UNDERSTANDING THE RELATIONSHIP BETWEEN PROCESS PARAMETERS AND CRITICAL QUALITY ATTRIBUTES OF TABLETS PRODUCED BY BATCH AND CONTINUOUS GRANULATION FOR A LOW-DOSE CAFFEINE FORMULATION USING DESIGN OF EXPERIMENTS APPROACH

By

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ABSTRACT FOR THE THESIS

Understanding the relationship between process parameters and critical quality attributes of tablets produced by batch and continuous granulation for a low-dose Caffeine formulation using design of experiments.

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Wet granulation is the process of particle size enlargement by inducing agglomeration of individual particles by addition of a liquid binding agent. Granulation is an integral step during pharmaceutical manufacturing for solid doses, which is usually followed by unit operations such as drying, milling and finally tableting and coating. This process can be performed in both batch and continuous forms. Granulation process is typically known to alleviate problems of powder handling, non-uniform distribution of active pharmaceutical ingredients (API), segregation and poor flow properties of powders/blends. However, as pharmaceutical manufacturing is evolving to include Quality by Design (QbD), numerous opportunities of research in the areas of continuous manufacturing and Process Analytical Technology (PAT) are now being explored, allowing for improvement in existing batch manufacturing and in continuous manufacturing.

The objective of the thesis is to study the effect of process conditions employed during granulation on the final quality attributes of tablets prepared. For this study tablets were

prepared by granules produced in a high-shear batch granulator (HSG) and a continuous twin screw granulator (TSG) with the aim of comparing the robustness of the two processes and quality attributes of tablets for a broad range of operating conditions. A four component low-dose formulation with Caffeine as API was selected for the purpose of the study. The formulation consisting of 44% (w/w) MCC Avicel PH101, 44% (w/w) monohydrate a-lactose, 8% (w/w) Caffeine as the API and 4% (w/w) Polyvinylpyrrolidone was pre-blended and used for granulation experiments.

In this dissertation, parameters such as liquid-solid (L/S) ratio, wet-massing time and chopper speed were varied to produce granules in a face-centered DoE augmented with 3 center points. Granules produced were analyzed for granule size distribution, porosity, aspect ratio and Hausner ratio. Characterization of the twin-screw granulator was carried out by setting up a d-optimal DoE with operational parameters; namely, (L/S) ratio, feeder throughput, screw RPM, granulator barrel temperature, and screw configuration variations. The design space was optimized by the size distribution of the granules and torque to determine the most significant parameters. Granules produced from both equipment were used to make flat-faced tablets. The robustness of the two granulation processes were compared by critical attributes such as granule size distribution, porosity, tablet hardness, tablet dissolution profiles, content uniformity of the active ingredient and the optimum operation design spaces of the processes.

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Thank you.

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Chapter 1: Introduction

1.1 Granulation

Granulation is the process of size enlargement, where fine particles agglomerate to form larger and stronger granules. (Tardos, Khan et al. 1997) It is considered to be one of the most important unit operations in the pharmaceutical solid dose manufacturing process (Keleb, Vermeire et al. 2004). While working with solid dosages, granulation step helps improve the flowability of material, improve content uniformity, decreases chances of material segregation or de-mixing (Oka, Kašpar et al. 2015) and eases material handling in downstream processes. From the manufacturing scheme presented in figure below, it can be inferred, any inefficiencies and quality lapses in this step would in turn effect the high quality performance of all forthcoming operations.

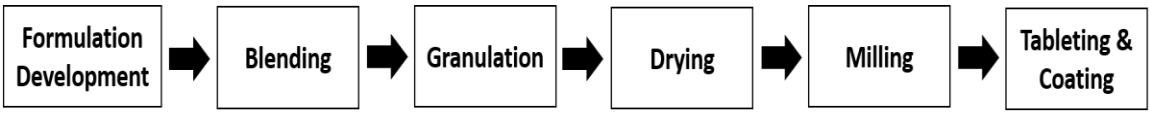


Fig 1.1: Unit operations in solid dose manufacturing.

The granulation step in solid dose manufacturing can be performed in batch and continuous mode. In the batch mode, the material is fed into a vessel, and mixed for a certain amount of time. Binder is added to the vessel and granules are formed during the wet-massing step. Batch processes are standalone processes, and the product formed has to be removed and transferred to the next equipment for further processing. Pharmaceutical manufacturing is predominantly carried out in batch mode, where the equipment is used to produce a batch of granules at the required process conditions, emptied and reused for the same or different product. In continuous granulation, powder and binder is continuously fed into the

equipment and the granules are collected immediately after they are formed and exit the system. Granules formed after the equipment reaches steady state are collected and transported to the next operations.

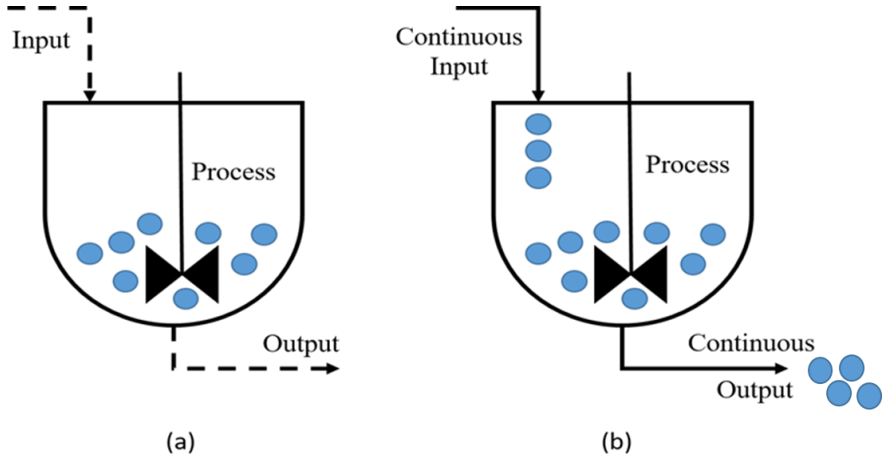


Fig 1.2: (a) Batch Process, (b) Continuous process.

Several techniques are available to carry out wet granulation which differ in the mechanism and the type of equipment. The selection of the technique depends on the requirements of the process and required product specifications. Factors such as material properties, production rate, granule properties, integration with upstream and downstream operations, and the unique advantages of each technique and their disadvantages need to be considered. (Vervaet and Remon 2005).

1.1.1 High Shear Granulation

High shear granulation is one of the most prevalent forms of wet granulation in pharmaceutical manufacturing in batch mode. In high-shear granulators, powders are fed into a vessel or chamber which houses an impeller or a rotatable shaft with blades. On addition of liquid binder via dripping or spraying, the binder is mixed into the powder by

the impeller and particle densification is initiated. The rotating impellers cause mixing, liquid penetration and granule growth, and the choppers break the granules into spheres.

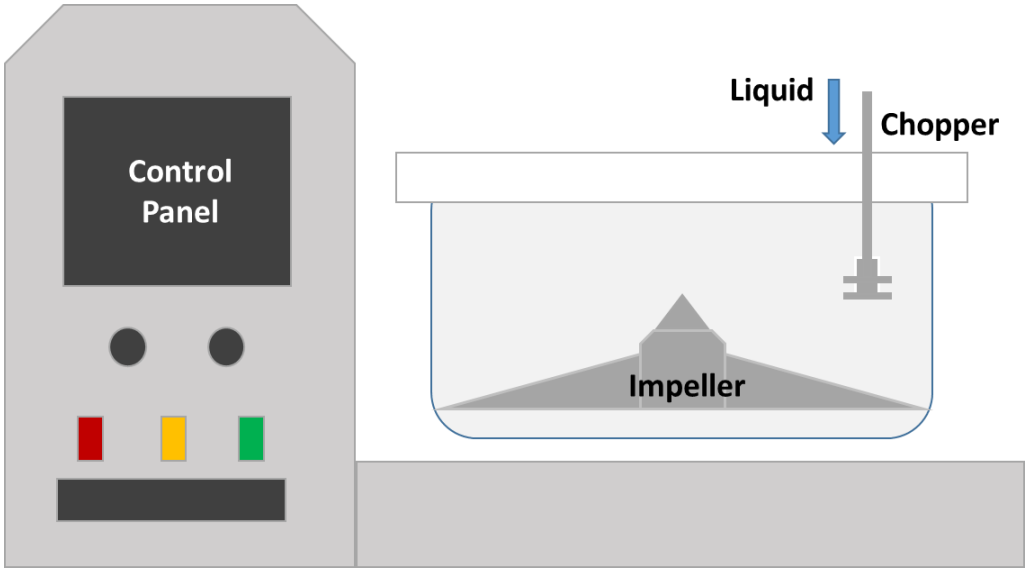


Fig 1.3: Schematic of high-shear granulator with impeller and chopper.

The granule size and physical properties depend on material throughput, liquid addition, impeller speed and chopper speeds. The main advantage of high-shear granulation is that it can handle even highly cohesive materials and with the extensive know-how available, the results are easily scalable and reproducible. Batch granulation regime maps were first developed by Iveson et al. (Iveson and Litster 1998) and have now become the basis for the investigations carried out by future groups. Hapgood et al. (Hapgood, Litster et al. 2003) extended this approach to understand the nucleation behavior in liquid addition by dripping versus spraying technique. Woyna-Orlewicz et al (Woyna-Orlewicz and Jachowicz 2011) studied a total of seven parameters with two levels each to identify the top three process parameters to be L/S ratio, wet-massing time and impeller speed using a Plackett-Burman design for wet high-shear granulation. The work by Pandey et al (Pandey, Tao et al. 2013) studied the effect of process parameters using a population balance model

on physical characteristics of granules such as particle size distribution and porosity and validated the model with experimental data from a high-shear granulator. Oka et al (Oka, Kašpar et al. 2015) recently showed the effect of L/S ratio, wet-massing time and impeller speed is statistically significant to the particle size distribution using a DoE approach.

1.1.2 Twin Screw Granulation

Twin-screw granulation is the most studied technique for continuous granulation. The equipment typically employs rotating screws in a barrel which mix, coalesce and transport the material to the outlet. The screws aide in particle wetting and agglomeration. The process is similar to extrusion, but the granule shape depends on the screw arrangement and not a die block. The quality of the granules depends on factors such as the screw speed, screw arrangement, quantity of binder and temperature. (Vervaet and Remon 2005).

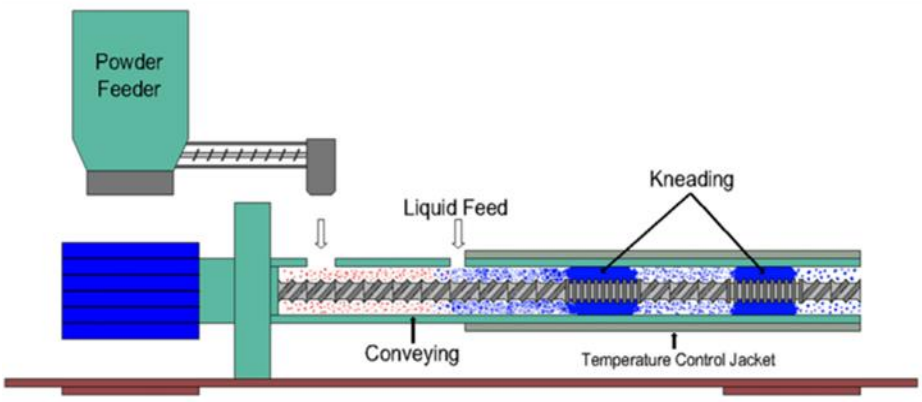


Fig 1.4: (a) Twin-screw granulator schematic adapted from Seem et al. (Seem, Rowson et al. 2015)

The advantage of this technique is that it provides flexible, rapid and reproducible agglomeration and the process is not as labor intensive. Unlike the fluidized bed spray granulation, the granules collected from this technique are wet and would require drying before further processing. Also, the many changeable parameters can lead to loss of material during process optimization.

The twin-screw granulator was first used as a method for pharmaceutical compositions by Gamlen et al (Gamlen and Eardley 1986) and Lindber et al. (Lindberg, Tufvesson et al. 1987). Publications by Dhenge et al. (Dhenge, Cartwright et al. 2012, Dhenge, Washino et al. 2013) and by Tu et al. (Tu, Ingram et al. 2013) have emphasized on regime maps which are specific to twin-screw granulators. Recent studies on twin-screw granulators focus on characterizing the equipment and understanding the granulation operation as a function of design and process parameters. The effect of screw configurations (El Hagrasy and Litster 2013, Sayin, El Hagrasy et al. 2015, Vercruysse, Burggraeve et al. 2015), powder throughput (Dhenge, Cartwright et al. 2011), liquid-to-solid ratio (El Hagrasy, Hennenkamp et al. 2013), rotational speed (Kumar, Alakarjula et al. 2015) and powder properties (Djuric and Kleinebudde 2010) have been investigated and validated. A complete review of the material published on twin-screw granulators has been summarized by Seem et al. (Seem, Rowson et al. 2015) in their recent paper.

1.2 Quality by Design Methodology

Performing operation in continuous mode offers several benefits over the batch mode. Continuous manufacturing is highly prevalent in chemical and food industries, but not yet fully adopted in the pharmaceutical industry. Continuous manufacturing allows integration of multiple unit operations and thus has fewer steps. This ensures reduced manual handling of material, product consistency, increased safety, and increased efficiency. Continuous operations have shorter processing times and hence require smaller equipment and facilities. The flexibility and operability in lower volumes reduces inventory, work-in-progress material, lowers, capital costs, and lowers the ecological footprint. Increase in production capacity or scale-up involves running the processes for longer duration and

increasing throughput, while in batch operation, one would be required to invest a huge amount of capital to procure larger equipment and facilities.

Although continuous manufacturing offers multiple advantages over the traditional batch manufacturing, the transition from batch to continuous methods in pharmaceutical manufacturing has been sluggish. The methods and procedures used to manufacture pharmaceutical products in batch mode are well established and reasons such as inflexibility, high-cost of transition, infeasibility for lower volumes of production, and regulatory approvals have delayed the move to continuous mode of operation. (Seem, Rowson et al. 2015) Pharmaceutical companies also prefer batch operations because it offers more flexibility to the operator to switch from one product to the other easily in the same equipment and accommodates offline quality control. A paradigm shift from batch to continuous would require pharmaceutical companies to adopt and embrace creative approaches to manufacturing. This transition would require dedicated investments in terms of time, cost, resources and labor.

Regulatory bodies like the US Food & Drug Administration (USFDA) and European Medicine Agency (EMA) have encouraged these companies to shift to safer and more streamlined processes. To ensure efficient drug manufacturing, the USFDA made several changes to the cGMPs (Good Manufacturing Practices) in the year 2002, and established more stringent regulatory controls on pharmaceutical companies. (Sangshetti, Deshpande et al. 2014).

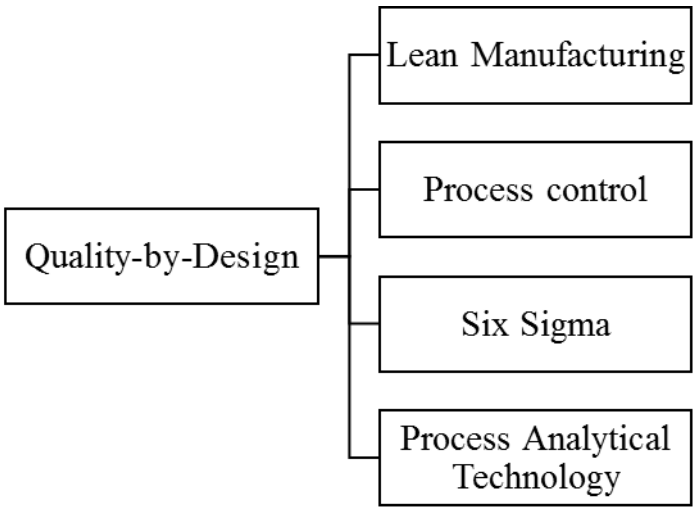


Fig 1.5: Approaches to implement Quality-by-design.

The guidelines endorsed concepts of implementing Quality-by-Design (QbD) and Process Analytical Technology (PAT) tools to promote improved understanding and adoption of innovative tools to perform timely quality checks and controls on critical quality attributes for processes. The importance of quality in pharmaceutical manufacturing cannot be overstated. It is imperative to meet the quality standard every single time to be able to provide the best treatment to a consumer. The International Conference on Harmonisation (ICH) guideline issued in 2004 defines Quality-by-Design (QbD) as a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding, process control, based on sound science and quality risk management. The QbD approach urges that quality cannot be tested into a product, but has to be built into it. Application of the QbD framework involves designing quality into every step of pharmaceutical manufacturing and understanding that quality assurance is a continuous process and it requires in-depth knowledge of processes. (Haleem, Salem et al. 2015). Implementation of PAT tools, use of statistical data analysis are ways to adopt the quality-by-design (QbD) framework. QbD/PAT-based strategies are laying the foundation to

transition toward continuous manufacturing in pharmaceutical production. (Plumb 2005, Wu, White et al. 2011). Regulatory agencies, the industry and academia must collaborate to foster end-to-end process control and shifting to continuous manufacturing is the way to implement and instil QbD in pharmaceutical processes.

