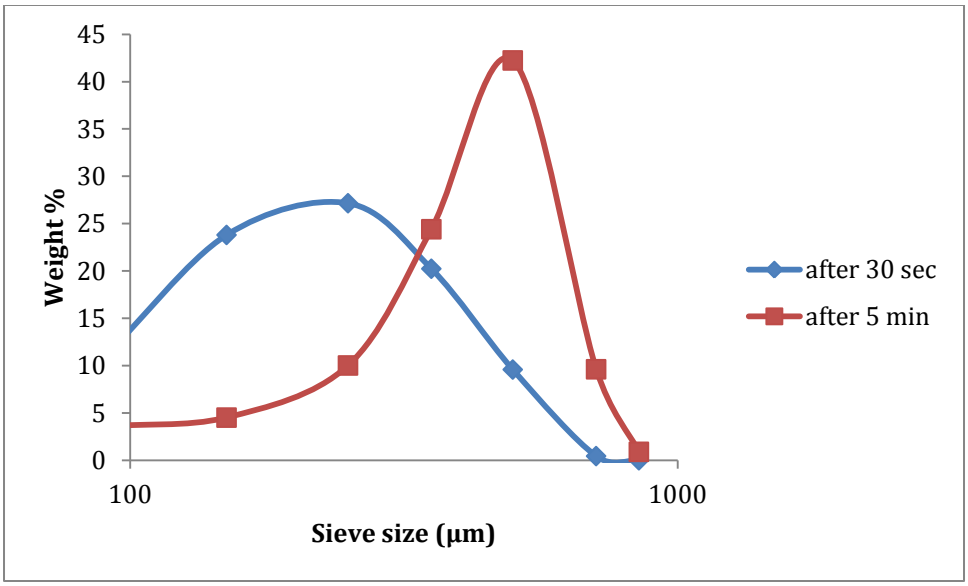


Figure 2.13 Log normal particle size distribution of CAF-4 after 30 seconds of milling and after 5 min of milling

It was observed that after 30 seconds of milling the mass of granules collected was 251.4 g. The input batch had approximately 285 grams that were lower than 1000µm, which is about the size of the screen. From the figure 2.13 it can be seen that as the time taken for milling increased the Particle size distribution shifted towards and the d50 of the granules increased. This can be attributed to the fact that initially during the mill cycle the particles which are already smaller than the screen size try to escape the mill, simultaneously there is occurrence of breakage but the majority of particles that escape are the already existing smaller particles. This explains also explains the huge exodus of particles initially, 251.4 g in 30 seconds, but by the end of 5 min cycle only 445.3 grams was collected. Therefore quasi static regime dominates the initial phase of milling which is later taken over by the impact regime.

2.5.3 Impact of input batch size on d50 of milled product

It has been observed that input batch size has an effect mill throughput; in this section the effect of input batch size on d50 of milled product will be studied.

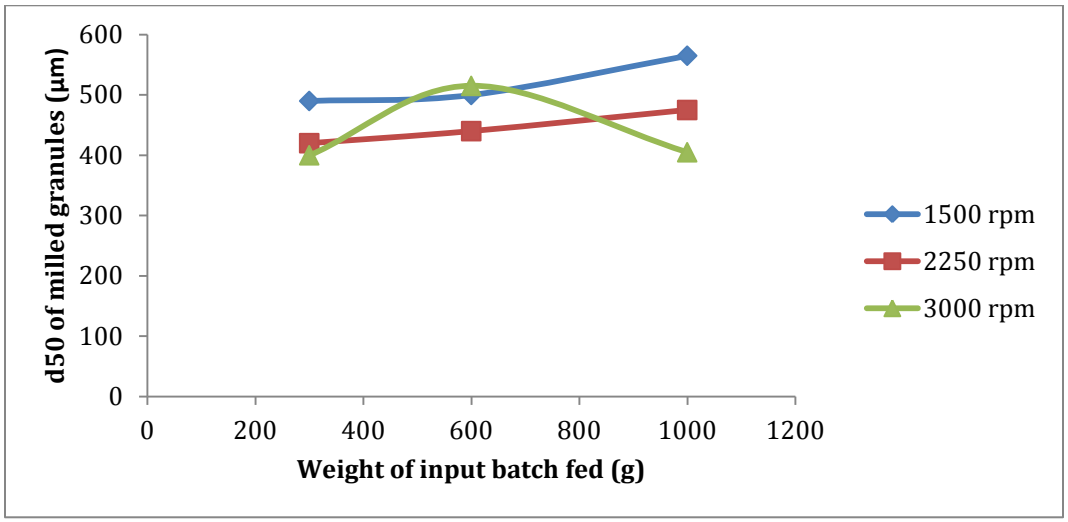


Figure 2.14: Plot showing the effect of input batch size on milled product d50 at different impeller speeds.

In the above graph it can be seen that between 300 g input mass, 600 g input mass and 1000 g input mass, 300 g has the lowest milled product d50. This is due to the fact that milling follows impact regime in the low fill level because of which there is more breakage due to impact. It can further be observed that d50 of the milled product is inversely proportional to mass of input batch fed. We see an exception for 3000rpm between medium and high fill levels; this might be because of the different regimes in which these two fill levels operate. High fill level being an impact regime towards the end leads to more breakage of particles thereby decreasing the d50 in comparison to the cusp regime of medium level.

2.5.4 Effect of Milling on Span

As mentioned earlier span in one of the parameter by which PSD is described. Span is a measure for the width of the distribution. Span is given by,

$$span = \left(\frac{d90 - d10}{d50}\right)$$

A lower span is always desired as a lower span means a narrower distribution. But as d50 of granules increases a larger difference in d90 and d10 is also going to result in a smaller span because of the large d50, i.e. granules with a d90, d50, d10 of 675 µm, 440 µm, 115µm respectively has the same span as the granules with a d90, d50, d10 of 2410 µm, 1500 µm, 500 µm respectively. Therefore span should always be considered with caution and it is best to use span alongside PSD graph as a measure of width of a size distribution curve.

span before milling	span after milling
1.84	1.27
1.84	0.76
1.84	1.52
1.84	1.01
1.84	1.26
1.84	1.36
1.84	1.03
1.84	1.21
1.84	1.31

Table 2.9 Span for a sample before and after milling at various mill conditions

The above table describes the span values before and after milling for the samples in table 2.4. Granules with the same formulation, granulated at the same settings are subjected to milling at different conditions. One way Anova was performed on span to verify the effect of milling and it

was found that milling has a statistically significant impact on span, with F value being 117.0153 and F crit being 4.49 and a P value of 9.11E-09.

Anova: Single Factor

SUMMARY

Groups	*Count*	*Sum*	*Average*	*Variance*
span before milling	9	16.56	1.84	5.55E-32
span after milling	9	10.41203	1.156892	0.03589

ANOVA

Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	2.099861725	1	2.099862	117.0153	9.11E-09	4.493998
Within Groups	0.28712304	16	0.017945			
Total	2.386984764	17				

Table 2.10 Anova table for effect of milling on span

From the P-value and F crit value it can be seen that milling has a significant effect on span and milling decreases the width of the PSD of the granules. The mill and granulation parameters used for testing the effect of milling on span are mention in the appendix, table A 1.4.

2.5.5 Effect of milling on Friability of milled granules

As discussed earlier friability is the measure of granule strength. Friability was measured by allowing the sample to falling shocks along with 200 glass beads, about 4mm in diameter, for 10 min in a friabilator. The table 2.7 describes the friability values before and after milling for the samples in table 2.4. In the table 2.7 we can see that there are instances of both increase and decrease of friability after milling. This can be attributed to the fact that during milling due to the collisions of the particles with the impeller and among themselves new fractures might appear and the old fractures might get longer. This leads to lowering of granule strength, at the same time it is also known that as the particle size decreases it becomes difficult to break the granule, as it requires more energy to pass the threshold energy.

Friability (before milling)	**Friability (after milling)**
4.10	2.1
4.10	4
4.10	2.5
4.10	1.2
4.10	3
4.10	4.7
4.10	3.9

4.10	1.6
4.10	5

Table 2.11 Friability for a sample before and after milling at various mill conditions

The above table describes the friability values before and after milling for the samples in table 2.4. Granules with the same formulation, granulated at the same settings are subjected to milling at different conditions. One way Anova was performed on friability to verify the effect of milling and it was found that milling has a statistically significant impact on friability, with F value being 4.76 and F crit being 4.49 and a P value of 0.044. Therefore, milling effects friability of granules and the strength of the milled granules depends on crack propagation/ new crack emergence and the milled size of the granules. As mentioned earlier the strength of the granule might decrease when the existing cracks in the granules promulgate and at the same time when the particle size decreases it becomes more difficult to break them down further.