1.3 Objective

This study was carried out with the objective of understanding the batch and continuous granulation process parameters and interpret how they affect the physical characteristics of granules and tablets, and also to compare the robustness of these two techniques with a general idea on our response requirements and constraints. Although a direct comparison of these two techniques is difficult considering the fundamental difference in their mechanisms and operations, this study was focused on comparing the quality attributes of the granules and tablets produced rather than comparing the process parameters itself. There is however, limited literature comparing the two processes. More recently Beer et al. (Beer, Wilson et al. 2014) published their work on how to replicate granule & tablet properties produced from a HSG using a TSG. The effect of process parameters was applied only to study that particular technique and establish optimal operating conditions for that equipment. The main aims of the thesis are:

i) Studying the influence of process parameters on granule and tablet CQAs for HSG.
ii) Characterization of TSG, determining the optimal design space and studying the influence of process parameters on granule and tablet CQAs.
iii) Comparing the robustness of batch high-shear granulation and continuous twin-screw granulation.

Performing such a study is crucial in this era pushing towards adopting continuous manufacturing in the pharmaceutical industry. Companies and universities are investing resources to perform extensive research to decode the basics of continuous manufacturing. However, there is always a need to compare the benefits of new manufacturing techniques with the existing techniques to comprehend and justify the need for change and investment. This study is a small step towards achieving the giant leap towards improved pharmaceutical manufacturing.

1.4 Experimental Schematic

The experimental plan applied for the completion of this research work is represented in the schematic below.

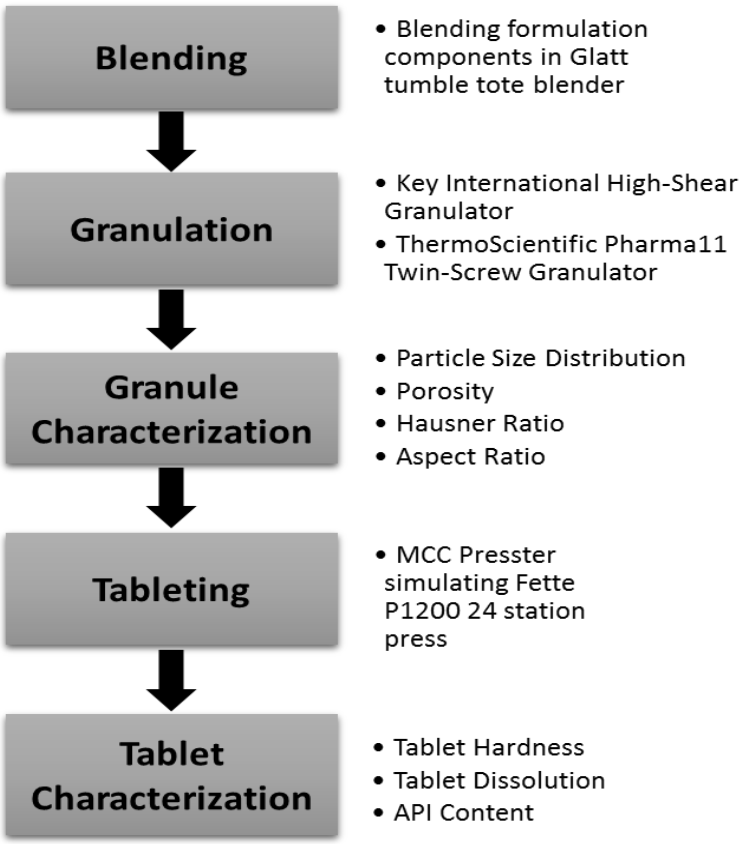


Fig 1.6: Experimental schematic.

Chapter 2: Experiments on High-Shear Batch Granulator

2.1 Granulator Components

The batch granulation experiments were performed on the Key International table-top high shear granulator Fig (2.1, a). The granulator consists of a 2.4L steel vessel which is fixed on the main unit. A 3-blade impeller is a separate component which is fixed after the installation of the granulation vessel. Fig (2.1, b).

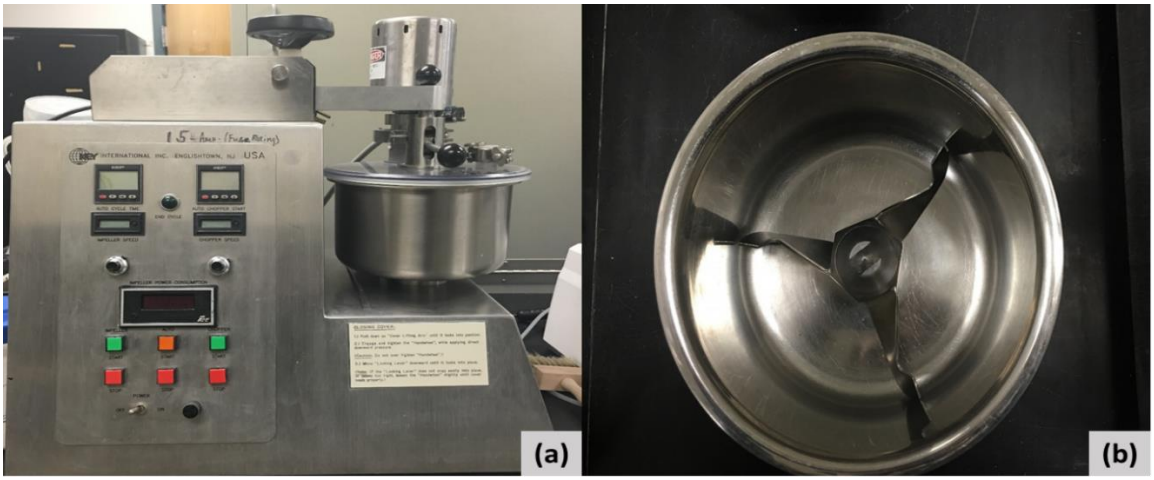


Fig 2.1: (a) KG5 Key International high-shear granulator (b) Granulator vessel and impeller.

The granulator vessel is sealed shut by a transparent plastic lid through a lever attached to the main body of the equipment. The chopper assembly and provision for liquid inlet are attached to the plastic lid. The operation of the granulator and rotation speeds of the impeller and chopper can be individually controlled by the dials on the control panel.

2.2 Material and Formulation

A solid dosage drug typically comprises of several materials combined along with the drug substance to form a tablet ready for consumption. The drug substance is the active

ingredient, while the inactive ingredients are called excipients. Excipients are added to the drug formulation for reasons such as improving flow properties of the material, improving compressibility of the formulation, improving tablet hardness and yield. For the experiments a four component blend was formulated with three inactive ingredients and one active ingredient.

In this study a four component formulation was premixed in the Glatt tumble tote blender. The formulation consisted of 8% (w/w) regular caffeine as the active pharmaceutical ingredient, and three inactive ingredients, namely α-lactose monohydrate, microcrystalline cellulose Avicel PH 101 and Polyvinylpyrrolidone. The quantities and physical properties of the ingredients and premix is detailed in Table (2.1) and Table (2.2).

Ingredient	***% w/w***
Caffeine	8
Polyvinylpyrrolidone (PVP)	4
MCC Avicel PH 101	44
α-lactose monohydrate	44

Table 2.1: Formulation components and percentages.

Ingredient	***D10 (μm)***	***D50 (μm)***	***D90 (μm)***	ρ_{bulk} ***(g/cm^3)***	ρ_{tapped} ***(g/cm^3)***
Caffeine	8.6	39.5	78.7	0.56	0.77
MCC Avicel PH 101	19.1	58.7	132.5	0.35	0.45
α-lactose monohydrate	13.7	78.4	159.5	0.52	0.79
Premix	12.8	50.5	98.5	0.43	0.63

Table 2.2: Physical properties of components.

2.3 Granulation Mechanism and Procedure

The steps in the wet batch granulation process are: selection of batch quantity, dry mixing, followed by liquid addition, wet massing and then stoppage. The wetting of the powder

bed and nucleation takes place in the liquid addition stage and continue till the next stage. Further growth, consolidation and agglomeration take place during the wet-massing stage aided by the impeller rotation. Granule attrition and densification takes place simultaneously due to the shear provided by the chopper.

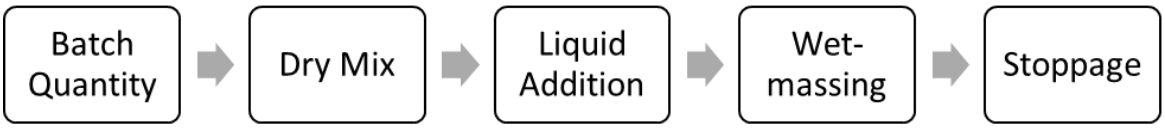


Fig 2.2: Steps in batch granulation process.

In the Key International batch granulator, 250g of the premix was first weighed and added to the granulation vessel. The vessel is closed and the granulator is turned on by starting the impeller and chopper. The impeller rotation speed was maintained constant at 200 RPM. The chopper speed was adjusted based on the settings for each batch. The premix was dry blended for a total of 2 minutes. After two minutes, the granulation liquid was input by dripping distilled water into the granulator via a peristaltic pump for 2 minutes as represented in the figure above. The total amount of liquid needed to achieve the required L/S ratio was calculated based on the batch quantity and water-addition time. This was used to adjust the pump value.

The wet-massing time begins from the point the liquid addition is stopped. During this step, the water added to the vessel activates the binder in the premix. The high shear rotation provided by the impeller blades causes formation of granules and affects granule shape and porosity (Oka, Kašpar et al. 2015). The chopper blades break down the large agglomerates/lumps and impart density to the granules.

2.4 Process Parameters and levels

Wet high-shear granulation has several input and output parameters, while gives us the ability to vary multiple design and process parameters. Parameters such as wet-massing time, impeller speed, chopper speed, L/S ratio, fill-level and so on can be varied. In this study three parameters were chosen and each was varied at three levels. The parameters and levels are listed in Table 2.3:

Process Parameters	***Levels***
Wet-massing Time (min)	1, 3, 5
L/S Ratio	0.35, 0.45, 0.55
Chopper Speed	4000, 5000, 6000

Table 2.3: Process parameters and levels for batch granulation study.

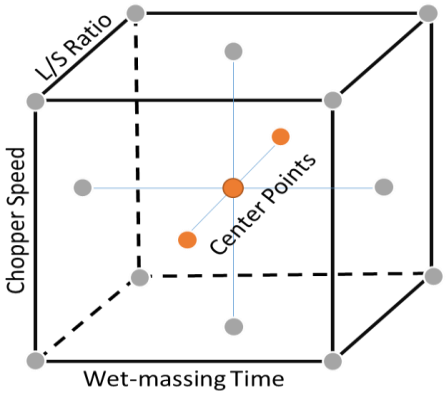
Although impeller speeds are suggested in literature to be a more important to the granulation process, for this study the impeller speed was kept constant at a low speed of 200 RPM. Impeller speed does not have a significant impact on the granule size distribution at low to medium speeds, but higher impeller speeds cause increased coalescence and agglomeration producing very large granules. (Pandey, Tao et al. 2013) In order to control the growth and densification of granules, chopper speed play a critical role. As the aim of this research is to understand how granulation process parameters affect tablet CQAs, there is a greater reasoning for controlling granule growth with the motivation of producing sufficient granules for tableting and analysis.

Levels for varying the L/S ratio was selected based on previous studies conducted on low-dose formulations with comparable quantities of excipients, binder and active ingredient. Extended wet-massing times have little to no impact on granule properties, hence wet-massing time was selected as per the findings of Woyna-Orlewicz et al. (Woyna-Orlewicz and Jachowicz 2011)

2.5 Design of Experiments

With the many levels of each factor, it becomes crucial to opt for a methodical and systematic approach to perform experiments. Design of experiments (DoE) concept was applied to determine the significance of the various parameters and to understand the relationship between the various parameters and the response attributes.

Based on the process parameters and levels of each, a total of $3^3 = 27$ experiments would be required (full-factorial DoE). In order to optimize the number of runs without compromising on the statistical relevance of the experiments, a face-centered cubic (FCC) design was utilized to carry out experiments with the Key International batch high-shear granulator.



Process Parameters	*Levels*
Wet-massing Time (min)	1, 3, 5
L/S Ratio	0.35, 0.45, 0.55
Chopper Speed	4000, 5000, 6000

Fig 2.3: Face-centered cubic Central Composite Design and process parameters.

The FCC design is a type of a central composite design which is a commonly used response surface design in cases where all factors have 3 levels. These models can efficiently model curvature in response surfaces, estimate 1st and 2nd order terms and give the user the flexibility to add more central and axial points by increasing the number of experiments. A total of 17 randomized experiments were generated by the FCC DoE augmented by 3 center points on JMP ©.

2.6 Characterization of Granules Properties

2.6.1 Granule Size Distribution

The granule size distribution was determined by performing sieve analysis. The granules from all batches were dried till the moisture content was lesser than 3%. The sieve analysis was conducted with 14 sieves on the Endecotts Octagon 2000 Sieve Shaker divided into two sets based on size: *Coarse* and *Fine*. Both sets were carried out for 15 minutes each at amplitude setting of 7.

The *coarse analysis* comprised of mesh sizes 5 (4000 µm), 8 (2360 µm), 10 (2000 µm), 14 (1400 µm), 18 (1000 µm), 20 (850 µm), 25 (710 µm), Pan_1 (< 710 µm).

The granules lower than mesh 25, were further sieved in the *fine analysis* comprising mesh sizes 35 (500 µm), 45 (355 µm), 60 (250 µm), 120 (125 µm), 170 (90 µm), 230 (63 µm), 400 (38 µm) and Pan_2 (<38 µm).

The granule mass collected in each mesh was noted to develop a distribution across the size range. The values of d10, d50, and d90 were obtained to calculate the span of the distribution. The distribution was also analyzed for the number of peaks or bumps.

$$span = \frac{d90 - d10}{d50} \quad .. (1)$$

2.6.2 Granule Density

The bulk density and tapped density of the granules from each batch was analyzed by using the Quantachrome International Autotap instrument. A 100ml cylinder was used to record the initial volume of a certain mass of granules, called V_0. The granules were then tapped 500, 750 and 1250 times to provide V_{500}, V_{1250}, V_{2500}. This procedure is repeated till the volume difference between two consecutive readings is lesser than 2% in accordance with the methods from USP chapter <616>.

The bulk density is calculated by V_0/mass of granules. The tapped density is calculated by the lowest obtained volume after tapping. These values were used to calculate the Hausner Ratio (HR) and Compressibility Index (CI). Every sample was measured thrice and average values were recorded.

2.6.3 Granule Porosity

3g of granules between the size range of 1000-2000 µm were used to measure the granule porosity for each run. The true density of the material was measured in Micromeritics ® Accupyc II 1340 in a 10 cm^3 chamber with Helium as the gas media. Measured values of true density for each run were inputted in the Micromeritics ® Geopyc 1360 to compute the envelope density in a 12.7 mm chamber-piston set and hence determine the porosity of the granules.

2.6.4 Granule Shape

5g granules between the sizes 1000-2000 µm from each run was weighed and examined to determine the granule shape. The Eyecon™ 3D high speed imaging camera by Innopharma Labs was used to collect high resolution images and record the aspect ratio of the granules

which were analyzed to provide information regarding the shape. A total of 25 images were captured of the same sample from different positions for each run.

2.6.5 Tableting

For the purpose of tableting, granules from the size range 250-710 µm were used. After sieve analysis, the granules withheld by mesh 35 (500 µm), 45 (355 µm), 60 (250 µm) were collected and used for making tablets. Granules in the size range of 400-500 µm are ideal for tableting; granules larger than these are milled and recycled back into the tableting line.Each tablet was made with 350 mg of granules in the MCC Presster simulating the Fette P1200 24 station tablet press. A 10 mm diameter flat-faced cylindrical die-piston tooling arrangement was fixed in the Presster. The die and the piston tooling were coated with Magnesium Stearate as the lubricant. A total of 10 tablets prepared with compressive force of 10 ± 0.5 kN were collected for further analysis for each batch.

2.6.6 Tablet Hardness Testing

To determine the crushing force and tensile strength, 3 tablets from each batch were measured for thickness using calipers and weighed. Dr. Schleuniger Pharmatron Model 6D Tablet Tester was used for measuring tablet breaking force.

The instrument consists of a two metal plates, which move inwards and crush the tablet placed in between them. The experiments were carried out as per the procedures listed in USP Chapter <1217>. The force required to fracture the tablet is measured in Newton (N). The tensile strength (MPa) σ_x of a tablet of diameter D with a thickness H is calculated by the following formula, where F is the crushing force:

$$\sigma_x = \frac{2\,F}{\pi\,D\,H} \qquad \text{.. (2)}$$

2.6.7 Tablet Dissolution Testing

6 tablets from each batch were checked for weight and thickness for performing tablet dissolution testing. Agilent Technologies 708 DS- Dissolution Apparatus 2 consisting 8 basket-paddle setup was used.

As per the USP (published 2010) method for low-dose Caffeine tablets, 900 ml DI water was used as the dissolution media, heated and maintained at 37.3 °C. Paddle rotation speed was set at 50 RPM. Caffeine provides the sharpest absorption peak in the UV-Vis Spectrometer at 273 nm. Known concentrations of caffeine dissolved in DI water were analyzed by the spectrometer to develop a dissolution calibration model which correlates the caffeine concentration with UV-Vis absorption. During the test, samples reads were collected at 273 nm every 3 minutes over a period of 4 hours for each batch.

The dissolution test data was used to develop a percentage (%) API dissolved vs time graph to provide information regarding the dissolution profile and to determine the end point of API release from the drug. The data was also used to determine the percentage of API in each batch, and thereby infer the content uniformity.

2.7 Results & Discussions

2.7.1 Design of Experiments

A total of 17 randomized experiments were generated by the FCC DoE augmented by 3 center points on JMP ©. The experiments and analysis were run in the randomized order generated by the software. Measurements obtained from analysis of granules and tablets were inputted as the responses. The design, parameters and their responses are presented below in Fig (2.4).

	Pattern	L/S Ratio	Wet-massing Time (min)	Chopper Speed	d10	d50	d90	Span	99% Dissolution Time (min)	Hausner Ratio	Compressibility Index	% API	Aspect Ratio	Breaking Force	Tensile Strength	Granule Porosity
1	000	0.45	3	5000	123	302	3788	12.14	96	1.15	13.29	9.18	0.769	147.33	2.82	40.23
2	+−+	0.55	1	6000	618	1442	4680	2.82	93	1.1	9.38	9.16	0.833	193.33	3.7	39.75
3	000	0.45	3	5000	503	2058	4957	2.16	78	1.22	17.95	9.35	0.833	155.67	2.99	40.13
4	+++	0.55	5	6000	1351	2043	4179	1.38	72	1.13	11.81	9.24	0.833	122	2.28	23.78
5	−+−	0.35	5	4000	210	437	3315	7.11	96	1.18	15.29	10.82	0.833	145.67	2.77	45.37
6	+−−	0.55	5	4000	1121	2035	4041	1.43	48	1.17	14.44	9.17	0.833	127	2.36	27.62
7	−++	0.35	5	6000	203	441	3241	6.89	72	1.16	13.71	11.2	0.833	140	2.61	41.52
8	000	0.45	3	5000	274	566	3251	5.26	81	1.13	11.72	9.52	0.833	144	2.72	40.18
9	−−+	0.35	1	6000	123	299	3862	12.51	102	1.16	14.09	14.35	0.833	167.33	3.18	59.72
10	−−−	0.35	1	4000	311	645	3317	4.66	117	1.21	17.24	13.87	0.833	176.67	3.35	57.18
11	0a0	0.45	1	5000	264	717	4658	6.13	90	1.15	13.29	9.76	0.909	167	3.2	48.45
12	00a	0.45	3	4000	412	799	3857	4.31	72	1.15	12.99	9.17	0.833	124.67	2.39	39.3
13	+−−	0.55	1	4000	460	919	4190	4.06	84	1.1	9.21	8.9	0.833	138	2.62	38.73
14	A00	0.55	3	5000	783	1707	3818	1.78	90	1.08	7.55	8.96	0.833	152.67	2.95	29.72
15	00A	0.45	3	6000	340	1474	4680	2.92	81	1.18	15.58	9.27	0.833	165.67	3.21	35.24
16	0A0	0.45	5	5000	443	756	2952	3.32	63	1.17	14.29	8.86	0.833	135.67	2.62	36.09
17	a00	0.35	3	5000	59	359	3851	10.56	78	1.21	17.31	11.32	0.833	146.67	2.72	50.13

Fig 2.4: Randomized runs of FCC DoE for batch granulation and responses.

2.7.2 Granule Size Distribution

Granule size distribution (GSD) is a way to represent the size range of all granules formed during the granulation process. Standard vibrating sieves were used to sift through the granules and segregate them into different size classes. The mass of granules in each size class was recorded. The mid-point of each size class and the mass fraction in the respective size class was plotted to develop the distributions.

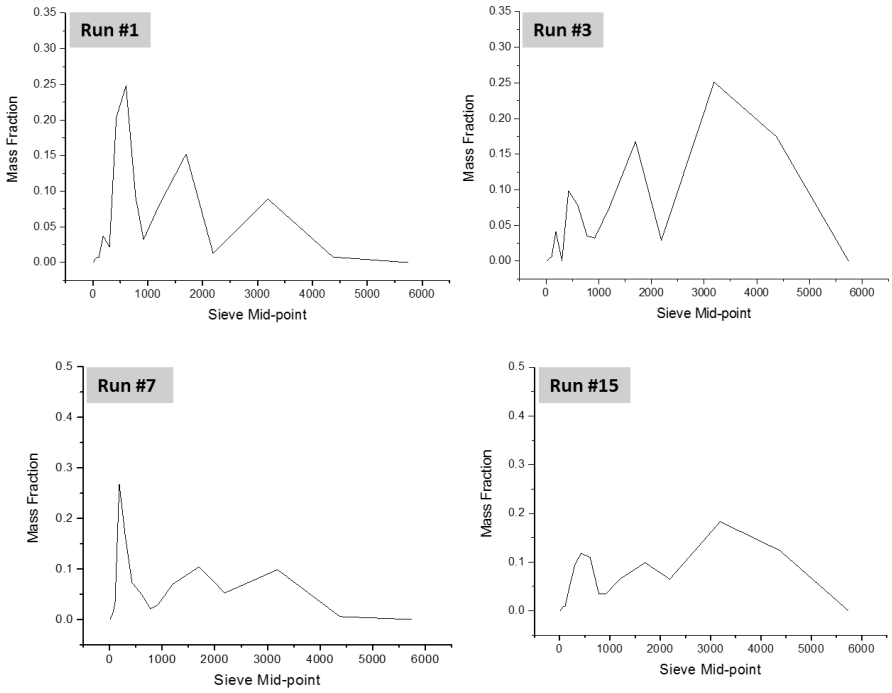


Fig 2.5: Granule size distributions for select runs from FCC DoE for batch granulation.

Ideally, one aims to achieve a distribution which would look like a narrow Gaussian distribution. A narrow distribution with a single sharp peak around the required size class indicates a controlled granulation process, such that changes in process conditions have minimal effect on the granule growth. For the ease of downstream pharmaceutical operations following granulation, very fine and very large granules are not desirable. (Hagrasy, Cruise et al, 2013) Such granules can be recycled by re-granulating the fines and milling the oversized granules.

From the initial GSDs for all runs, it was observed that all distributions are very wide and have multimodal peaks. Fig (2.5) represents the GSDs for some select batches. Selection of suitable batches for tableting based on the distributions was difficult as the GSDs were of poor quality.

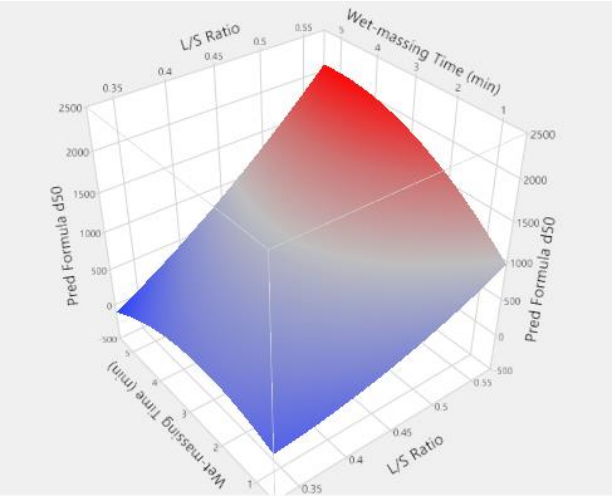


Fig 2.6: Response surface plot for d50 µm.

From the response surface plot for d50, we can infer wet-massing time and L/S ratio influence d50 of granules produced. Wet-massing time has curved effect on d50, where the d50 increases with increasing wet-massing time till a certain value (3.88 min), and then decreases as the wet-massing time is increased further. In comparison to wet-massing time,

L/S ratio is a more dominant factor for the d50, where increasing the L/S ratio would increase the d50 in the range operated.

The distributions for all runs failed to provide concrete information regarding preference of one run over the other or shine any light on which process parameter is more critical. This presented the need of statistical analysis to determine which factors are important. For the purpose of selecting granules for tableting while maintaining consistency, granules between the size range of 250 to 720 µm.

2.7.3 Granule Flow

Hausner ratio and the compressibility index are good indicators of flow. They can be calculated by the following formula:

$$Hausner\ Ratio\ = \frac{\rho_{tapped}}{\rho_{bulk}} \quad .. (3)$$

$$Compressibility\ Index = 100\ \times \frac{\rho_{tapped} - \rho_{bulk}}{\rho_{tapped}} \quad .. (4)$$

The bulk and tapped densities for the calculation of the Hausner Ratio (HR) and Compressibility Index (CI) was measured in the Autotap instrument as mentioned earlier for all 17 runs. For the purpose of obtaining useful data, the experiments were performed as per procedures listed in USP chapter <616> and <1174>. It is important to note, that the measured values are not intrinsic properties of granules. They depend on the technique and instruments for measurement.

Hausner Ratio and Compressibility Index values measured for the granules produced in all runs of the high-shear granulator indicate good flow properties as per the USP scale of flowability represented in Table (2.4). Analysis of the DoE model for Hausner Ratio and

Compressibility Index indicated the L/S ratio as a significant parameter providing p-values of 0.020 and 0.0172 respectively. Runs with 0.55 L/S ratio were found to have good flow properties as per Table (2.4). However, the ANOVA results provide R^2_{adj} values were 0.375 and 0.368 respectively, making the analysis inconclusive and statistically unreliable.

Hausner Ratio	Compressibility Index (%)	Flow Character
1.00 to 1.11	≤ 10	Excellent
1.12 to 1.18	11 to 15	Good
1.19 to 1.25	16 to 20	Fair
1.26 to 1.34	21 to 25	Passable
1.35 to 1.45	26 to 31	Poor
1.46 to 1.59	32 to 37	Very poor
> 1.60	> 38	Very, very poor

Table 2.4: Scale of Flowability: Experimental Considerations for the CI and HR

The data from all the runs of the batch high-shear granulator, were therefore studied by prediction profilers to understand trends and effects of different process conditions. The prediction profiler tool generated by JMP © during the model analysis provides detailed information about the behavior of the model. It provides an interactive interface to show how changes in process parameters would affect responses. The sensitivity of the responses can be gauged via a simulation for each factor throughout the entire range of variation.

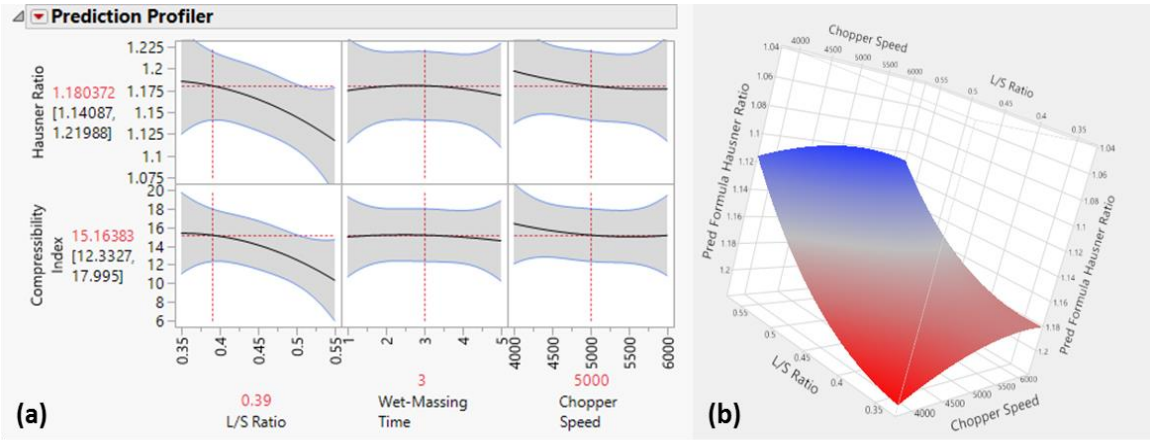


Fig 2.7: (a) Prediction profiler with Hausner Ratio and Compressibility Index as responses (b) response surface plot for Hausner Ratio.

In the Fig (2.7, a), steep slope for the L/S ratio indicates a higher influence of this parameter on both the responses. The chopper speed and wet-massing time have a flatter curve, indicating the lack of significant influence of these two parameters on the responses. With the aim of achieving improved flow properties of granules, the parameter L/S ratio can be varied on the interactive profiler.

A similar inference can be made by analyzing the response surface plot in Fig (2.7, b), where increasing L/S ratio produces granules with a lower Hausner Ratio. Chopper speed has a similar but flatter effect on the flow properties of granules. As per the USP standards in Table (2.4), the HR and CI value was set at a maximum of 1.18 and 15 respectively, which provides the minimum L/S ratio of 0.39. Operating the granulator in 0.39 to 0.55 L/S ratio would provide granules with good flow properties. Further, increasing the chopper speed from 5000 to 6000 would lower the Hausner Ratio/Compressibility Index, promoting the formation of granules with enhanced flow properties.

2.7.4 Eyecon ™ 3D Imaging

14 of the 17 batches produced granules with aspect ratio = 0.83 for granules from 1000-2000 µm. A higher aspect ratio represents the sphericity of the granules. The shape of the granules is known to be influenced by the impeller tip speed. Higher impeller speeds and wet-massing time are known to produce granules with improved shape and higher size as found by Oka et al. (Oka, Kašpar et al. 2015) With the aim of controlling and limiting the growth of granules, the impeller speeds were maintained at the low speed of 200 RPM.

Fig (2.8) represents the granule images captured by Eyecon™ for some select runs for granules between 1000-2000 µm. High settings (+++) of chopper speed, L/S ratio and wet-

massing time produce granules with a definite shape and structure as in Fig (2.8, a), while low settings (---) of chopper speed, L/S ratio and wet-massing time produce flaky and crumbly granules as in seen in Fig (2.8, b). This indicates the ability for better material coalescence and large sized granules in runs where material spends a longer duration in the granulator.

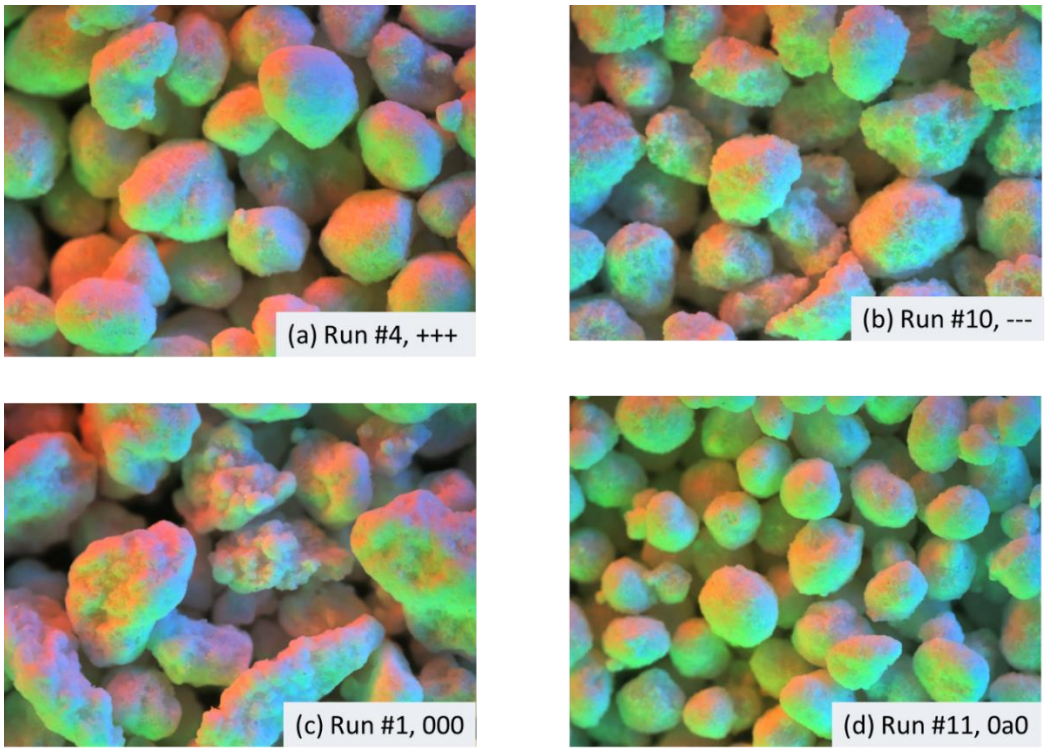


Fig 2.8: Eyecon images for select runs from FCC DoE.