Anova: Single Factor

SUMMARY

Groups	*Count*	*Sum*	*Average*	*Variance*
Friability (before milling)	9	36.9	4.1	8.87E-31
Friability (after milling)	9	27.99062	3.110069	1.852394

ANOVA

Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	4.409837	1	4.409837	4.761229	0.044364	4.493998

Within Groups	14.81916	16	0.926197
Total	19.22899	17	

Table 2.12 Anova table for effect of milling on Friability

The mill and granulation parameters used for testing the effect of milling on friability are mention in the appendix, table A 1.4.

2.5.6 Effect of milling on Porosity of milled granules

Porosity is very important as it affects the tablet compressibility. Too low porosity values means the granules are very dense, which affects tablet compaction and dissolution. On the other hand, high porosity could lead to formation of brittle and weak granules.

Porosity (%)- before milling	Porosity(%)- after milling
43.6641	43.89
43.6641	41.41
43.6641	44.78
43.6641	39.64
43.6641	41.55
43.6641	41.15
43.6641	41.51
43.6641	39.58
43.6641	42.91

Table 2.13 Porosity values before and after milling

The above table describes the porosity values before and after milling for the runs in this section. For like all the other runs in this section the formulation and granulation parameters have been kept constant and milling was performed at different Impeller speed and mass of input batch fed conditions.

One way Anova as performed on porosity also, it was found that milling has a statistically significant effect on Porosity. F value of this Anova test is 9.83 and F crit being 4.49 and a P value of 0.006. Hence milling effects porosity, the porosity of the granules after milling might increase or decrease depending on whether pore volume per granule volume increases or decreases after milling. During milling, the length of pores of the pre-milled granules might decrease after the granules break; the pores also might break open. This leads to change in pore volume to granule volume during milling.

Anova: Single Factor

SUMMARY

Groups	*Count*	*Sum*	*Average*	*Variance*
Porosity (%)-before milling	9	392.976	43.6641	5.68E-29
Porosity(%)-after milling	9	376.42	41.8244	3.0988 03

ANOVA

Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	15.2294965	1	15.2295	9.829278	0.006391	4.493998
Within Groups	24.7904222	16	1.549401			
Total	40.0199188	17				

Table 2.14 Anova table for effect of milling on Porosity

The mill and granulation parameters used for testing the effect of milling on porosity are mention in the appendix, table A 1.4.

2.5.7 Effect of milling on Bulk Density and Tap density of milled granules

For Bulk and Tap density Anova was conducted to test the statistical significance and it was found that both are statistically significant with P values of 0.000499 and 2.91E-07 respectively. Since Bulk density is an important property for further downstream processing and is necessary for the development of tablet press model, an attempt was made to develop a simple regressive predictive model for Bulk Density.

RPM	**Batch size (g)**	**L/S ratio**	**bulk density (g/ml)**	**tap density (g/ml)**
2250	600	0.55	0.6901	0.8133
1500	1000	0.55	0.7213	0.8109
2250	300	0.55	0.6970	0.7990

3000	600	0.55	0.7644	0.8534
1500	300	0.55	0.7278	0.8114
3000	1000	0.55	0.6996	0.8345
1500	600	0.55	0.7067	0.8105
2250	1000	0.55	0.7342	0.8254
3000	300	0.55	0.6732	0.7775
3000	600	0.45	0.6444	0.7824
3000	600	0.5	0.6277	0.7667

Table 2.15 Bulk Density and Tapped Density values used for the regression model

By regressing the above data the following equations were developed,

$$\text{Bulk Density} = 5.3298 - 0.3607m - 20.7723d50 + 0.2279m^2 + 24.2549d50^2 - 4.7145d10^2 \quad (7)$$

In the above equation m is the mass of the input feed (kg); d50 and d10 mentioned in the equation (7) are that of the milled granules in mm.

For the above equation Regression Statistics were as follows, $R^2 = 0.9534$, Adjusted $R^2 = 0.8370$ and significance F = 0.1124. The above equation was validated and the error was found to be around 10%.

Similarly an equation for Tap Density was also developed,

$$\text{Tapped Density} = 5.387 - 0.1081m - 20.4044d50 + 0.0563m^2 + 23.2487d50^2 - 4.0797d10^2 \quad (8)$$

In the above equation m is the mass of the input feed (kg), d50 and d10 mentioned in the equation (8) are that of the milled granules in mm.

For the above equation Regression Statistics were as follows, R^2 = 0.995, Adjusted R^2 = 0.983 and significance F = 0.0119. The above equation was validated and the error was also found to be around 10%.

Regression parameters used for the regression of bulk and tap density are mentioned in the appendix, A 1.5 and A 1.6 respectively.

2.5.8 Effect of mill screen type on % fines of milled granules

Screen of a comil affects the Particle size distribution of the milled granules. It is considered one of the most important parameters that effect the PSD as it determines the upper limit of the milled particles and also aids in breakage of particles in the comil. A comil has two types of screens, a grated screen and a normal screen. A grated screen has sharp edged bores drilled towards the inside of the screen compared to the round bores of a normal screen. The screen sizes used here 991µm for a normal screen and 1013µm screen for a grated screen.

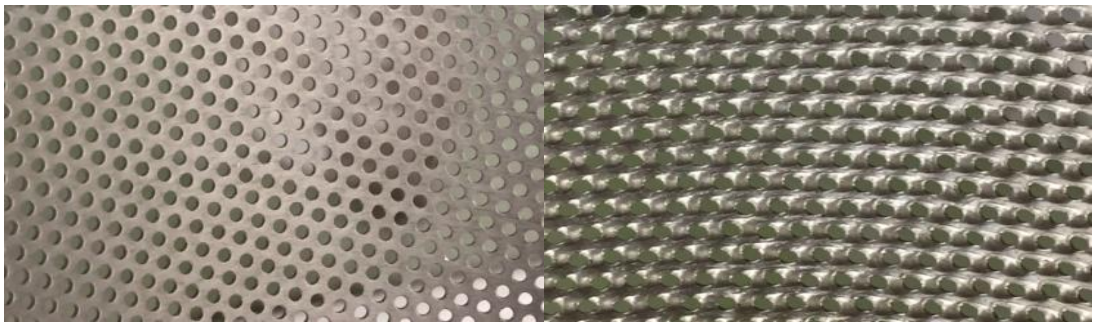


Figure 2.15 Bores of a normal screen (left hand side image), bores of a grated screen (right hand side image)

RPM	batch fed (g)	Milled mass (g)	d50 (µm)	d90 (µm)	d10 (µm)	span	%fines	Friability (%)	Porosity (%)	Bulk density (g/ml)	Hausner Ratio
3000	300	248.87	400	645	120	1.3125	14.51	5	42.91	0.673	1.155
3000	600	420.21	515	710	190	1.0097	5.03	1.2	39.64	0.764	1.116
3000	1000	747.5	405	660	110	1.3580	7.03	4.7	41.15	0.6996	1.193

Table 2.16 Mill Parameters and Milled granule properties for normal screen runs

RPM	batch fed (g)	Milled mass (g)	d50 (µm)	d90 (µm)	d10 (µm)	span	%fines	Friability (%)	Porosity (%)	Bulk density (g/ml)	Hausner Ratio
3000	300	283.5	425	700	79	1.4612	11.60	3.256	42.35	0.7002	1.2015
3000	600	580.4	442	710	82	1.4208	10.36	3.420	41.06	0.7004	1.1739
3000	1000	950.3	460	762	82	1.4783	11.2	3.185	40.8	0.6996	1.1608

Table 2.17 Mill Parameters and Milled granule properties for Grated screen runs

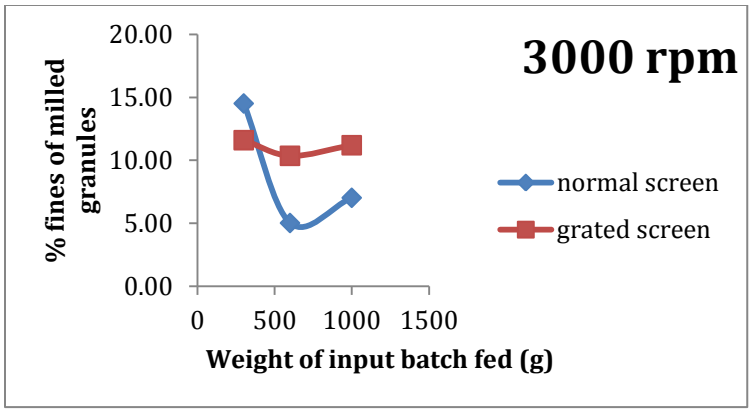


Figure 2.16 Plot showing the effect of input batch size on %fines of milled product for normal and grated screen types at an impeller speed of 3000 rpm

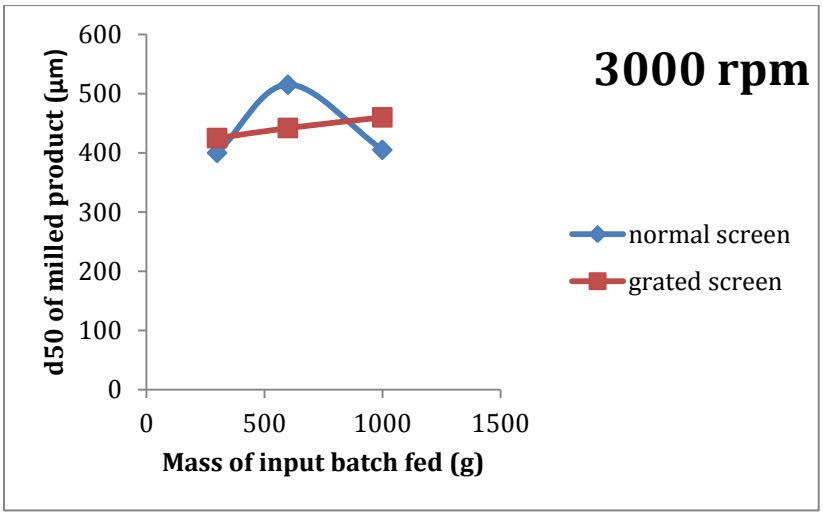


Figure 2.17 Plot showing the effect of input batch size on d50 of milled product for normal and grated screen types at an impeller speed of 3000 rpm.

Verheezen et al [30] states that for a grated screen the residence time of a particle in the mill is low as it forces the in-size particles to exit the mill. Therefore this results in more size reduction in a mill with normal screen due to increased residence time. Schenk and Plank [29] observed that the same effect and stated that the grated screen generates fewer fines.

But instead of stating decreased residence time as the reason for fewer fines with a grated screen they proposed a new theory, according to which the grated surface texture of grated screen aids in the breakage of granule by chipping of fragments from large agglomerates.

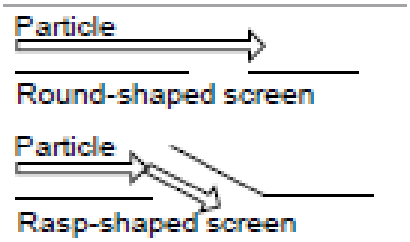


Figure 2.18 Figure showing the possible particle exit routes for a normal screen (round shaped screen) and a grated screen (rasp-shaped screen) [30]

From the figure 2.14 it can be observed that on the contrary to Schenk and Plank the grated screen has more number of fines for both 600 grams and 1000 grams input feed at an impeller speed of 3000 rpm. This shows that weight of input batch fed has an effect on the effect of screen type. As opposed to the conclusion drawn by Verheezen et al[30], it can also be observed from figure 2.15 that d50 of milled product is lower for input batch size of both 300 and 1000g.

From the figure 2.14 it can be observed that both types of screens have similar trends for % fines vs. weight of input batch fed, at 3000 rpm. From table 2.12 and 2.13 it can be seen that for the same mill cycle time of 5 min the final milled amount is more for each run of grated screen, which means the grated screen runs have shorter residence time in the mill. Therefore the lower percentage of fines for grated screen cannot be because of longer residence times of grated screens than normal screens but is because of more breaking due to the rough surface texture of the grated screen.

CHAPTER 3: EFFECT OF GRANULATION PARAMETERS AND BINDER ADDITION

Apart from the mill processing parameters such as mill Impeller Speed, mass of input batch fed, screen size, screen type etc, the other parameters that can affect the output of a mill are the input material properties. Material properties like particle size of input batch, hardness etc. can play a significant role in critical quality attributes of the output granules. This work is an attempt to study the effect of some of these parameters on the critical quality attributes of the out milled granules.

In the present study input to the comil is the product of wet granulation. Many of the properties of the granules formed by wet granulation are affected by the process parameters of wet granulation like the liquid to solid ratio, impeller speed, wet massing time, chopper speed etc. Apart from these parameters one more important aspect that alters the properties of granules is its formulation. Liquid to solid ratio and impeller speed are chosen as the granulation parameters to study their effect on milled product. The effect of Binder strength was studied using Polyvinylpyrrilodine (PVP K-30) as the binder.

3.1 Equipment and Experimental Procedure

Micro crystalline cellulose Avicel PH101, Lactose Monohydrate and Caffeine were premixed using a tote blender for 30 minutes, at 25 rpm, in the ratio of 46%, 46% and 8 %respectively. The batch size of tote blender is 6.5 kgs. These pre-blends were used to study the effect of liquid to solid ratio (L/S ratio) and Impeller speed on the milled product. To study the effect of binder addition no premixing as performed. A 2.4 L batch granulator (Key-International table-top high

shear granulator) at various granulator settings with a batch size of 300 grams was used for granulation. These granules are then air dried for 48 hours, to less than 3% of moisture content, before milling them in a conical screen mill (Quadro 197-R) at conditions described in the table below.

Impeller speed	**3000 rpm**
Mass of input batch	550 grams
Screen size	991 µm
Screen type	Normal (round)
Mill run time	30 seconds

Table 3.1 Mill parameters employed

3.2 Effect of Liquid to Solid ratio of input granules on milling

Liquid to Solid ratio (L/S ratio) is the ratio between the mass of liquid added while granulation and the mass of the input batch fed. L/S ratio is an important parameter of wet granulation that significantly effects the Particle size distribution and porosity of the granules [25, 41, and 42]. In the present work, L/S ratio was varied from 0.45 to 0.55, based on previous experimentation. Initially dry pre blends are added to the granulator and are mixed for 2 min followed by 2 min of water addition time; in these 2 min all the water pertaining to that batch of granulation is added. After this the 3 min of wet massing time is carried out, during which both impeller and chopper are operated. For all the runs in this section 8% caffeine, 46% Avicel PH 101 and 46% Lactose Monohydrate formulation was used.

	Granulation Parameters			Input granule PSD		
	Impeller speed (rpm)	Chopper speed	% water	d50 (µm)	d90 (µm)	d10 (µm)
CAF-1	170	6000	45	600	1900	190
CAF-2	170	6000	50	1060	2070	280
CAF-3	170	6000	55	1400	2150	470

Table 3.2 Granulation parameters employed, mill parameters employed and PSD of the input feed granules, for the study of effect of L/S ratio of input granule on milled granules

			Post mill properties				
	% water	milled mass at 30 sec (g)	d50 (µm)	d90 (µm)	d10 (µm)	span	% fines
CAF-1	45	315.55	212	438	105	1.571	8.18
CAF-2	50	279	220	410	105	1.386	7.73
CAF-3	55	133.5	385	618	140	1.242	5.38

Table 3.3 PSD of the milled granules and the amount of granules milled, for the effect of L/S ratio of input granule experiments

	% water	**Friability before milling (%)**	**Friability post milling (%)**	**Porosity before milling (%)**	**Porosity post milling (%)**	**Bulk Density before milling (g/ml)**	**Bulk Density post milling (g/ml)**	**Hausner ratio before milling**	**Hausner ratio post milling**
CAF-1	45	12.5	22.5	48.4152	52.2556	0.6302	0.6444	1.0963	1.2143
CAF-2	50	5	16.8	41.67	46.4814	0.7085	0.6277	1.0940	1.2214
CAF-3	55	3.346	3.7	40.52	53.9402	0.6441	0.7325	1.1409	1.1042

Table 3.4 Friability, Porosity, Bulk Density and Hausner ratio, before and after milling, for the effect of L/S ratio of input granule experiments

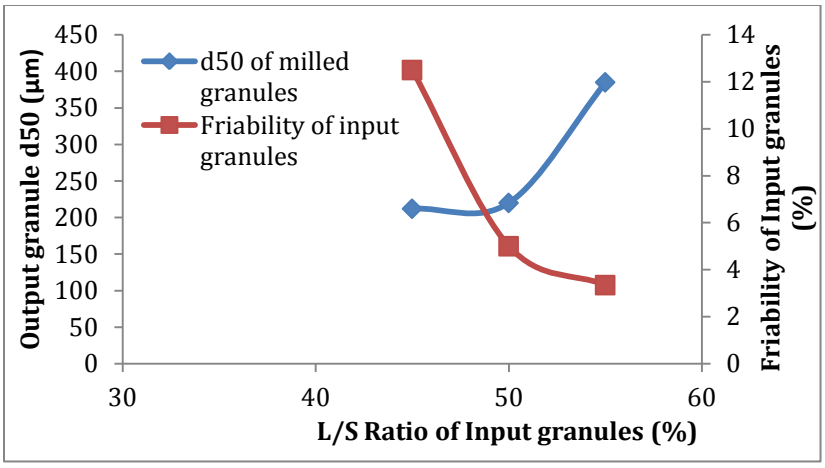


Figure 3.1 Comparison of Output granule d50 vs. L/S ratio of input granules, Friability of Input granules vs. L/S Ratio

From the figure 3.1 it can be seen that as the L/S ratio increases the d50 of the milled granules decreases and also the friability of input granules increases with the L/S ratio. It is known that as the L/S ratio increases the granules become denser and harder[43, 44] thereby decreasing the friability of granules and as the friability of input granule decreases it becomes difficult for the mill to break it, thereby leading to higher d50. It can also be seen that with increase in the L/S ratio the particle size of input granules increased which might have also added as reason to the increasing milled granule d50 trend.