The batches producing irregular shaped granules were found to be operated at medium settings (000) of L/S ratio (0.45), wet-massing time (3 minutes) and chopper speeds (5000). Each lump represents a cluster of very small granules stuck to each other due to moisture as it can be observed in Fig (2.8, c). The run with low setting for wet-massing time, and middle levels of L/S ratio and chopper speed (0a0) produced smaller granules with a higher aspect ratio as seen in Fig (2.8, d). This provides good insight into setting operating

conditions for controlled granule size distribution without compromising on the shape and flow properties. This also corresponds with the findings from the sieve analysis results for producing a higher quantity of granules in the 250-710 micron size range for making tablets.

2.7.5 Granule Porosity

Porosity is an important response measured for granules as this factor gives insight about granule structure and strength. Very low porosity values indicates 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.

ANOVA results provide a p-value = 0.001 and R^2_{adj} = 0.98, implying high significance of this response. Several parameters, first order, second order and interaction parameters were identified as critical based on the parameter estimates; namely, L/S ratio, wet-massing time, [wet-massing time* wet-massing time], [wet-massing time*chopper speed], [chopper speed *chopper speed] in order of decreasing significance.

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	39.593239	0.490887	80.66	<.0001*
L/S Ratio(0.35,0.55)	-9.432	0.362776	-26.00	<.0001*
Wet-massing Time (min)(1,5)	-6.945	0.362776	-19.14	<.0001*
Chopper Speed(4000,6000)	-0.819	0.362776	-2.26	0.0585
L/S Ratio* Wet-massing Time (min)	0.36625	0.405596	0.90	0.3965
L/S Ratio*Chopper Speed	-0.18875	0.405596	-0.47	0.6558
Wet-massing Time (min)*Chopper Speed	-1.40625	0.405596	-3.47	0.0104*
L/S Ratio*L/S Ratio	0.771831	0.700862	1.10	0.3072
Wet-massing Time (min)* Wet-massing Time (min)	3.116831	0.700862	4.45	0.0030*
Chopper Speed*Chopper Speed	-1.883169	0.700862	-2.69	0.0312*

Fig 2.9: Parameter estimates for granule porosity.

Response surface plot for Porosity in Fig (2.10, a) shows the variation of L/S ratio and wet-massing time which are both critical parameters for this response. Higher wet-massing time

and higher L/S ratio produces granules of lower porosity. As the granules spend a longer time in the granulator, densification occurs resulting in lowered porosity. From Fig (2.10, b) we can infer how chopper speed alone has very low impact on granule porosity and wet-massing time is a dominant parameter for granule porosity. These results correspond with the finding of Oka et al. (Oka, Kašpar et al. 2015)

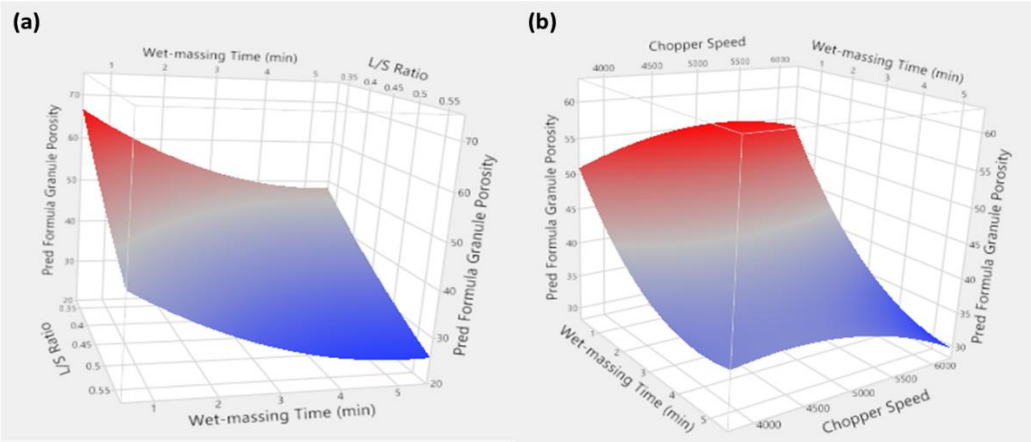


Fig 2.10: Response surface plot for granule porosity (a) wet-massing time and L/S ratio, (b) wet-massing time and chopper speed.

2.7.6 Tablet Hardness

Tableting may not always be the final step in pharmaceutical manufacturing of solid dosages. The tablets formed are not only analyzed for quality, they may undergo further processes such as coating or inscribing drug/potency onto the surface and packaging. All these processes would induce stress onto the tablet. Therefore, measuring tablet hardness or tensile strength is a way to determines if the tablets can withstand the stresses from upcoming processes. Tablet hardness is a critical quality attribute measured to establish quality and consistency between the different batches. Tablet hardness involves measuring

the amount of force required to break or crush a tablet. This force can be used to compute tensile strength of the tablet based on the geometry.

Tablet hardness or tensile strength can be used as a quality control tool or as a measurement to indicate appropriate process conditions for upstream processes. The fluctuations in the crushing force and tensile strength shows how the process conditions such as wet massing time, L/S ratio and chopper speed effects the granules and thereby affect the tablet quality attributes. While it is critical that tablets are strong enough to withstand further processing, extremely hard tablets could also impact other CQAs such as tablet disintegration and dissolution. Very hard tablets would require a long time for disintegration and therefore, increase the time for complete drug release in the body. Irregularities and fluctuations in tablet hardness within the same batch would result in difference in performance and therapeutic affect a consumer would derive from it due to variable tablet dissolution dynamics.

On analysis in JMP © it was found wet-massing time (p-value = 0.00885) was a statistically significant parameter affecting the hardness of tablets. In the Fig (2.11), the bar representing wet-massing time crosses the blue vertical line indicating significance.

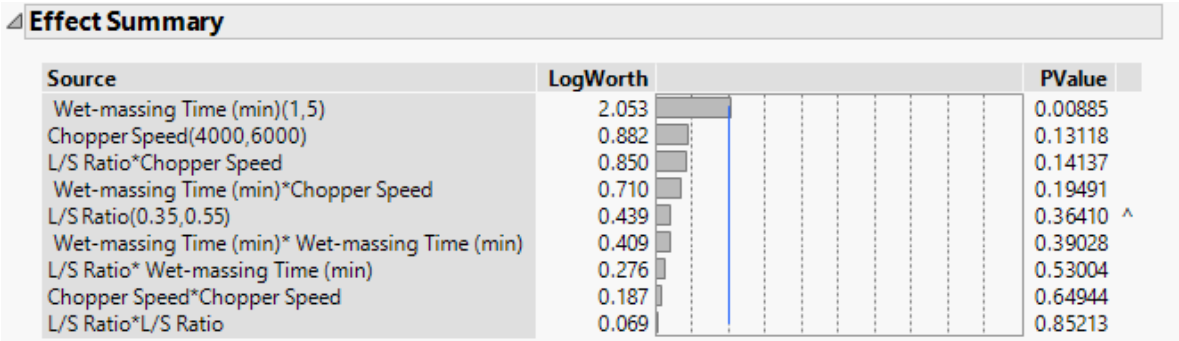


Fig 2.11: Effect summary for tablet hardness.

The influence of wet-massing time was simulated by using the Prediction Profiler in Fig (2.12, a). Wet-massing time is represented by a steep curve in the profiler, which represents an important association of indirect proportionality between the parameter and the two responses. Low wet-massing times result in higher tensile strength and crushing force for tablets, whereas, increasing the wet-massing time lowers the tensile strength and crushing force. The opposite relationship can be observed for chopper speed in the profiler, where low chopper speeds result in lower crushing force and tensile strength of tablets. Similar effect can be observed in the response surface in Fig (2.12, b), where wet-massing time and chopper speeds influence tablet hardness in the identical trend as noted in the Prediction Profiler, with wet-massing time as a more dominating parameter.

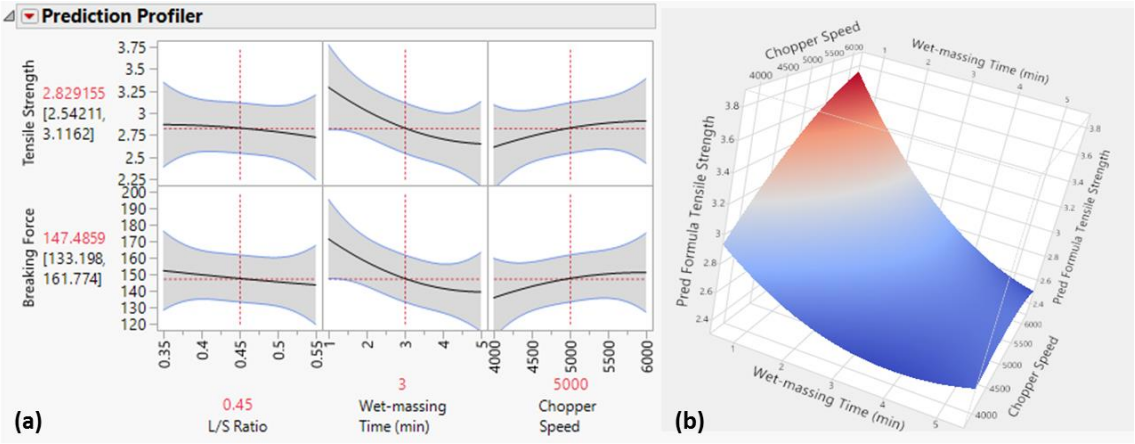


Fig 2.12: (a) Prediction profiler for breaking force (N) and tensile strength (MPa) as responses (b) response surface for tensile strength.

From the response surface plot, we can infer a relation between the chopper speed and porosity of granules that higher chopper speeds would produce relatively denser granules for this range of operation in this size class.

2.7.7 Dissolution Profiles

Dissolution tests are commonly carried out as a way to monitor the amount of API content in solid dosage forms. It is a critical quality attribute (CQA) measured for tablets, to ensure uniformity and consistency through all batches. Dissolution testing is also used as a tool to establish bioequivalence in generic drug manufacturing. During dissolution testing, 6 tablets from each run were weighed and measured for thickness and dissolved in 900 ml of distilled water for 4 hours in accordance with the method mentioned in USP Chapter <711> in Apparatus 2 (paddles). The concentration of drug released was measured every three minutes to develop dissolution profiles. These profiles map the change of API concentration in the tablet with respect to time and determine the rate of release. This information is critical for understanding the release dynamics of the tablets, drug solubility, and drug permeability in the GT track, mimicking in-vivo studies and establishing drug bioavailability.

Dissolution profiles for some select batches are represented in Fig (2.13). The dissolution profiles for the runs vary starkly and represent dissimilar rates of release. Tablets from few runs dissolved rapidly in the media and reach 100% release in less than 15 minutes, which is termed as immediate release (IR). Rapid release tablets indicate rapid disintegration, high solubility and high permeability. This would reasonably imply lack of bioavailability issues for these tablets.

Runs #4, #5, #6, #7 and #16 have quick release rates and consistent profiles for all the 6 tablets tested. These five runs were found to have high wet-massing time of 5 min. It can be inferred, high wet-massing times during granulation produces immediate-release tablets

with smooth and consistent dissolution profiles. These results also confer with the findings from the tablet hardness testing where high wet-massing time produced tablets of lower tensile strength, which would in turn reduce disintegration time and cause a fast release of drug in the dissolution media.

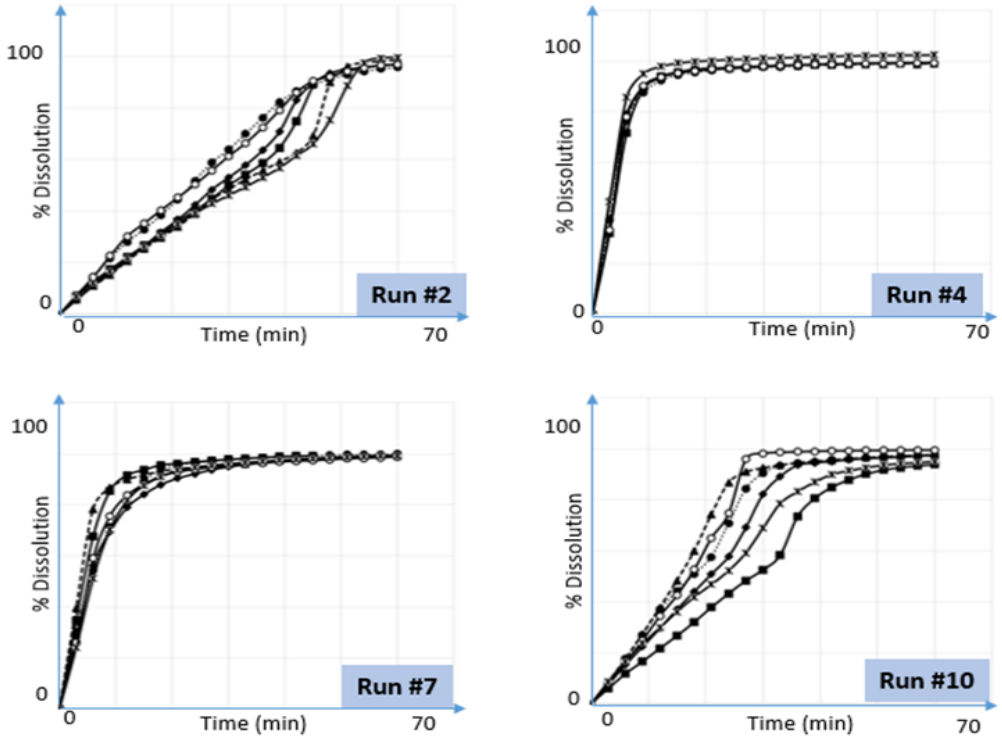


Fig 2.13: Dissolution profiles for select runs.

On the other hand, runs #2, #9, #10 and #13 have a slow release rate and have inconsistent profiles within the batch. Poor quality of dissolution profiles are an indicator of variance and irregularity in the concentration of API in the tablet and poor granulation process. All these runs were found to have the least wet-massing time of 1 minute, which allows us to infer that insufficient or lower wet-massing times can result in unbalanced distribution of API and excipients in the granules and thereby effect the quality and potency of tablets.

From the conclusions above, it would be reasonable to note that process conditions have a significant effect on the drug release dynamics. Wet-massing time has emerged as an important parameter to better understand the dissolution of drug in the media, and how altering the duration during the granulation can be critical and detrimental to the quantity and release rate of the API in solid dosages.

2.7.8 API Content Uniformity in Tablets

The concentration of the drug dissolved was recorded every 3 minutes during dissolution testing. This information was inputted in the calibration model to determine the final concentration of the drug released and therefore determine the amount of active ingredient in each tablet of each batch.

Known concentrations of Caffeine was dissolved in distilled water to make samples and the absorption in the UV-Vis spectrometer was recorded. The absorption was plotted against the concentration to develop the calibration model.

$$Absorbance = 45.569 \times Concentration - 0.0024 \quad \ldots (5)$$

Concentration at 100% dissolution was used to determine the total quantity of Caffeine in each tablet. It is assumed that the API is homogeneous through the entire granule size distribution, and the granules have 8% API as in the blend. However, on calculation, all batches were found to have more than 8% of Caffeine. Some runs were found to be highly concentrated with over 14% API in the tablets.

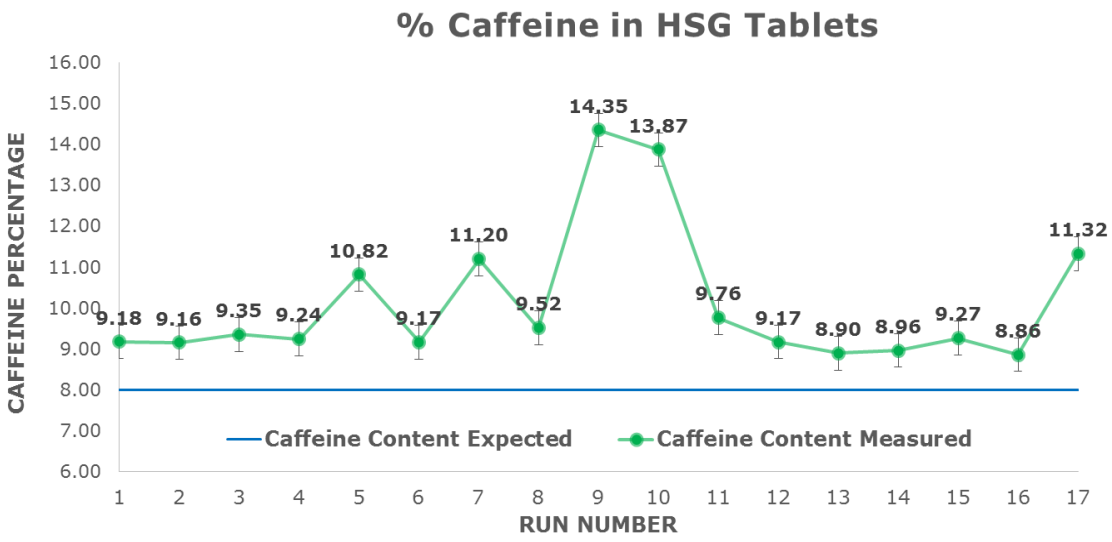


Fig 2.14: API content in tablets from 17 runs.