It can also be explained with help of different regimes that govern during a milling operation. Since the mill was run only for 30 seconds the majority of the cycle would have been dominated by the quasi static regime. From Table 3.3 it can be seen that CAF-1 (0.45 L/S ratio) has the maximum granules under the screen size of 991µm followed by CAF-2 (0.5 L/S ratio) and finally CAF-3 (0.55 L/S ratio) has the least amount of granules below 991µm. The d10's of the input batches are also in the same order 0.45<0.5<0.55. In Quasi static regime the main reason for throughput of is due to the exit of already existing granules that are smaller than the screen size

of 991 µm. This effect is also reciprocated in the mass of granules collected after milling which can be seen in milled amount column of Table 3.4. Thus leading to observed trend of d50 for the output granules.

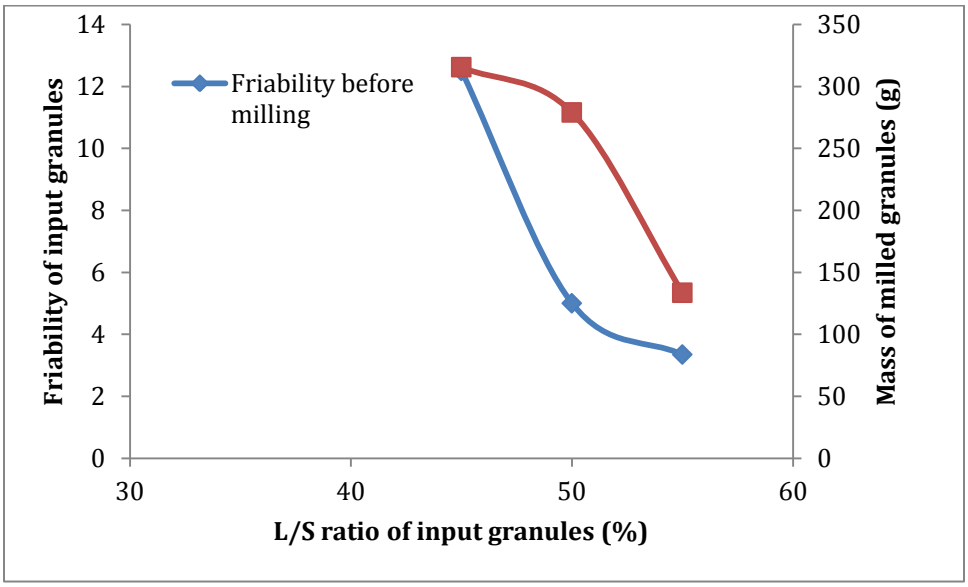


Figure 3.2 Comparison of Input Granules Friability vs. L/S ratio of input granules, weight of milled granules vs. L/S ratio of input granules.

The above figure shows that as friability of input granule decreases the weight of milled granules also decreases. This is attributed to the increase in strength of the granules due to decrease in friability. The trend of mass of milled granules as explained earlier could also be because of the quasi static regime.

3.3 Effect of Impeller Speed of Granulator on milling

Previously in many studies it was reported that Impeller speed has a significant effect on critical quality attributes of granules in high shear wet granulation [41]. Impeller aids in granule growth, consolidation and agglomeration during the wet massing stage of batch granulation. Due to the high speed rotation created by the impeller, formation of granules

takes place and it also affects the particle shape and porosity [25]. It was found that very high impeller speeds increased agglomeration and lead to formation of very large granules [42]. Therefore for this section low to medium impeller speeds of 150 to 190 rpm are chosen. For all the runs in this section 8% caffeine, 46% Avicel PH 101 and 46% Lactose Monohydrate formulation was used.

	Granulation Parameters			**Input granule PSD**		
	Impeller speed (rpm)	Chopper speed	% water	d50	d90	d10
CAF-4	150	6000	55	1000	2120	280
CAF-3	170	6000	55	1400	2150	470
CAF-5	190	6000	55	750	1700	450

Table 3.5 Granulation parameters employed, mill parameters employed and PSD of the input feed granules, for the effect of Impeller Speed of Granulator experiments

	RPM	**milled mass at 30 sec**	**d50 (µm)**	**d90 (µm)**	**d10 (µm)**	**Span**	**% fines**
CAF-4	150	251.4	290	500	110	1.3448	7.83
CAF-3	170	133.5	385	618	140	1.2416	5.38
CAF-5	190	326.38	485	665	310	0.7320	1.875

Table 3.6 PSD of the milled granules and the amount of granules milled, for the effect of Impeller Speed of Granulator experiments

	RPM	Friability before milling (%)	Friability post milling (%)	Porosity before milling (%)	Porosity post milling (%)	Bulk Density before milling (g/ml)	Bulk Density post milling (g/ml)	Hausner ratio before milling	Hausner ratio post milling
CAF-4	150	4.1	6.9	43.66 41	48.73 22	0.6731	0.6888	1.1216	1.1555
CAF-3	170	3.346	3.7	40.52	53.94 02	0.6441	0.7325	1.1409	1.1042
CAF-5	190	6.676	3.75	41.23	49.86	0.6455	0.7915	1.1149	1.0795

Table 3.7 Friability, Porosity, Bulk Density and Hausner ratio, before and after milling, for the effect of L/S ratio of input granule experiments

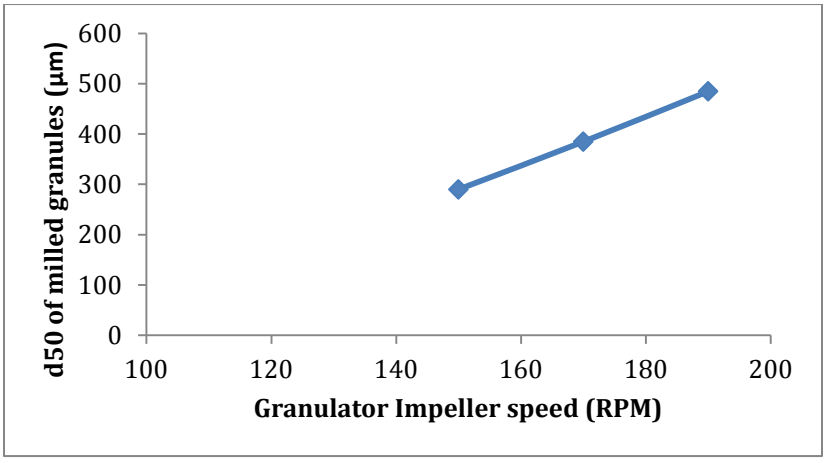


Figure 3.3 Plot showing the effect of impeller speed on milled granule d50

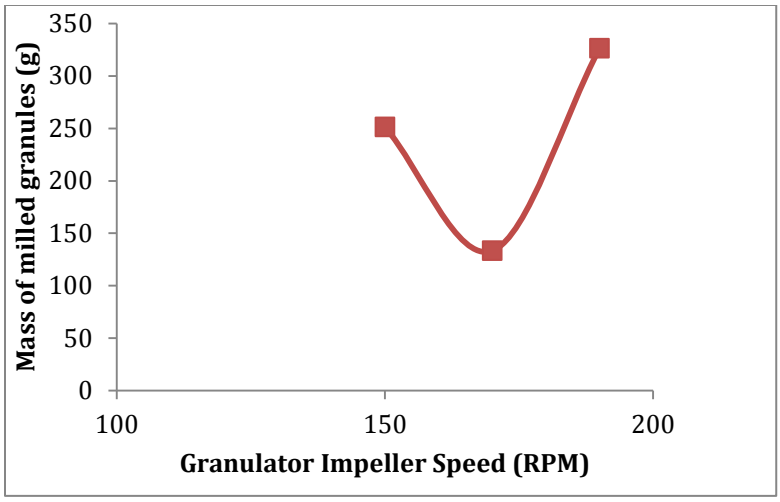


Figure 3.4 Plot showing the effect of impeller speed on mass of milled granules collected

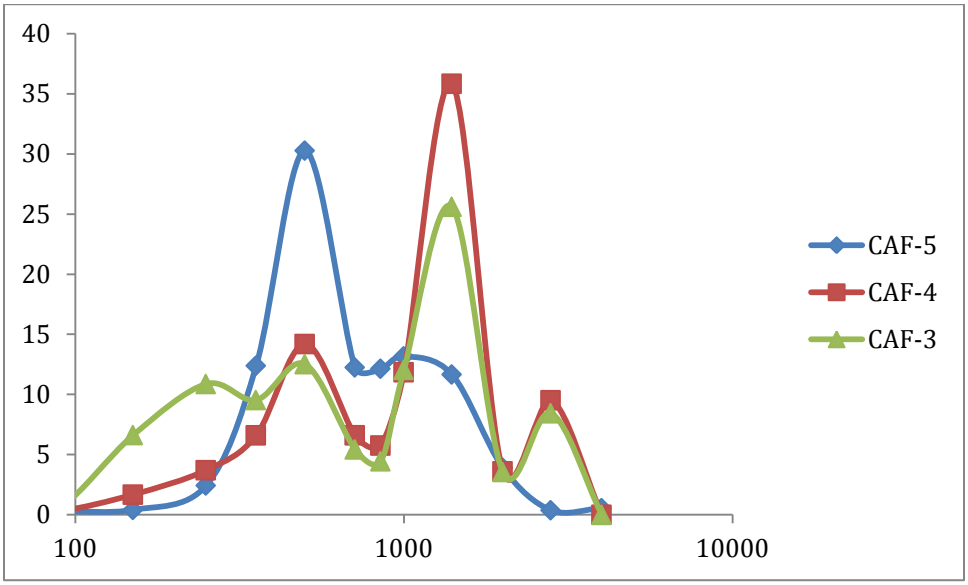


Figure 3.5 Plot showing the Log normal Particle Size Distributions of granules processed with 150 rpm (CAF-6), 170 rpm (CAF-5) and 190 rpm (CAF-8)

From figure 3.3 it can be observed that with increase in impeller speed there is an increase in the milled granule d50. Though the explanation to this trend is not clear from the d50's or the friability's of input CAF -4 (150 rpm), CAF-3 (170 rpm) and CAF-5 (190 rpm) granules, from the plot of figure 3.5 it can be seen that the distributions of the granulation batches aids the

understanding of this trend. From the plot, it can be observed that CAF-5 has a much narrow distribution with a peak around 500µm. Between CAF-4 and CAF-3 it can be seen that though both of them have a peak at similar position between 1000 and 2000µm (around 1400µm), the peak of CAF-4 is much smaller than that of the CAF-3. As discussed earlier mostly for the first 30 seconds of milling cycle the Quasi static regime dominates, therefore the mass of milled granules collected is in the order of CAF-5 > CAF-4 > CAF-3, as seen in the figure 3.4.

Granulation batch	mass below 1000µm (g)
CAF-5	422.14
CAF-4	284.96
CAF-3	201.18

Table 3.8 Mass of granules below 1000g for each granulation batch

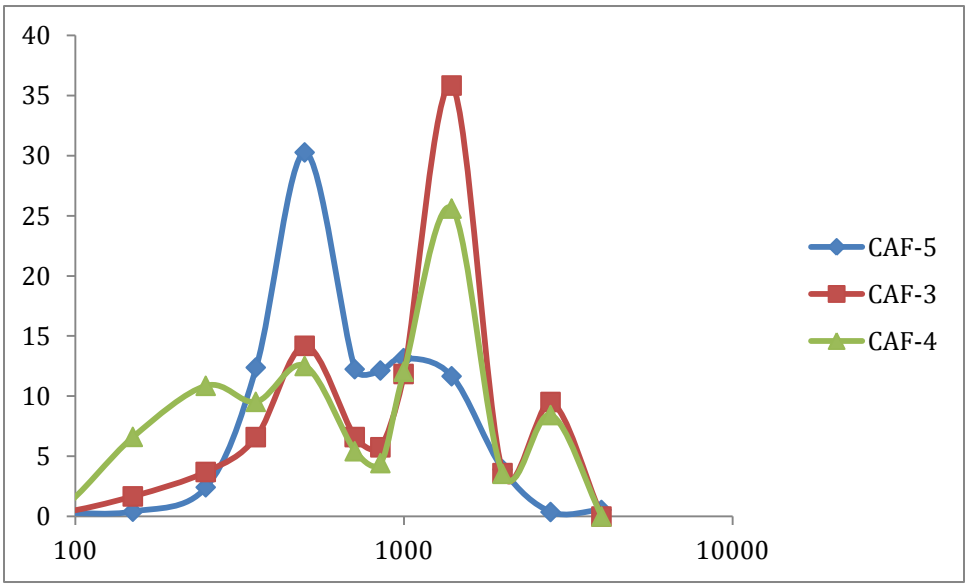


Figure 3.6 Plot showing the Log normal particle size distribution for granules that are smaller than 1000µm, for each granulation batch.

From Table 3.10 and figure 3.6 we can see that CAF-5 has a lot of particles that are in the region between 500µm and 1000µm, especially around 500µm which might have escaped the mill during the quasi static regime of the first 30 seconds of the mill cycle. Similarly CAF-4 has a lot of particles lower than 500µm which could have escaped the mill during the 30 seconds of mill cycle leading to the lowest d50. CAF-3 has the lowest amount of granules that are below 1000µm and their distribution is in between CAF-4 and CAF-5 because of which its d50 value is also in the middle.

3.4 Effect of Binder addition to the formulation on Milled granules

As mentioned earlier apart from the process parameters and equipment parameters one of the most important properties that affect the granules are input material properties. For example the solubility of the Active Pharmaceutical Ingredient affects the wetting of the drug and thereby PSD, hardness, segregation etc. Excipients are added to the formulation for various reasons like to improve the flow properties of the material, to strengthen the tablet, to improve compressibility of the material etc. Therefore the properties of excipients like flowability, hydrophobicity all play a role in the quality of the granule and hence the tablet. Particle size distribution and the amount of individual materials in the formulation also have a significant effect on the critical quality attributes of tablets.

For that reason the current section focuses on studying the effect of binder addition on the milled product. Binder is added to a formulation to increase the cohesiveness of the powders, so that they can bond together and form granules which under compaction can be made into a tablet [45]. For the present work Polyvinylpyrrilodine (PVP K-30) is being used as the binder. In this study different amount of binder is added in each granulation run and

the effect of this change in binder amount in the formulation on the milled granules is being studied.

During granulation weighed, determined according to the formulation, batches of MCC Avicel PH-101, Lactose Monohydrate, Caffeine and PVP were added to the granulator to make a 300 grams batch. These unblended powders were mixed for 2 min followed by 2 min of water addition time at predetermined Impeller and L/S ratio settings. Finally the blend was subjected to 3 min of wet massing time. For this section the granulation and mill parameters were kept constant. Similar to the effect of granulation parameters, here also the mass of input batch fed was around 550 grams.