The fluctuations and deviation from the expected concentration of Caffeine in all runs is an indication of poor and unreliable granulation process. It can also be observed that the granules between 250-710 µm are more concentrated with the API as opposed to 0-249 µm and 711+ µm being mostly comprised of excipients. These observations also deviate from those of Kaspar et al. (Kaspar, Tokárováa et al, 2013) who reported uniform distribution of acetaminophen in granules from all size classes produced in a 3.9L Key International high-shear granulator using a liquid-spray method.

2.8 Process Optimization

2.8.1 Granulation

Contour Profiler is an extremely handy tool for determining the optimal operating condition or optimal design space for a process. This tool was used to better understand the effect of process parameters on the responses and how to nullify the undesired effects and find the optimal conditions based on the custom needs of the process. The shaded regions show the influence of a parameter on the process. The aim of the Contour Profiler is the

maximization of the unshaded region as per the process limitations or desired response constraints. Performing granulation in the unshaded region would ensure the limits set on the responses would be accounted for and be in the desired range.

In the case of batch granulation in the Key International granulator, constraints for three responses namely, d10, d50 and d90 were set with the aim of –

- Limiting fine granules below 100 µm which would cause dusting.
- Limiting large granules above 4200 µm for ease of downstream processes and material handling.
- Maximizing the quantity of granules below 700 µm for the purpose of tableting.
- Determining optimal operation conditions based on the constraints.

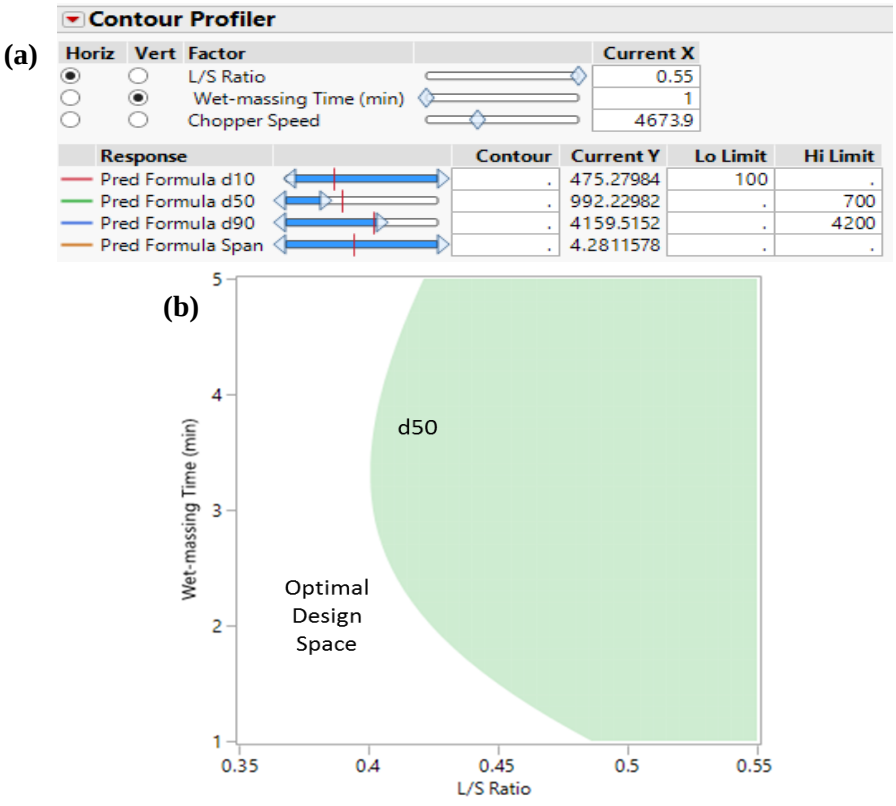


Fig 2.15: (a) Contour Profiler for granulation process optimization (b) design space.

2.8.2 Tableting

Tableting process is a critical unit operation in solid dose manufacturing. The final quality attributes of tablets rely on the reproducibility and uniformity of upstream processes, especially the granulation unit operation. Contour Profiler was used for determining the optimal design space for the tableting process by maximizing the unshaded region as per the process limitations or desired response constraints.

In the case of tableting process, out of the many responses collected for the study, d50, Hausner Ratio (HR) and tensile strength (TS) were selected and set with the aim of –

- Maximizing the quantity of granules below 700 µm for the purpose of tableting.
- Ensuring good flow properties of granules for ease of downstream processes and material handling.
- Ensuring rapid release of drug in dissolution testing based on experimental results.

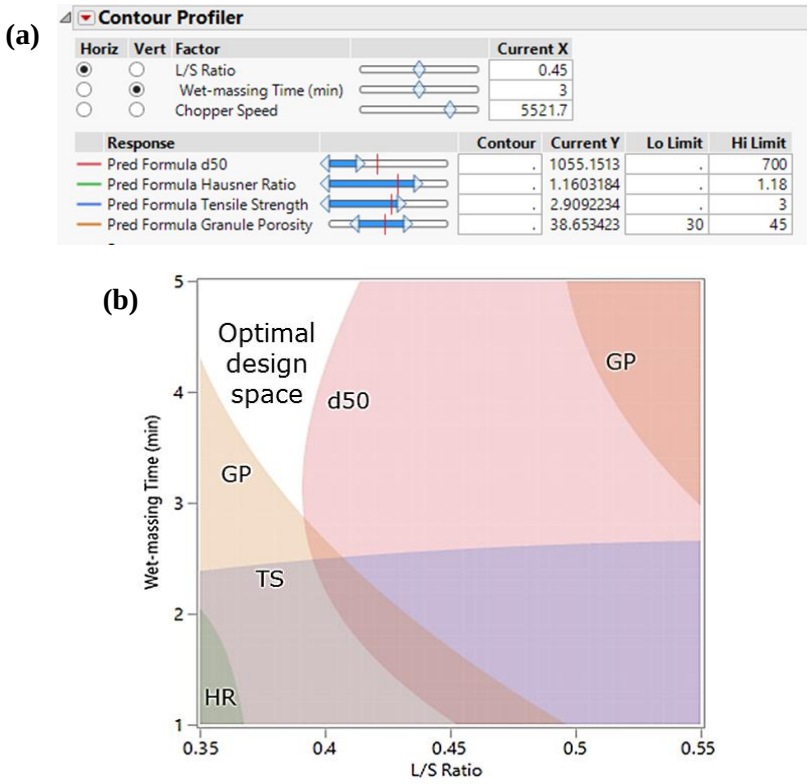


Fig 2.16: (a) Contour Profiler for tableting process optimization (b) design space.

Chapter 3: Characterization of Continuous Twin Screw Granulator

3.1 Granulator components

The twin-screw granulator/extruder is ever so popular for the operational flexibility and versatility it offers. Twin-screw granulator houses two rotating identical screws inside a barrel, which can be segmented into different zones, such that the powders are fed into the equipment in zone 1, followed by liquid addition in zone 2 and different stages of granulation occurring in the remaining zones. The twin screws can be configured in multiple arrangements with various types of elements, such as, conveying elements (low shear), kneading elements (high shear) and distributive mixing elements (medium shear). (Djuric and Kleinebudde 2008) as shown in Fig (3.1).

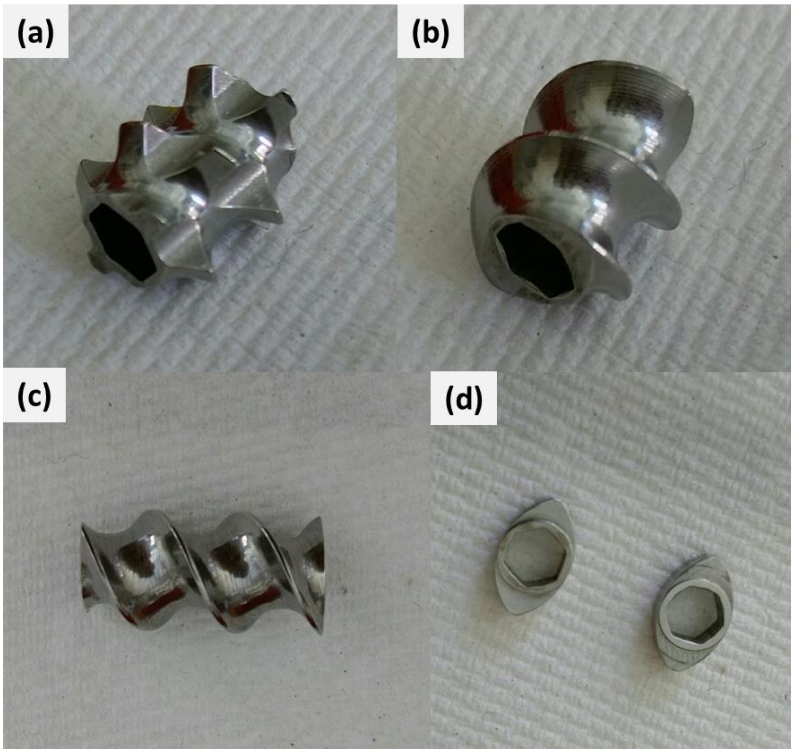


Fig 3.1: (a) Distributive feed screw-DFS, (b) Conveying element-CE, (c) Conveying screw-long, (d) Kneading elements-KE.

The conveying elements Fig (3.1 b), serve the purpose of conveying or pushing forward the material/granules in the barrel, while the kneading elements Fig (3.1, d), knead and agglomerate the powders. The distributive mixing elements called as the distributive feed screw Fig (3.1, a), contribute to distribute and mix the powders and liquid binder. (Keleb, Vermeire et al. 2004) The configuration of kneading elements can also be varied based on the angle of orientation or cutting (forward or backward). The twin-screw granulator has a choice for liquid addition location and allows modular barrel temperature control during operation. The residence time distribution of the twin-screw granulator is a function of the screw configuration, orientation angle of screw elements, material throughput, screw RPM and length of the screws.

3.1.1 Screw Elements and Configurations

With every element having a unique functionality and usage, there are several combinations that can be explored. The design, orientation, arrangement and quantity of the screw elements impart unique properties to the granules produced. The variations in screw configuration leads to change in the mechanism that dominates the granulation and therefore affect granule properties like granule size distribution, granule microstructure and porosity (Thompson and Sun 2010).

Thermo Scientific Pharma 11 granulator comes with a default screw configuration depicted in Fig (3.2, c). For this study, the screw configurations were altered by changing the number of kneading elements, their angle and orientation and the inclusion of a distributive feed screw. The remainder of the screw length was fitted by adding conveying elements. Fig (3.2, a) shows a screw configuration used for a few experiments where the DFS was

eliminated and all 5 KEs were placed at 90°. Fig (3.2, b) depicts a screw configuration which includes the DFS and a total of 14 KEs separated by a CE in the center.

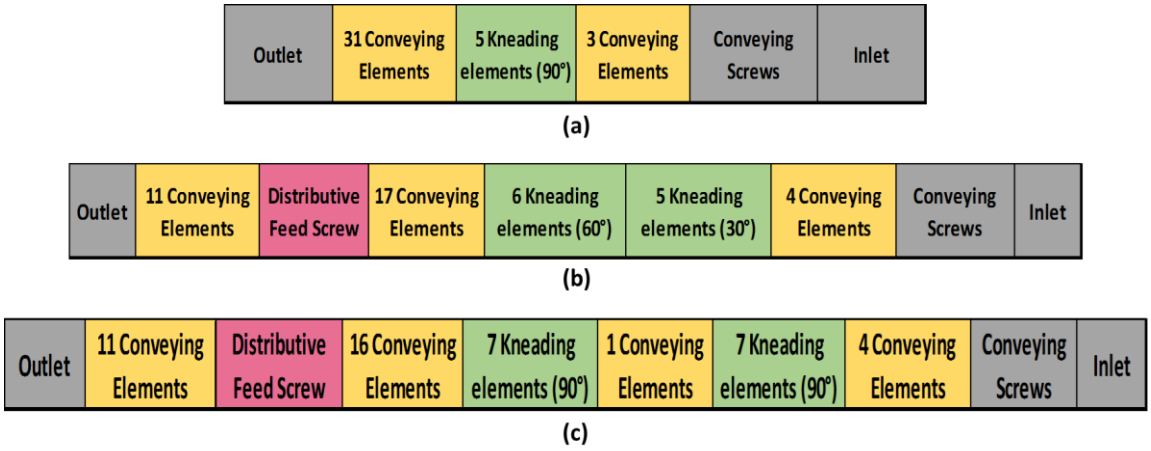


Fig 3.2: Select screw configurations for TSG characterization experiments.

3.2 Granulation Mechanism and Procedure

In the twin-screw granulator, the conveying elements (CEs) are responsible for transporting the material while offering low shear. As the powder is fed into the barrel, these screws push the material from one zone to the next. As liquid binder is dripped or sprayed, the powder get mixed with the liquid droplets as they are conveyed, this is the nucleation step. Distributive mixing elements or Distributive Feed Screws (DMEs) aide and improve the distribution and penetration of the liquid droplets throughout the powder bed. These elements offer medium shear and assist in the granule growth by nucleation. The kneading elements (KEs) offer high shear and induce granule growth. The KEs are responsible for agglomerating and shaping the granules. The screw elements are typically arranged in a way to achieve low shear mixing in CEs, followed by improved two-phase distribution by DMEs, followed by high shear densification performed by KEs and transport to the outlet

by CEs. The properties of granules such as shape, granule size distribution, porosity, and structure are dependent on the number of CEs, KEs and DMEs and on the configuration.

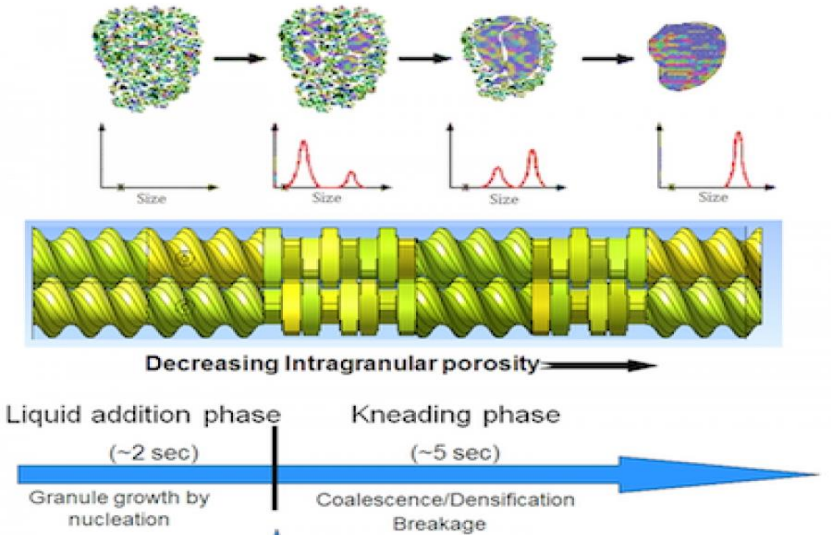


Fig 3.3: Granulation mechanism in a twin-screw granulator adapted from Kumar et al. (Kumar, Gernaey et al. 2013)

For the characterization study conducted on the 11mm TSG, the same low-dose four component formulation was premixed in the Glatt tumble tote blender comprising of 8% (w/w) regular caffeine, 44% (w/w) α-lactose monohydrate, 44% (w/w) microcrystalline cellulose and 4% (w/w) Polyvinylpyrrolidone as in the experiments carried out with the Key International high-shear granulator.

The experimental setup consists of a K-tron K-SFS-24 feeder operating in gravimetric mode continuously feeding premix into the granulator. The granulating liquid (distilled water) was dripped into the TSG via a peristaltic pump. The granules formed were collected for each run with the setting and operation conditions as per each run. After collection, granules were air dried till the moisture content was less than 3%. The continuous granulation setup is shown in Fig (3.4).