The following table shows the granulation settings used for experiments in this section,

	Granulation Parameters		
	Impeller speed (rpm)	Chopper speed (rpm)	% water
CAF-4	150	6000	55
CAF-6	150	6000	55
CAF-7	150	6000	55

Table 3.9 Granulation parameters used for effect of binder addition experiments

	Formulation				Input granule PSD		
	% caffeine	% Avicel PH-101	% Lactose monohydrate	% PVP (K-30)	d50 (µm)	d90 (µm)	d10 (µm)
CAF-4	8	46	46	0	1000	2120	280
CAF-6	8	45	45	2	1020	2010	480
CAF-7	8	44	44	4	1900	3200	1075

Table 3.10 Formulation employed, mill parameters employed and PSD of the input feed granules, for the effect of Binder Addition experiments

			Post milled properties				
	% PVP	milled amount at 30 sec	d50 (µm)	d90 (µm)	d10 (µm)	span	% fines
CAF-4	0	251.4	290	500	110	1.3448	7.83
CAF-6	2	210.1	538	685	220	0.8643	5.255
CAF-7	4	26.2	355	780	30	2.1127	27.3135

Table 3.11 PSD of the milled granules and the amount of granules milled, for the effect of Binder Addition experiments

	% PVP	Friability before milling (%)	Friability post milling (%)	Porosity before milling (%)	Porosity post milling (%)	Bulk Density before milling (g/ml)	Bulk Density post milling (g/ml)	Hausner ratio before milling	Hausner ratio post milling
CAF-4	0	4.1	6.9	43.6641	48.7322	0.6731	0.6888	1.1216	1.1555
CAF-6	2	3.9	3.970	38.54	45.26	0.5768	0.7277	1.1469	1.1294
CAF-7	4	2.812	7.66	34.68	35.24	0.5645	0.6278	1.1549	1.2951

Table 3.12 Friability, Porosity, Bulk Density and Hausner ratio, before and after milling, for the effect of Binder Addition experiments

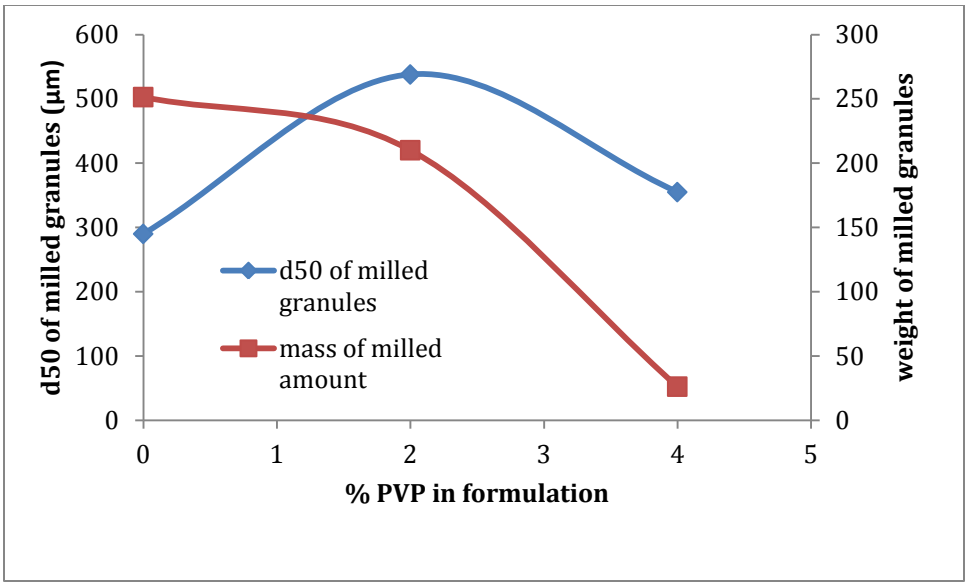


Figure 3.7 Plot showing the effect of %PVP in formulation on d50 of milled granules

It can be observed in the Figure 3.7 that initially with the increase in %PVP the d50 of the milled granules increased, this is due to the increase in strength and particle size of input granule especially the d10. As mentioned earlier the mill is dominated by quasi static regime during the first 30 seconds of milling and since the d10 of CAF-6 is also greater than that of CAF-4, CAF-4 has lower d50 than CAF-6.

On further increasing %PVP the d50 dropped, this might be due to the fact that the strength and particle size of the input granule increased so much that even the d10 is higher than the screen size of 991µm. This means that due to the lack of many granules under the screen size of 991µm, this batch was dominated by Impact regime. Since the granules were too large and hard the residence time of the granules in the mill increased drastically there by taking more number of hits and resulting in lower PSD. The same reasoning can be stated for the mass of granules collected at the end of mill cycle trend too.

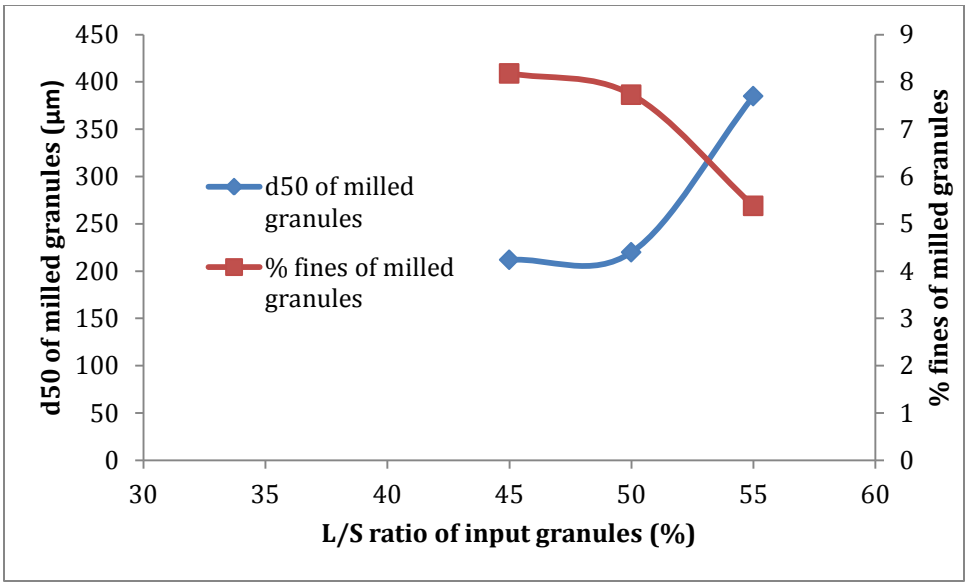


Figure 3.8 Plot showing the effect of L/S ratio on the d50 of milled granules and on the % fines of the milled granules

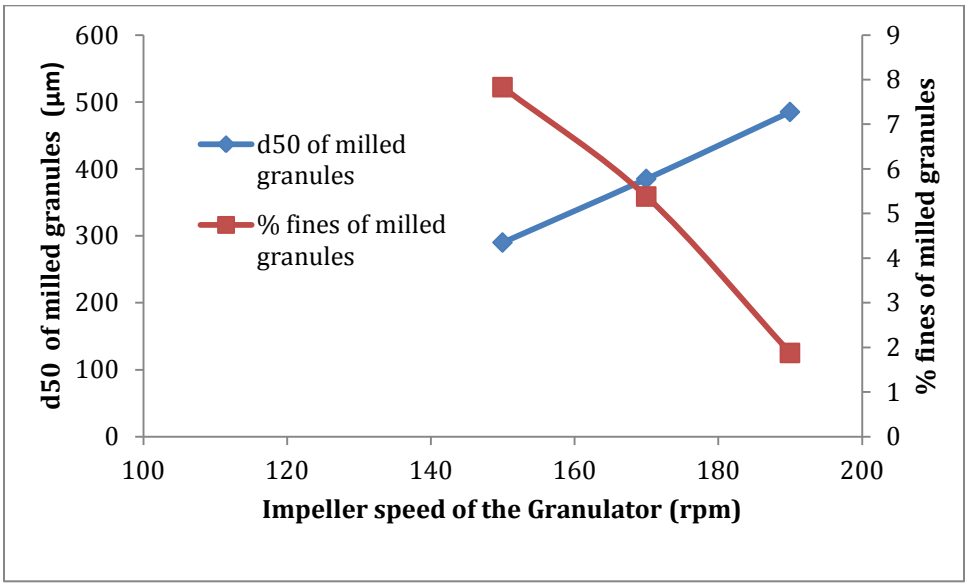


Figure 3.9 Plot showing the effect of Impeller speed on the d50 of milled granules and on the % fines of the milled granules

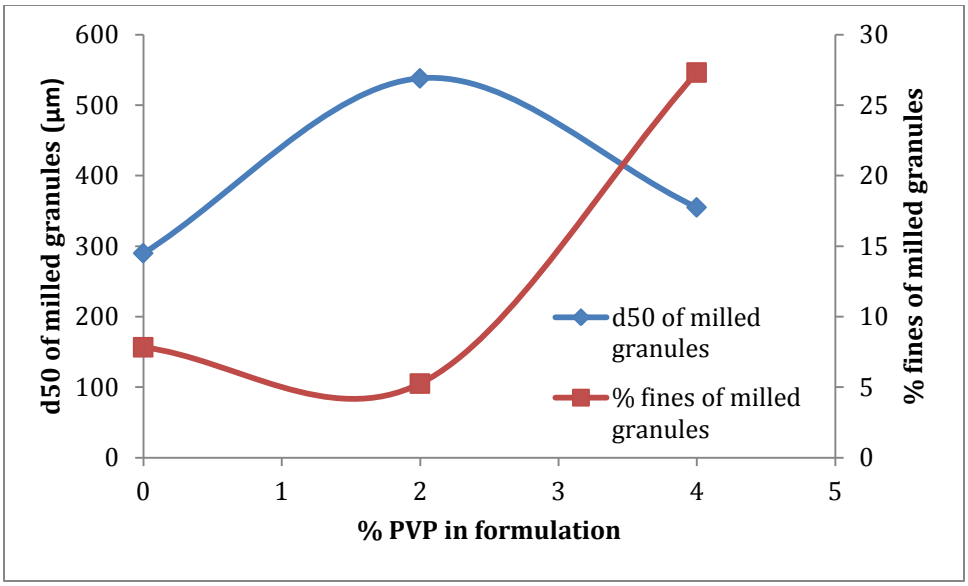


Figure 3.10 Plot showing the effect of %PVP in the formulation on the d50 of milled granules and on the % fines of the milled granules