Fig 3.4: Continuous granulation in the Thermo Scientific Pharma 11mm

3.3 Process Parameters and Levels

The modular nature of the twin-screw granulator presents an opportunity to vary multiple process and design variables. Some of the critical process parameters that can explored in the continuous twin screw granulators are: liquid to solid ratio, screw rotational speed and material throughput. A number of design parameters such as liquid binder addition position, powder addition position, screw configuration, orientation angle for the kneading elements and barrel temperature can also be investigated. However, in this study, the location for material and binder were not included.

Characterization of any equipment requires a more detailed consideration of all factors affecting the response variable. In the characterization study for the Thermo Scientific Pharma 11mm TSG, multiple conditions were examined to determine the parameters and levels to be changed for the study. The levels for each parameter was chosen such that extreme cases of operation can be tested. With the intention of covering a wide range of

operation, the following combinations of design parameters and process parameters were altered:

Process Parameters		
Parameter	*Levels*	*Values*
Throughput (kg/h)	3	0.4, 0.8 & 1.2
Screw RPM	3	200, 500 & 800
L/S ratio	3	0.35, 0.45 & 0.55
Design Parameters		
Parameter	*Levels*	*Values*
Distributive feed screw	2	Yes or No
No. of kneading elements	3	5, 9 & 14
Stagger angle of kneading elements	3	30°, 60° & 90°
Barrel temperature (°C)	3	25, 35 & 45

Table 3.1: Parameters for Pharma 11mm TSG

3.4 Design of Experiments

The operational flexibility with the twin-screw granulator makes it essential to undertake a methodical approach for characterization and to investigate how these process and design parameters affect the granule properties and the quality attributes of any downstream unit operations expected to be carried out with the granules such as drying, tableting, coating and so on. Design of experiments (DoE) was applied to determine the significance of the various parameters and to understand the relationship between the various parameters and the response attributes. The numerous possibilities provide interesting and challenging

opportunities for experimentation and process optimization. In the characterization study, the number of factors and the levels makes performing a full factorial design difficult.

	Throughput	Screw RPM	L/S Ratio	Number of KE	KE Stagger angle	Barrel Temperature	DFS	D10	D50	D90	Span	Torque
1	1.2	800	0.55	5	30	45	no	314	582	867	0.95	1.28
2	0.4	800	0.35	5	30	45	no	223	421	808	1.39	2.25
3	0.4	200	0.55	5	30	45	no	215	426	876	1.55	1.46
4	1.2	800	0.35	14	30	25	yes	353	644	884	0.82	3.53
5	0.4	200	0.55	14	90	25	yes	223	430	958	1.71	1.99
6	0.4	800	0.55	5	90	45	yes	287	486	724	0.9	0.87
7	1.2	200	0.55	5	90	45	yes	187	396	755	1.43	1.86
8	1.2	800	0.35	5	90	25	yes	193	392	909	1.83	2.43
9	0.4	800	0.55	5	90	25	no	251	445	728	1.07	1.37
10	1.2	800	0.35	5	90	45	no	193	408	945	1.84	2.2
11	0.4	200	0.55	5	30	25	yes	205	403	910	1.75	1.55
12	1.2	800	0.35	14	30	45	no	364	645	876	0.79	3.15
13	0.4	200	0.35	14	30	25	yes	237	695	1556	1.9	4.16
14	1.2	800	0.55	14	90	25	no	394	667	924	0.79	1.65
15	1.2	200	0.55	14	30	45	no	•	•	•	•	•
16	1.2	200	0.35	5	30	45	no	85	339	1172	3.21	3.58
17	0.4	200	0.35	5	90	45	yes	98	297	888	2.66	1.33
18	0.4	800	0.35	14	90	45	yes	219	417	842	1.49	2.38
19	1.2	200	0.35	5	30	25	yes	98	375	1144	2.79	3.22
20	1.2	800	0.35	5	30	45	yes	282	534	1113	1.56	2.71
21	0.4	200	0.55	14	30	45	yes	274	556	995	1.3	2.17
22	0.4	800	0.35	14	90	25	no	197	403	890	1.72	2.16
23	0.4	800	0.55	14	30	25	yes	392	657	905	0.78	1.62
24	0.4	800	0.55	14	30	45	no	454	723	1258	1.11	1.56
25	0.4	200	0.55	14	30	25	no	221	492	1171	1.93	2.79
26	0.4	200	0.35	14	30	45	no	209	644	1507	2.02	3.98
27	1.2	800	0.35	5	30	25	no	237	518	1194	1.85	3.03
28	1.2	200	0.55	5	90	25	no	189	437	855	1.52	2.16
29	1.2	200	0.55	14	30	25	yes	•	•	•	•	•
30	0.4	200	0.35	5	90	25	no	93	299	907	2.72	0.9
31	1.2	800	0.55	14	90	45	yes	399	691	1175	1.12	1.4
32	1.2	800	0.55	5	30	25	yes	304	606	1011	1.17	1.67
33	0.8	500	0.45	9	60	35	yes	278	578	1240	1.66	2.11
34	0.8	500	0.45	9	60	35	no	296	582	1142	1.45	2.26
35	1.2	200	0.35	14	90	45	yes	128	318	1058	2.92	5.31
36	0.4	200	0.55	14	90	45	no	235	451	1013	1.73	1.91
37	1.2	200	0.35	14	90	25	no	112	365	1007	2.45	5.67
38	0.8	500	0.45	9	60	35	no	306	560	1064	1.35	2.28
39	0.4	800	0.35	5	30	25	yes	199	400	858	1.65	2.28
40	0.8	500	0.45	9	60	35	yes	324	578	1102	1.35	2.26

Fig 3.5: D-Optimal DoE for characterization of ThermoScientific Pharma11 TSG

A D-Optimal design was generated to list 40 randomized runs to collect granules from the granulator on JMP ©. D-optimal designs help estimate parameters without any bias and works for experiments with any number of parameters, levels and constraints. Characterization experiments typically require a lot of experiments and resources, D-Optimal design is particularly applicable in cases of resource limitation or in cases with need for improved resource management. These types of designs can be used regardless of

the type of model the experimenter wishes to fit, like the order or number of interactions. These designs can also be used to study experiments with any type of objective like screening, response surfaces and so on and can include both qualitative and quantitative parameters in the design. In this case a combination of continuous and categorical variables were set to study the first order and second order interactions.

3.5 Characterization of Granules Properties

Granules were collected from a total of 38 runs out of the 40 listed in the DoE. Two runs #15 and #29, both of which were set at low L/S ratio, higher material throughput and low screw speeds resulted in clogging of the equipment and the granules could not be collected. No responses were recorded for these runs, and were left blank for the design.

An additional experiment, run #41* was also performed. This run comprised of middle levels of material throughput (0.8 kg/hr), L/S ratio (0.45), and screw RPM (500) with the equipment default configuration as shown in Fig (3.2, c) for comparison with the screw configurations explored in this study. The granules from 39 batches were air dried till the moisture content of granules was recorded below 3%.

Granule size distribution was determined by sieve analysis and granule shape was measured using Eyecon ™ 3D imaging for 38 DoE runs and 1 default screw configuration run (#41*). The physical characterization of the granules was performed using the same methods and techniques as for the Key International high-shear granulator.

3.6 Tableting

Based on the preliminary responses measured and collected through the 39 runs, 11 runs were selected for tableting. The responses included measuring the torque values observed

during granulation and the granule size distributions of all runs after performing sieve analysis. The selection of the runs was done on the basis of a mono-modal granule size distribution. These 11 runs were chosen for further characterization such as granule flow properties, granule porosity, tableting, tablet hardness testing, tablet dissolution testing and uniformity in tablet API content. The selected runs are shown below in Table (3.2).

Run #	Throughput (kg/hr)	Screw RPM	L/S Ratio	Kneading Elements	KE Stagger Angle	Barrel Temp (°C)	DFS
1	1.2	800	0.55	5	30	45	no
4	1.2	800	0.35	14	30	25	yes
6	0.4	800	0.55	5	90	45	yes
9	0.4	800	0.55	5	90	25	no
12	1.2	800	0.35	14	30	45	no
14	1.2	800	0.55	14	90	25	no
23	0.4	800	0.55	14	30	25	yes
24	0.4	800	0.55	14	30	45	no
31	1.2	800	0.55	14	90	45	yes
32	1.2	800	0.55	5	30	25	yes
41*	0.8	500	0.45	11	30&60	35	yes

Table 3.2: 11 runs selected for tableting from 40 runs of D-Optimal design

3.7 Results & conclusions

3.7.1 Granule Size Distribution

The granules collected from all 41 batches were dried and sieved in sieve sizes starting from 38 µm to 4000 µm. The granule size distribution was mostly bimodal and multimodal with 25% runs producing a mono-modal distribution.

The d10, d50 and d90 values for all runs showed fluctuations, although the span for the distributions remained low and varied from 0.78 to 3.21 across all 38 runs indicating controlled size growth during granulation, which is supported by moderately lower d90 values observed in all batches. The mixture of different typed of screw elements across the length of the TSG barrel imparts density and shape to granules, while limiting the quantity

of very fine and very large granules produced. The average d50 measured for 39 runs was 498.97 µm, indicating a higher quantity of granules to be produced in the size class used for tableting process.

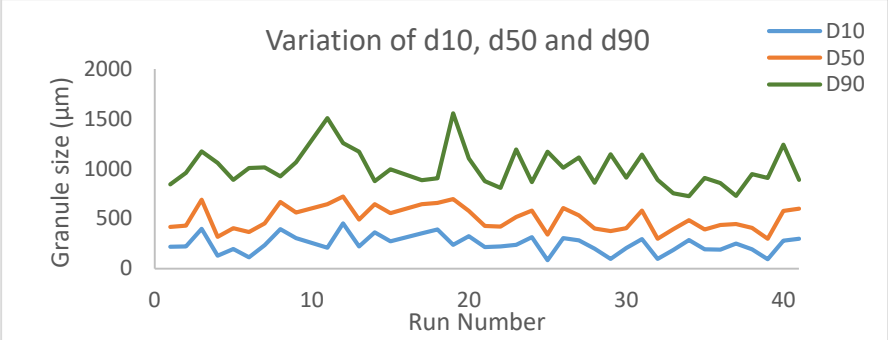


Fig 3.6: Variation of d10, d50 and d90 for Pharma 11mm TSG runs.

The granule size distributions were plotted for all the runs of the TSG design in Fig (3.6). Runs which produced mono-modal distributions were selected for further characterization of granules.

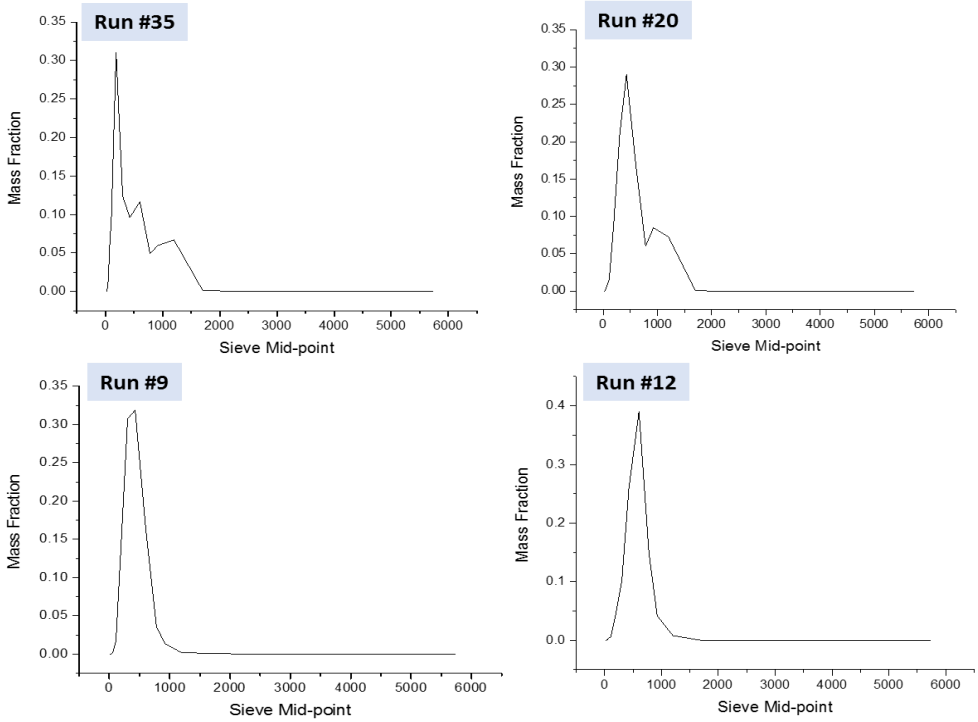


Fig 3.7: GSD for select runs from 41 experiments of TSG.

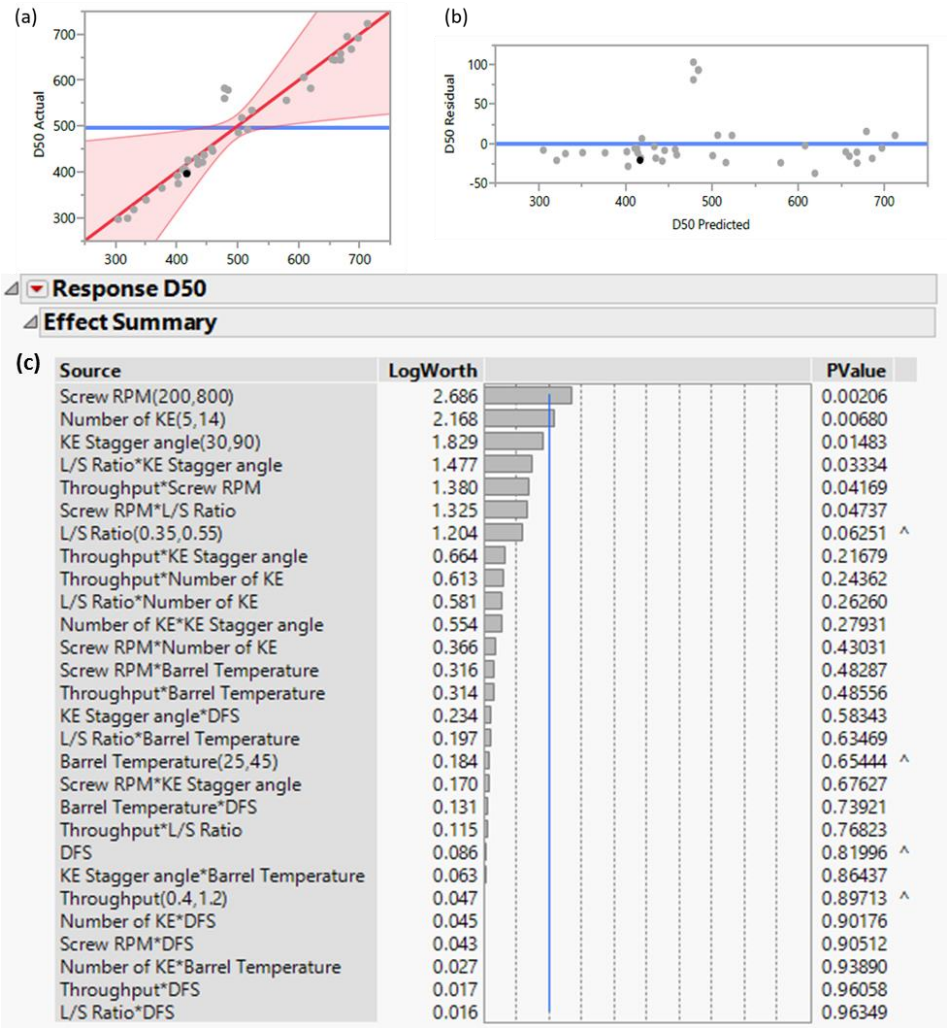
The granules from these runs were used to make tablets and measure the tablet CQAs. Granule size distributions of some runs are shown in Fig (3.7).

Runs #20 and #35 are some examples of multimodal and broad distributions found in the TSG experiments. Run #9 and #12 indicate a narrow distribution peaking around 500 µm. This indicates a large quantity of granules being collected in this size class which is ideal for pharmaceutical manufacturing.

The initial ANOVA results reveal that design parameters were more critical and detrimental as compared to process parameters in influencing the granule size distribution. The goodness of model fit (R^2_{adj} = 0.67) and a randomly scattered residuals plot depict a few outliners in Fig (3.8, a) and Fig (3.8, b).

The p-values<0.05 are indicated in Fig (3.8,c) which identify the significant parameters to be: screw RPM, number of kneading elements, KE stagger angle and interaction parameters and [L/S ratio* KE stagger angle], [Throughput*Screw RPM], [L/S Ratio*Screw RPM] in order of decreasing significance.

Response surface plot for d50 in Fig (3.9) shows a linear relationship with the screw RPM and the number of kneading elements, increasing screw RPM and KE results in increased d50, with the screw RPM being the more dominant factor.