In figure 3.8 and in figure 3.9 it can be seen that the trend of d50 of milled granules and %fines of milled granules is exactly opposite, i.e. lower is the d50 more are the fines generated. In other words, it is not possible to achieve a large degree of size reduction without intensive fines formation [30]. But on observing Figure 3.10 it can be seen that though 4% PVP does not have the lowest milled d50 it has the largest fines generated. This again like the earlier case is because of the unusual increase in residence time of 4% PVP which lead to intense multiple impacts thereby leading to high level of fines formation. Therefore there can be two different mechanisms of fines formation due to a comil which result in different levels of fines generation, for the same screen size.

4 CONCLUSIONS AND FUTURE WORK

4.1 Conclusions

The aim of this thesis was to understand the effect of mill parameters, mass of input batch and mill impeller speed, along with the effect of granulation parameters, Liquid to solid ratio and granulation impeller speed, on milled granules. The effect of screen type and the effect of % PVP in formulation were also studied. To enable the study of mill parameters and granulation parameters formulation with 8% caffeine, 46 % MCC Avicel PH-101 and 46% mono hydrate lactose was used. For effect of binder addition % of PVP used was varied in the formulation with % of caffeine being constant at 8%.

Performing a DoE has facilitated a clear understanding of the effect of mill parameters and it was found that both the factors, mass of input batch and mill impeller speed, need to be studied. The study helped in demonstrating that relationships can be built between mill parameters and critical quality attributes of granules, and that they can be used to aid in optimization analysis.

It was found that the exit of particles from the mill follows first order kinetics. The lowest time taken for 50% completion of mill cycle, within the impeller range of 1500 to 3000 rpm and input batch size range of 300 grams to 1000 grams is around 45 seconds. The mill settings for this lowest time were in between 800 and 900 grams of input batch size and between 1800-2050 rpm of impeller speed. It was also found that both the impeller speed and the mass of input batch affect the milled granule PSD.

In this study, it was observed that milling in a conical screen mill follows two different regimes, quasi static regime and impact regime. Escape of particles from the mill in a quasi static regime is dominated by the exit of the particles in the mill that are already smaller than the screen size of the mill and this is due to the movement of particles. In an impact regime the exit of particles is due to size reduction of particles, caused by the impeller of the mill. Higher input batch size and low impeller speeds favor the quasi static regime, whereas the opposite trend is found to favor the impact regime. Both these regimes always coexist in a mill conical screen mill cycle. Milling using a conical screen mill was also found to impact other critical quality attributes like bulk density, tap density, friability and porosity. Predictive regression models were developed for throughput of the mill, bulk density and tap density for usage in further downstream processing.

Granulation impeller speed and liquid to solid ratio were observed to affect the milled granules. With increase in liquid to solid ratio the d50 of the milled granules increased and % fines of the milled granules decreased. Similar trend was observed for granulation impeller speed. With the increase in % PVP in formulation the d50 of the milled granules increased on further increasing the % PVP there was a decrease in d50. An opposite trend was observed for % fines.

4.2 Future Research Opportunities

With the observations of the current work in mind, further studying the effect of input batch size would help in further understanding this effect and also could lead to inclusion of this parameter in predictive models for a more accurate prediction of PSD. A study focused on understanding the regimes of milling in a comil is highly recommended as this would help in providing a deeper insight into how these regimes coexist and the indicator of the shift of dominance of these regimes. As the critical parameters influencing of a comil have been

identified by this and previous studies, a study on comparison of critical quality attributes of tablet for the changes in these mill parameters would help us to enhance our understanding. Experimental investigation on the mechanism of breakage in a comil in a realistic setting would help to estimate better breakage values for the model.

APPENDIX:

m (kg)	v(m/s)	m^2	mv^2	m^2*v	m^2/v	SS
0.6	12.246	0.36	89.97871	4.41	0.029	0.780
1	8.164	1	66.6509	8.16	0.122	0.553
0.3	12.246	0.09	44.98935	1.10	0.007	0.758
0.6	16.328	0.36	159.9622	5.88	0.022	0.675
0.3	8.164	0.09	19.99527	0.73	0.011	0.522
1	16.328	1	266.6036	16.33	0.061	0.745
0.6	8.164	0.36	39.99054	2.94	0.044	0.708
1	12.246	1	149.9645	12.25	0.082	0.584
0.3	16.328	0.09	79.98108	1.47	0.006	0.841

A 1.1 Table with regression parameters for m_{final}

v^2	m^2v^2	m (kg)	v(m/s)	m^2	mv^2	m^2*v	τ
149.9645	53.99	0.6	12.246	0.36	89.97871	4.41	56.85
66.6509	66.65	1	8.164	1	66.6509	8.16	20.67
149.9645	13.50	0.3	12.246	0.09	44.98935	1.10	70.12
266.6036	95.98	0.6	16.328	0.36	159.9622	5.88	46.26
66.6509	6.00	0.3	8.164	0.09	19.99527	0.73	53.93
266.6036	266.60	1	16.328	1	266.6036	16.33	70.72
66.6509	23.99	0.6	8.164	0.36	39.99054	2.94	49.46
149.9645	149.96	1	12.246	1	149.9645	12.25	28.45
266.6036	23.99	0.3	16.328	0.09	79.98108	1.47	78.26

A 1.2 Table with regression parameters for τ

m^2v^2	m (kg)	v(m/s)	mv^2	m^2*v	mv	t_{50}
53.98723	0.6	12.246	89.97871	4.40856	7.3476	58.19475
66.6509	1	8.164	66.6509	8.164	8.164	48.6601
13.49681	0.3	12.246	44.98935	1.10214	3.6738	75.66352
95.97729	0.6	16.328	159.9622	5.87808	9.7968	62.48585
5.998581	0.3	8.164	19.99527	0.73476	2.4492	170.7606
266.6036	1	16.328	266.6036	16.328	16.328	78.63307
23.99432	0.6	8.164	39.99054	2.93904	4.8984	60.60249
149.9645	1	12.246	149.9645	12.246	12.246	55.19732
23.99	0.3	16.328	79.98108	1.47	4.898	70.62001

A 1.3 Table with regression parameters for t_{50}

Granulation Parameter	Value
Impeller Speed	150 rpm
Chopper Speed	6000 rpm
% water	55
Dry mixing time	2 minutes
Water addition time	2 minutes
Wet massing time	3 minutes

A 1.4 Granulation parameters to study the effect of mill parameters on span, friability, porosity, bulk and tap density

Impeller Speed (rpm)	Mass of input batch (g)
1500	300
2250	600
3000	1000

A 1.5 Mill parameters to study the effect of mill parameters on span, friability, porosity, bulk and tap density

m (kg)	d50(mm)	m^2	d50^2	d10^2	bulk density
0.6	0.44	0.36	0.1936	0.013225	0.6901
1	0.565	1	0.319225	0.1024	0.7213
0.3	0.42	0.09	0.1764	0.0225	0.6970
0.6	0.515	0.36	0.265225	0.0361	0.7644
0.3	0.49	0.09	0.2401	0.0324	0.7278
1	0.405	1	0.164025	0.0121	0.6996
0.6	0.5	0.36	0.25	0.034225	0.7067
1	0.475	1	0.225625	0.015625	0.7342
0.3	0.4	0.09	0.16	0.0144	0.6732

A 1.6 Table with regression parameters for bulk density

m (kg)	d50(mm)	m^2	d50^2	d10^2	tap density
0.6	0.44	0.36	0.1936	0.013225	0.8133
1	0.565	1	0.319225	0.1024	0.8109
0.3	0.42	0.09	0.1764	0.0225	0.7990
0.6	0.515	0.36	0.265225	0.0361	0.8534
0.3	0.49	0.09	0.2401	0.0324	0.8114
1	0.405	1	0.164025	0.0121	0.8345
0.6	0.5	0.36	0.25	0.034225	0.8105
1	0.475	1	0.225625	0.015625	0.8254
0.3	0.4	0.09	0.16	0.0144	0.7775

A 1.7 Table with regression parameters for tap density

REFERENCES

1. Dana Barrasso, S.O., Ariel Muliadi, James D. Litster, Carl Wassgren, Rohit Ramachandran, *Population Balance Model Validation and Prediction of CQAs for Continuous Milling Processes: toward QbD in Pharmaceutical Drug Product Manufacturing.* J Pharm Innov 2013 **8**: p. 147–162.
2. BR, R., et al., *Particle size limits to meet USP content uniformity criteria for tablets and capsules.* J Pharm Sci 1996. **95**: p. 1049–1059.
3. AJ, R., H. A, and I. MG, *Modeling of particulate processes for the continuous manufacture of solid-based pharmaceutical dosage forms.* Processes, 2013. **1**: p. 67–127.
4. A, S., N. K, and H. P, *Cone milling of compacted flakes: process parameter selection by adopting the minimal fines approach.* Int J Pharm, 2012. **422**: p. 17-23.
5. Yin, S.X., et al., *Bioavailability enhancement of a COX-2 inhibitor, BMS-347070, from a nanocrystalline dispersion prepared by spray-drying.* Journal of Pharmaceutical Sciences. **94**(7): p. 1598-1607.
6. Loh, Z.H., A.K. Samanta, and P.W.S. Heng, *Overview of milling techniques for improving the solubility of poorly water-soluble drugs.* Asian journal of pharmaceutical sciences, 2015. **10**: p. 255-274.
7. M., A., *Assessment of biopharmaceutical properties*, in *Pharmaceutics: the science of dosage form design*, A. M, Editor. 2002, Churchill Livingstone: London. p. 253-273.
8. R, S., et al., *Flexible multipurpose continuous processing.* Pharm Process, 2012. **27**(6): p. 22-25.
9. Naik, S. and B. Chauduri, *Quantifying Dry Milling in Pharmaceutical Processing: A Review on Experimental and Modeling Approaches.* Journal of Pharmaceutical Sciences, 2015. **104**: p. 2401-2413.
10. S, C. and P. H, *Narrowing down equipments for particle size reduction of drug.* Chem Eng Prog, 2002. **98**: p. 50.
11. AF, A.-M. and S.e. C., *Fundamentals of early clinical drug development: From synthesis design*. 1 ed. 2006, New Jersey: Wiley.
12. Sadler, L.Y., D.A. Stanley, and D.R. Brooks, *Attrition mill operating characteristics.* Powder Technology, 1975. **12**(1): p. 19-28.
13. III, W.R., W. AB, and M. DA, *Formulation of poorly soluble drug*. 2012, Springer: New York.
14. ML, E., T. LA, and E.i.s. SI, *Use of a jet mill to obtain powders of pharmaceutical preparations.* Pharm Chem J 1972. **6**: p. 681-684.
15. N, M., et al., *Micronization of pharmaceutical substances in a spiral jet mill.* Powder Technology, 1999(104): p. 113-120.
16. Y, W. and P. F., *Parameter effects on dry fine pulverization of alumina particles in a fluidized bed opposed jet mill.* Powder Technology, 2011(214): p. 269-277.
17. A, V., et al., *Effects of mill design and process parameters in milling of ceramic (alumina-magnesia) extrudates.* 2012.
18. B, M., *Milling In Pharmaceutical dosage forms: unit operations and mechanical properties*, A. L and H. S, Editors. 2008. p. 175-193.
19. S. Yu, B.G., et al., *Experimental Investigation of Milling of Roller Compacted Ribbons.* The British Library.

20. Lantz, R.J., *Milling in Pharmaceutical Dosage Forms :Tablets*, H.A. Lieberman, J.B. Schwartz, and M. Dekker, Editors. 1990. p. 107-200.
21. EL, P., *Milling of pharmaceutical solids.* J Pharm Sci 1974(63): p. 813-829.
22. H, H., *Some notes on grinding research.* J Imp Col Chem Eng Soc, 1952(6): p. 1-12.
23. ME, A. and T. KMG, *Aulton's pharmaceutics: The design and manufacture of medicines*. 4 ed. 2013, Kidlington, Oxford, UK: Elsevier.
24. Iveson, S.M. and J.D. Litster, *Growth regime map for liquid-bound granules.* AIChE Journal, 1998. **7**(44): p. 1510-1518.
25. Oka.S and Kasper, *A quantitative study of the effect of process parameters on key granule characteristics in a high shear wet granulation process involving a two component pharmaceutical blend.* Advanced Powder Technology, 2015. **26**(1): p. 315-322.
26. Woyna-Orlewicz, K. and R. Jachowicz, *Analysis of wet granulation process with Plackett–Burman design– case study.* Acta Pol. Pharm, 2008. **68**(5): p. 725-733.
27. JE, B. and P. GE, *The effect of mill variables on a granulation milling process.* Drug Dev Ind Pharm, 1990. **16**(11): p. 1761-1779.
28. JJ, M. and A. NR, *The quantitative evaluation of a granulation milling process II. Effect of output screen size, mill speed and impeller shape.* Drug Dev Ind Pharm, 1984. **10**(5): p. 713-728.
29. Schenck, L.R. and R.V. Plank, *Impact milling of pharmaceutical agglomerates in the wet and dry states.* International Journal of Pharmaceutics, 2008. **348**(1): p. 18-26.
30. JJ, V., et al., *Milling of agglomerates in an impact mill.* Int J Pharm, 2004. **278**(1): p. 165-172.
31. Subero J, G.M., 120(3):232–243, *Breakage patterns of agglomerates.* Powder Technology, 2001. **120**(3): p. 232-243.
32. M, N. in *AIChE*. 2017.
33. BY, S., et al., *Particle size analysis in pharmaceutics: Principles, methods and applications.* Pharm Res, 2007. **24**: p. 203-227.
34. Convention, U.S.P., *United States Pharmacopeia*, in *Bulk Density and Tapped Density of Powders*. 2015, United States Pharmacopeial Convention.
35. M, W. and A. A., *Compression characteristics of granulated materials II. Evaluation of granule fragmentation during compression by tablet permeability and porosity measurements.* Int J Pharm 1990(62): p. 229-241.
36. Vercruysse, J., et al., *Continuous twin screw granulation: Influence of process variables on granule and tablet quality.* European Journal of Pharmaceutics and Biopharmaceutics, 2012. **82**: p. 205-211.
37. Wei Meng, et al., *Statistical analysis and comparison of a continuous high shear granulator with a twin screw granulator: Effect of process parameters on critical granule attributes and granulation mechanisms.* International Journal of Pharmaceutics, 2016. **513**: p. 357-375.
38. A.S, E.H. and C. P, *In-line Size Monitoring of a Twin Screw Granulation Process Using High-Speed Imaging.* J Pharm Innov, 2013. **8**(2): p. 90-98.
39. AU, V. and M. FJ, *Effect of operating conditions and design parameters in a continuous powder mixer.* Powder Technol 2011. **208**: p. 26-36.
40. Y, G., M. FJ, and I. MG, *Optimizing continuous powder mixing processes using periodic section modeling.* Chem Eng Sci 2012. **80**: p. 70-80.
41. Rao, S., *Understanding the relationship between process parameters and critical quality attributes of tablets produced by batch and continuous granulation for low-dose caffeine*

formulation using design of experiments approach, in *Chemical and Biochemical Engineering*. 2017, Rutgers University.

42. Pandey, P. and Tao, *A combined experimental and modeling approach to study the effects of high-shear wet granulation process parameters on granule characteristics.* Pharm. Dev. Technology, 2013. **18**(1): p. 210-224.
43. El Hagrasy, A.S., et al., *Twin screw wet granulation: influence of formulation parameters on granule properties and growth behavior.* Powder Technology, 2013. **238**: p. 108-115.
44. Sayin, R., A.S. El Hagrasy, and J.D. Litster, *Distributive mixing elements: towards improved granule attributes from a twin screw granulation process.* Chem. Eng. Sci., 2015. **125**: p. 165-175.
45. Lieberman, H.A., L. Lachman, and J.B. Schwartz, *Pharmaceutical Dosage Forms : Tablets*. Vol. 1. 1989, New York: Marcel Dekker.
46. Metta, N., M. Ierapetritou, and R. Ramachandran, *A multiscale DEM-PBM approach for a continuous comilling process using a mechanistically developed breakage kernel.* Chemical Engineering Science, 2018. **178**: p. 211-221.
47. Hancock, B.C. and T.A. Vendola, *Bruno C. Hancock, Thomas A. Vendola.* Pharmaceutical Technology, 2008. **32**(11).