Source	LogWorth	PValue	
Screw RPM(200,800)	2.686	0.00206	
Number of KE(5,14)	2.168	0.00680	
KE Stagger angle(30,90)	1.829	0.01483	
L/S Ratio*KE Stagger angle	1.477	0.03334	
Throughput*Screw RPM	1.380	0.04169	
Screw RPM*L/S Ratio	1.325	0.04737	
L/S Ratio(0.35,0.55)	1.204	0.06251	^
Throughput*KE Stagger angle	0.664	0.21679	
Throughput*Number of KE	0.613	0.24362	
L/S Ratio*Number of KE	0.581	0.26260	
Number of KE*KE Stagger angle	0.554	0.27931	
Screw RPM*Number of KE	0.366	0.43031	
Screw RPM*Barrel Temperature	0.316	0.48287	
Throughput*Barrel Temperature	0.314	0.48556	
KE Stagger angle*DFS	0.234	0.58343	
L/S Ratio*Barrel Temperature	0.197	0.63469	
Barrel Temperature(25,45)	0.184	0.65444	^
Screw RPM*KE Stagger angle	0.170	0.67627	
Barrel Temperature*DFS	0.131	0.73921	
Throughput*L/S Ratio	0.115	0.76823	
DFS	0.086	0.81996	^
KE Stagger angle*Barrel Temperature	0.063	0.86437	
Throughput(0.4,1.2)	0.047	0.89713	^
Number of KE*DFS	0.045	0.90176	
Screw RPM*DFS	0.043	0.90512	
Number of KE*Barrel Temperature	0.027	0.93890	
Throughput*DFS	0.017	0.96058	
L/S Ratio*DFS	0.016	0.96349	

Fig 3.8: (a) Goodness of fit (b) residuals plot (c) Effects summary for Pharma11mm TSG.

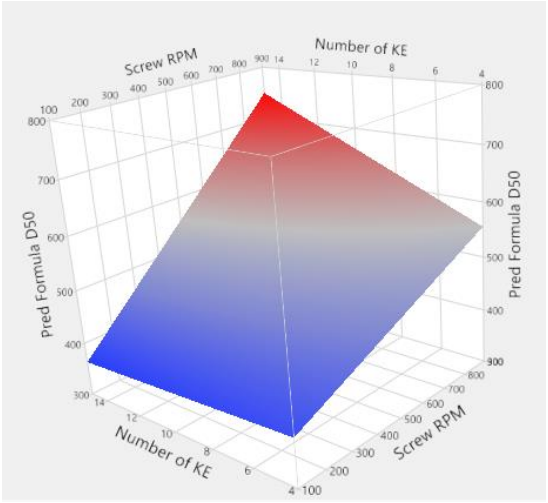


Fig 3.9: Response surface plot for d50 µm.

3.7.2 Granule Shape

All 41 runs from the TSG were analyzed for granule shape using Eyecon™. Granules collected between 1000 to 2000 µm were collected and aspect ratio for all runs was recorded as 0.83. A higher aspect ratio represents the sphericity of the granules. Parameters such as L/S ratio and screw configuration would affect the shape granules produced in that run. Eyecon™ images from some select batches are shown in Fig (3.10). It can be observed from this and Fig (3.5), how different operating conditions produce granules with different structure and shape. Granules from run #28 were found to be flaky despite a higher L/S ratio of 0.55, while granules from run #19 produced granules which appear to be dense and spherical with an L/S ratio of 0.35, implying the influence of other parameters on granule shape and appearance. It is interesting to note, despite a great difference in the appearance of granules in these runs, the aspect ratio was found to be the same. This would suggest the need of better technique to measure the granule shape.

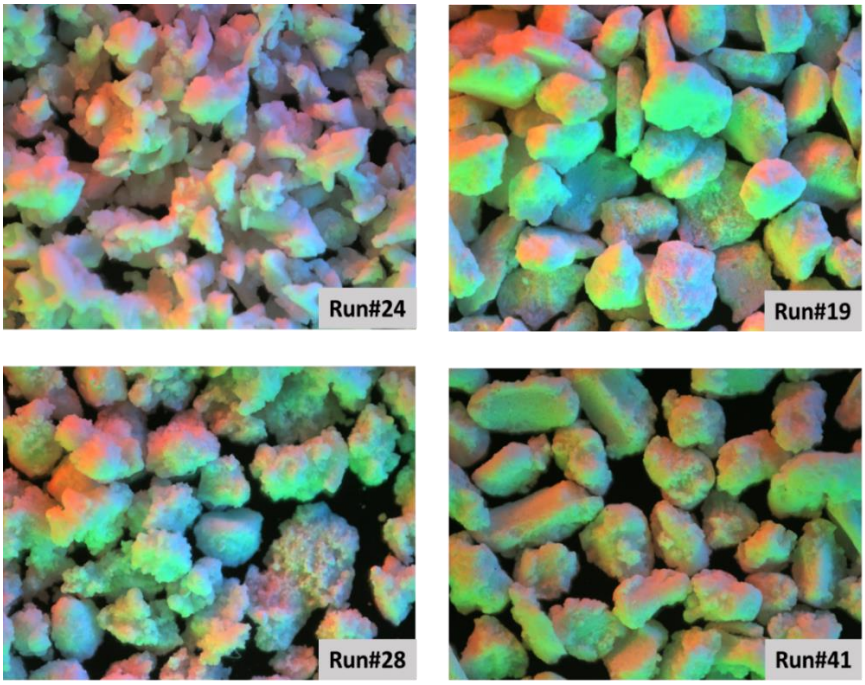


Fig 3.10: Eyecon ™ images for select runs from TSG.

3.7.3 Granule Flow

Bulk and tapped densities were measured for the 11 selected runs as per the methods specified in USP chapter <616> in the Quantachrome Autotap instrument. Bulk and tapped densities were measured in g/cm^3. These values were used to compute the Hausner ratio and compressibility index for the runs using equations (3) and (4).

Run #	Bulk Density	Tapped Density	Hausner Ratio	Compressibility Index
1	0.51	0.59	1.14	12.58
4	0.59	0.67	1.12	10.81
6	0.51	0.60	1.17	14.86
9	0.49	0.57	1.16	13.91
12	0.55	0.63	1.14	12.50
14	0.53	0.60	1.14	12.00
23	0.62	0.67	1.07	6.38
24	0.59	0.64	1.10	9.09
31	0.56	0.59	1.06	5.41
32	0.52	0.58	1.11	9.59
41*	0.54	0.60	1.11	9.68

Table 3.3: Measured values of bulk density, tapped density, Hausner Ratio and Compressibility Index for selected runs.

All runs produced a Hausner ratio between 1.06 and 1.17, and a compressibility index between 5 and 15. This allows us to classify all runs to have excellent to good flow properties as per the scale of flowability from USP chapter <1174> shown in Table (2.4).

3.7.4 Granule Porosity

Granule porosity was measured using the Accupyc 1360 and Geopyc II 1340 with granules collected from 1000 to 2000 µm. Due to insufficient granules from two runs #6 and #9 were not considered for porosity measurements. Multiple regression analysis was performed for all runs to investigate the effect of parameters on the response: porosity. As the screw RPM for all runs was 800, this parameter was excluded from the study.

The R^2_{adj} value was calculated to be 0.96 and with the F value (0.006<0.05), the model is considered to be a very good fit. The significance of each parameter was also estimated by the model. Material throughput (p-value = 0.001), L/S ratio (p-value = 0.003), number of kneading elements (p-value = 0.004), KE stagger angle (p-value = 0.007) were found to be statistically significant in predicting the porosity of granules. The regression equation for prediction of granule porosity (assumed linear) can be given as:

$$Porosity = -66.38 + 27.49\ (Throughput) + 124.73(L/S\ Ratio) + 1.75\ (Kneading\ Elements) - 0.22\ (KE\ Stagger\ Angle) \quad .. (6)$$

SUMMARY OUTPUT FOR GRANULE POROSITY

Regression Statistics	
Multiple R	0.99357924
R Square	0.98719971
Adjusted R Square	0.96159914
Standard Error	2.84460064
Observations	10

ANOVA

	df	*SS*	*MS*	*F*	*Significance F*
Regression	6	1872.186752	312.0311	38.561624	0.006239013
Residual	3	24.27525833	8.091753		
Total	9	1896.46201			

	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*Lower 95.0%*	*Upper 95.0%*
Intercept	-66.384722	9.6609813	-6.87143	0.00631	-97.13027646	-35.639168	-97.13027646	-35.639168
Throughput	27.490625	2.514295499	10.93373	0.00164	19.48901458	35.49223542	19.48901458	35.4922354
L/S Ratio	124.7375	14.22300318	8.770124	0.00312	79.47355608	170.0014439	79.47355608	170.001444
Kneading Elements	1.75027778	0.223492933	7.831468	0.00434	1.039023518	2.461532038	1.039023518	2.46153204
KE Stagger Angle	-0.2205417	0.03352394	-6.57863	0.00715	-0.327229806	-0.11385353	-0.327229806	-0.11385353
Barrel Temperatur	0.00770833	0.091809091	0.08396	0.93838	-0.284469168	0.299885835	-0.284469168	0.29988583
DFS	-4.7791667	1.836181815	-2.60277	0.08018	-10.6227167	1.064383366	-10.6227167	1.06438337

Fig 3.11: Multiple regression summary for granule porosity.

3.7.5 Tablet Hardness

Tablet hardness is a critical quality attribute measured to establish quality and consistency between the different batches. Tablet hardness involves measuring the amount of force required to break or crush a tablet. This force can be used to compute tensile strength of the tablet based on the geometry. 10 mm diameter flat-faced cylindrical tablets produced

with 10 ± 0.5 kN compression force were selected and crushed. Crushing force averaged from 3 tablets of each of the 11 selected runs were used to calculate the tensile strength σ_x of a tablet of diameter D with a thickness H is calculated by the following formula, where F is the crushing force:

$$\sigma_x = \frac{2\,F}{\pi\,D\,H} \qquad .. (7)$$

Multivariate regression analysis was performed on MS Excel to determine the influence of various parameters on the measured values of tensile strength (MPa) as seen in Fig (3.12). With the R^2_{adj} = 0.31 and p-value=0.357, there is no statistical significance that can be reached for tablet tensile strength.

SUMMARY OUTPUT FOR TENSILE STRENGTH

Regression Statistics	
Multiple R	0.878210206
R Square	0.771253166
Adjusted R Square	0.313759497
Standard Error	0.181177209
Observations	10

ANOVA

	df	*SS*	*MS*	*F*	*Significance F*
Regression	6	0.332024592	0.055337	1.685823	0.35799007
Residual	3	0.098475543	0.032825		
Total	9	0.430500135			

	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*Lower 95.0%*	*Upper 95.0%*
Intercept	3.433937204	0.615323502	5.580702	0.011359	1.475703197	5.392171211	1.475703197	5.392171211
Throughput	-0.3603212	0.160139541	-2.25005	0.109934	-0.869956689	0.149314294	-0.869956689	0.149314294
L/S Ratio	-1.88961993	0.905886044	-2.08594	0.128273	-4.772553619	0.993313769	-4.772553619	0.993313769
Kneading Elements	-0.00876923	0.014234626	-0.61605	0.58145	-0.054070164	0.036531701	-0.054070164	0.036531701
KE Stagger Angle	0.001800557	0.002135194	0.843276	0.461	-0.004994583	0.008595697	-0.004994583	0.008595697
Barrel Temperature	-0.00997822	0.005847469	-1.70642	0.186471	-0.028587481	0.008631033	-0.028587481	0.008631033
DFS	-0.07429686	0.116949385	-0.63529	0.570382	-0.446482	0.297888279	-0.446482	0.297888279

Fig 3.12: Multiple regression summary for tablet hardness.

However, elementary observations can be made from the data for the 10 runs from the DoE for tablet tensile strength. All selected runs were operated at 800 screw RPM, making this parameter irrelevant for analysis. High material throughput (1.2 kg/hr) and high L/S ratio

(0.55) produced tablets with lower tensile strength, indicating a need for a more conclusive study. No such observations could be made with other parameters.

3.7.6 Tablet Dissolution Profiles

Dissolution testing was performed for the 11 selected runs. 6 tablets from each run were weighed and measured for thickness and dissolved in 900 ml of distilled water for 4 hours in accordance with the method mentioned in USP Chapter <711> in Apparatus 2 (paddles). The rate of drug released was measured every three minutes in terms of absorption by the Agilent Technologies UV-Vis spectrometer. The absorption data was converted to concentration data by the calibration model to develop dissolution profiles.

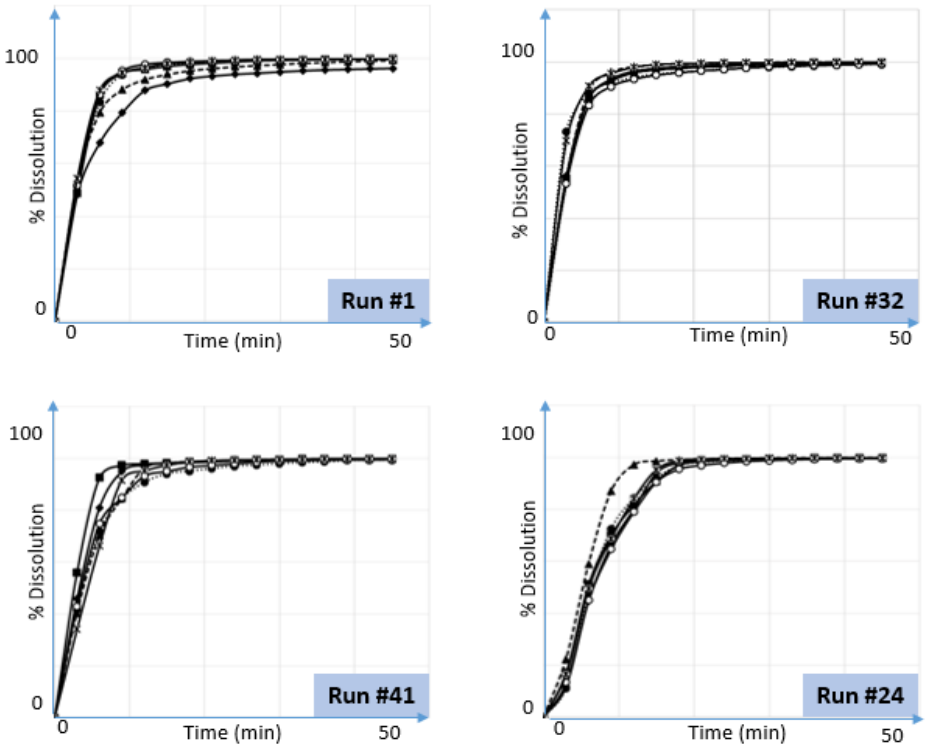


Fig 3.13: Dissolution profiles for select runs.

Dissolution profiles for some runs are represented in Fig (3.13). The dissolution profiles for the all runs were found to be very consistent in terms of profile and rates of release.

Tablets from all runs dissolved rapidly in the media and reached 100% release in less than 20 minutes, which is termed as immediate release (IR). Rapid release tablets indicate rapid disintegration, high solubility and high permeability.

Drug profiles are typically used as a quality control tool to show batch-to-batch consistency and uniformity within the batch. The similarity in the drug release profiles observed in the TSG experiments indicate a robust granulation process, irrespective of the changes in the process parameters.

3.7.7 API Content Uniformity in Tablets

The concentration of the drug dissolved was recorded every 3 minutes during dissolution testing. This information was inputted in the same calibration model as the Key International HSG to determine the final concentration of the drug released and therefore determine the amount of active ingredient in each tablet of each batch.

$$Absorbance = 45.569 \times Concentration - 0.0024 \quad .. (8)$$

Concentration at 100% dissolution was used to determine the total quantity of Caffeine in each tablet. As with the Key International HSG, the material fed into the K-Tron hopper was premixed with 8% Caffeine with the expectation of uniform drug distribution in granules and tablets. Granules between 250-710 µm from the 11 runs were collected for tableting and dissolution testing to determine the quantity of Caffeine.

The percentage API measured in all 11 runs were found to be with 8% to 9% range as seen in Fig (3.14). Three out of the eleven runs were measured to have Caffeine content between 8-8.5%. This indicates a fairly good content uniformity for all the runs, suggesting a well-controlled granulation process. The deviation from the expected 8% Caffeine content could

be due to higher concentration of API in this size class than the rest. Corrective action for the smaller levels of fluctuations could be attributed to the proper selection of a size range for tableting by studying the API distribution in the different size classes and then proceeding to tableting.

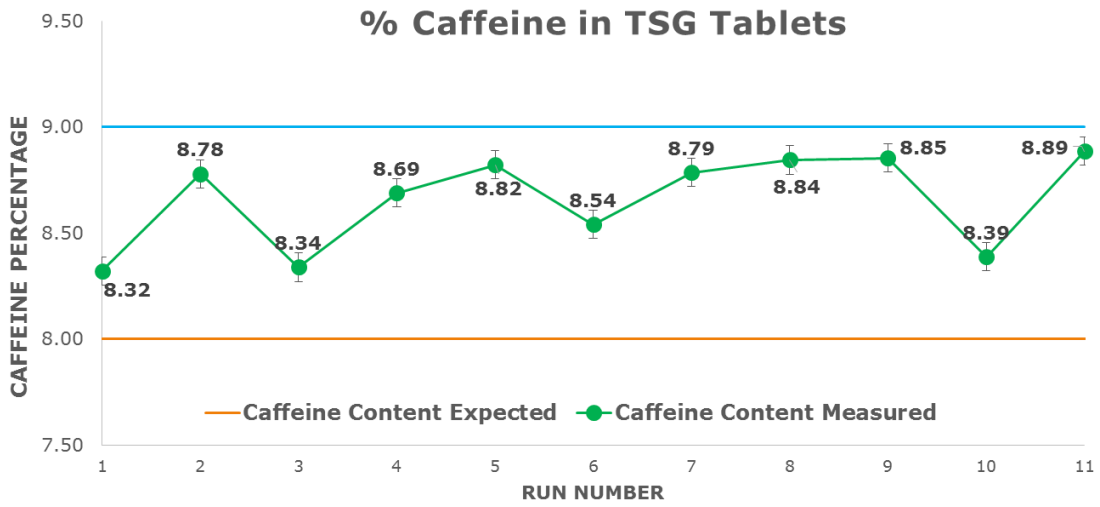


Fig 3.14: API content in tablets from 11 selected runs.

3.8 Process Optimization

Characterization of a process or equipment is one of the ways to fully understand the working of the equipment and to understand how parameters influence the quality and performance of the end result. The characterization of the Thermo Scientific Pharma 11 twin-screw granulator was undertaken to determine and quantify all the operational possibilities and capacities by covering the entire range of operation. D-Optimal design was chosen to conduct screening experiments and determine the design space using Contour Profiler tool in JMP for process optimization.

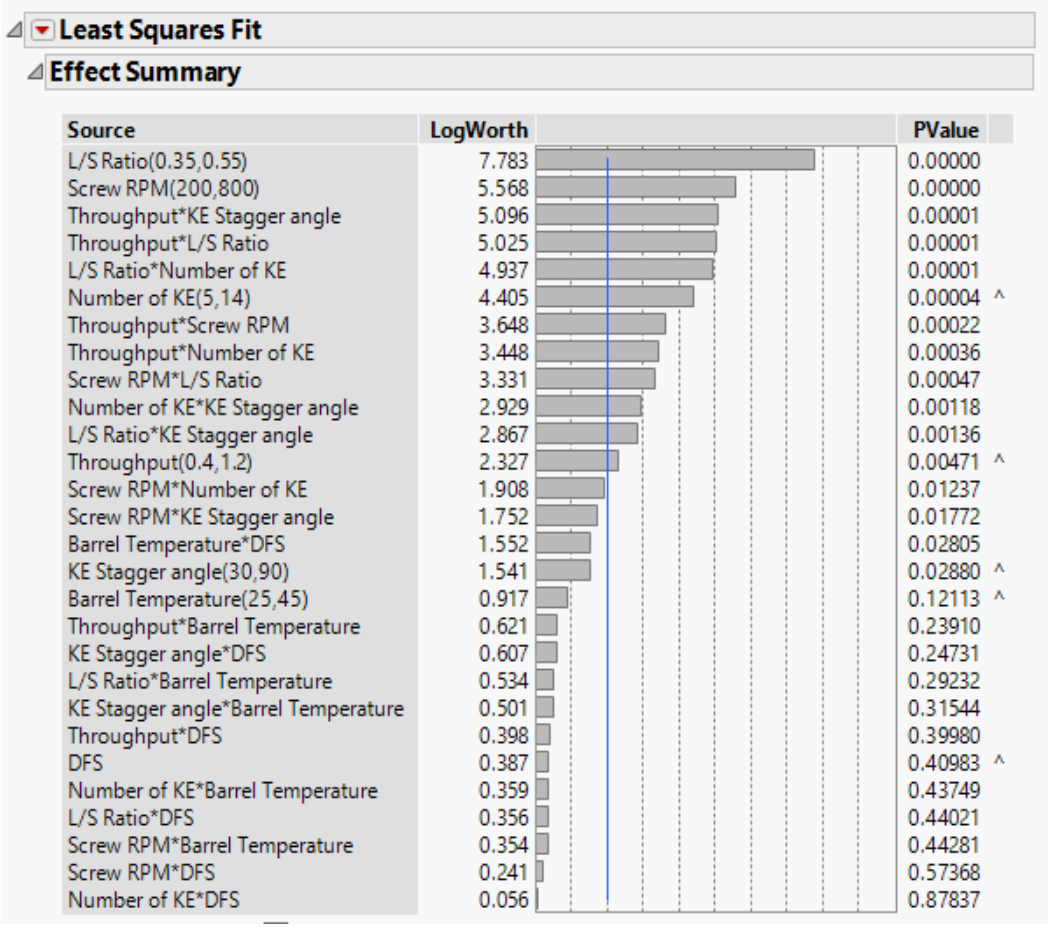


Fig 3.15: Effect summary for TSG.

In the screening experiments, d10, d50, d90 and granulation torque were used as the response variables. The effects summary for the screening model (R^2_{adj} = 0.67) list the significant parameters for all the responses measures in the model in Fig (3.15). Several first order and second order parameters have been identified with p-values below 0.05 which point toward the dependencies and strong interaction between these parameters, and how these interactions can influence the response variable.

The aim of the Contour Profiler is the maximization of the unshaded region as per the process limitations or desired response constraints. The shaded regions show the influence of a parameter on the process for the chosen response variables.

In the case of continuous granulation in the, the following constraints were set for the four responses namely, d10, d50, d90 and torque with the aim of –

- Limiting fine granules below 100 µm which would cause dusting.
- Limiting large granules above 2000 µm for ease of downstream processes and material handling.
- Maximizing the quantity of granules between 300-600 µm for the purpose of tableting.
- Limiting the span of granule size distribution to 3 with the aim of increased quantity of granules in the tableting range.
- Limiting the torque to 4 Nm for decreased power load and safe operation.

These constraints were then applied in the Contour Profiler tool. The settings of the process parameters where changed to maximize the unshaded portion of the profiler so as to determine the design space and optimum process conditions.

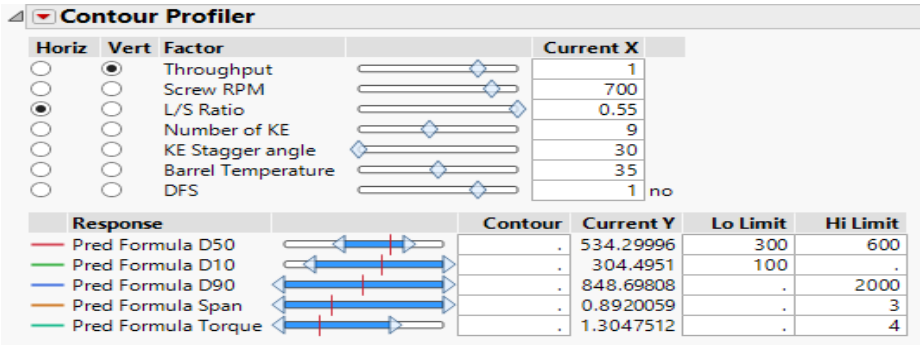


Fig 3.16: Contour Profiler settings for responses

At the above settings shown in Fig (3.16), the following design space is obtained. With a vast unshaded area available for granulation and small influence of the limit on d50 represented by the contour in the operating region highlighted in Fig (3.17).

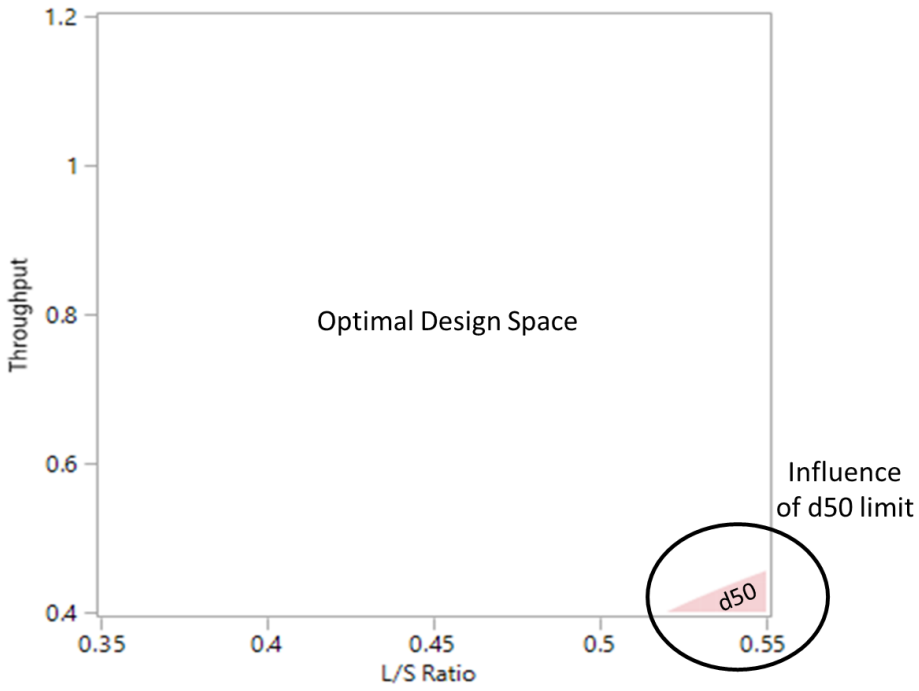


Fig 3.17: Design space for TSG.

On inputting these values in the regression equation (6) obtained for granule porosity, a total value of 38.86% is achieved. Porosity is a critical response for granulation process as well as tableting process and other CQAs measured along the way. Granule porosity between 35-45% would be well-suited, as the value is neither too high nor too low to impede any downstream operations.

Chapter 4: Conclusion and Future Work

4.1 Comparison of Granule and Tablet Attributes

Several attributes or responses were measured to physically characterize granules and tablets produced by both techniques. Responses obtained from the granule size distribution such as d10, d50, d90 and span are compared in Fig (4.1).

Box plots were used to graphically represent the distribution of each response. Box plots are a simple way to compare different groups of data without any influence of the probability distributions of the variables being assessed, allowing for a non-parametric comparison of the data. The top and bottom whiskers of the box plots represent the maximum and minimum values recorded for the responses. The top box represents the third quartile or 75% of the data, while the bottom box represents the first quartile of 25% of the data. The line dividing the two boxes is the median of the data.

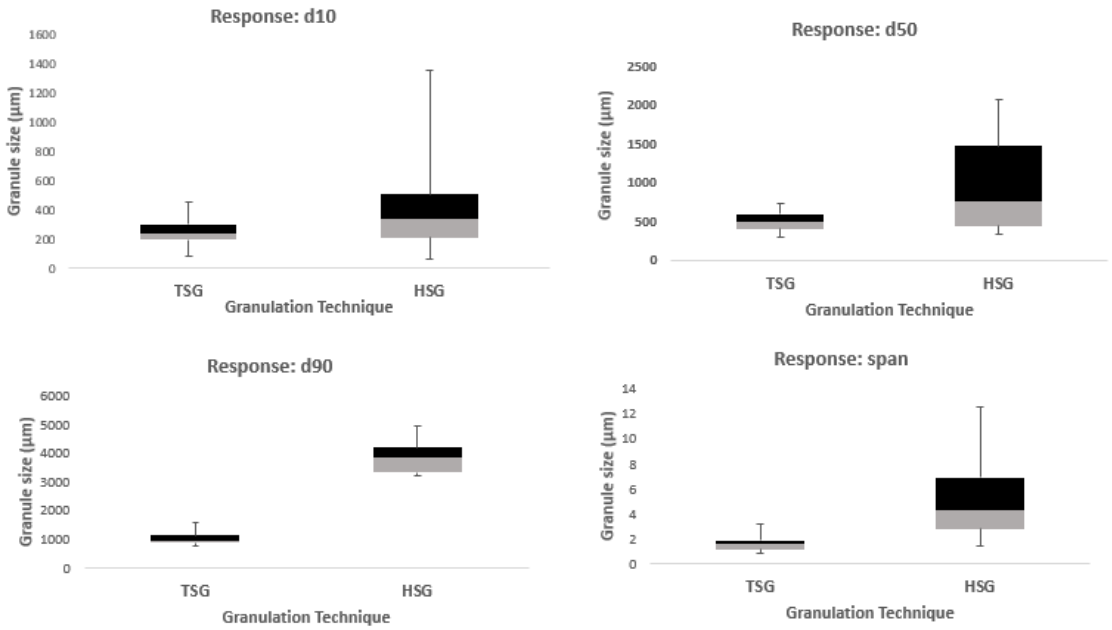


Fig 4.1: Box plots comparing d10, d50, d90 and span for TSG and HSG technique.

From Fig (4.1), we can clearly differentiate and compare the responses for both methods of granulation. The responses recorded for TSG represents a tight fit, with lesser dispersion of data. However, the opposite hold true for the HSG. The maximum and minimum values (represented by the whiskers) recorded for the TSG are below those recorded for HSG. The box plots indicate a wide distribution of the responses. We can therefore conclude, that the granules produced by the HSG are much larger and non-uniform as compared to those of the TSG. A narrow scatter of TSG shows a controlled and precise formation of granules, and a consistent granulation mechanism despite the variations in the screw configurations.

A similar inference can be made from Fig (4.2) for the granule porosity measured for the runs from TSG and HSG. Granules with % porosity values as high as 60% and as low as 23% was measured in the HSG, whereas granule porosity range for the TSG was between 24% to 42%, providing a smaller range of variation or fluctuation even while operating in extreme ranges of the process parameters considered.

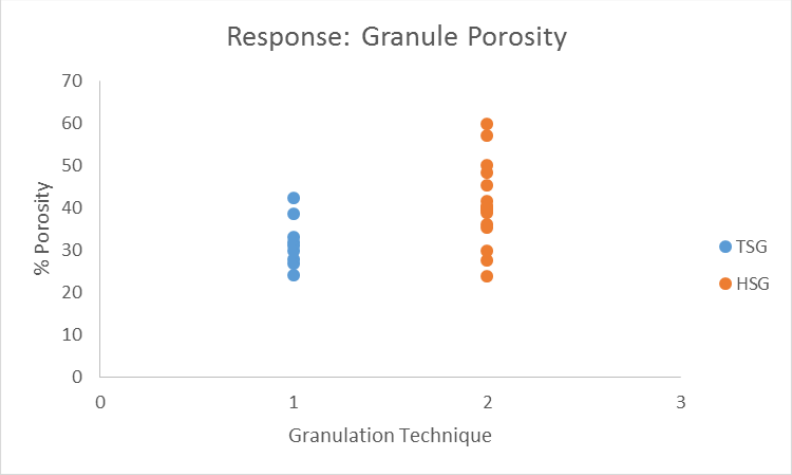


Fig 4.2: Scatter plot of granule porosity for TSG and HSG.

Granules produced from both TSG and HSG showed good flow properties, with low Hausner ratio and compressibility index. From the 3D images captured with Eyecon ™,

we can observe that HSG produced more spherical granules (Fig (2.8)) as opposed to elongated granules produced in the TSG (Fig (3.10)), although there was not much influence of the shape on the overall flow properties of the granules.

Critical quality attributes of tablets made with both granulation techniques were measured and compared, to understand how granulation conditions influence these responses. The aim of granulation is to ease downstream operations such as tableting and to achieve uniform distribution of API by reducing the chance of segregation. Tablets being the final end-product of solid dose manufacturing, the tablet CQAs are all the more sensitive and susceptible to changes in upstream process fluctuations.

Fig (4.3) compares the tablet hardness and Caffeine concentration in tablets made with TSG and HSG granules. Tablets produced in HSG and TSG showed comparable variation in tablet hardness, although HSG tablets were found to have higher values of breaking force. The percentage of Caffeine measured in TSG and HSG differed drastically. While tablets made from TSG granules showed a narrow distribution, with all runs ranging from 8.3% to 8.9%, there was a huge fluctuation observed in HSG tablets. The tablets were found to be highly concentrated with API and highly inconsistent from run-to-run which can be observed in the wide distribution of the box-plot.

A similar trend could be observed from the dissolution profiles. Tablets made from the HSG runs had flatter dissolution profiles with drug release rates ranging from 48 min to 117 min. All runs from the TSG were found to produce tablets with consistent dissolution profiles and short rates of release, averaging at 38 min.

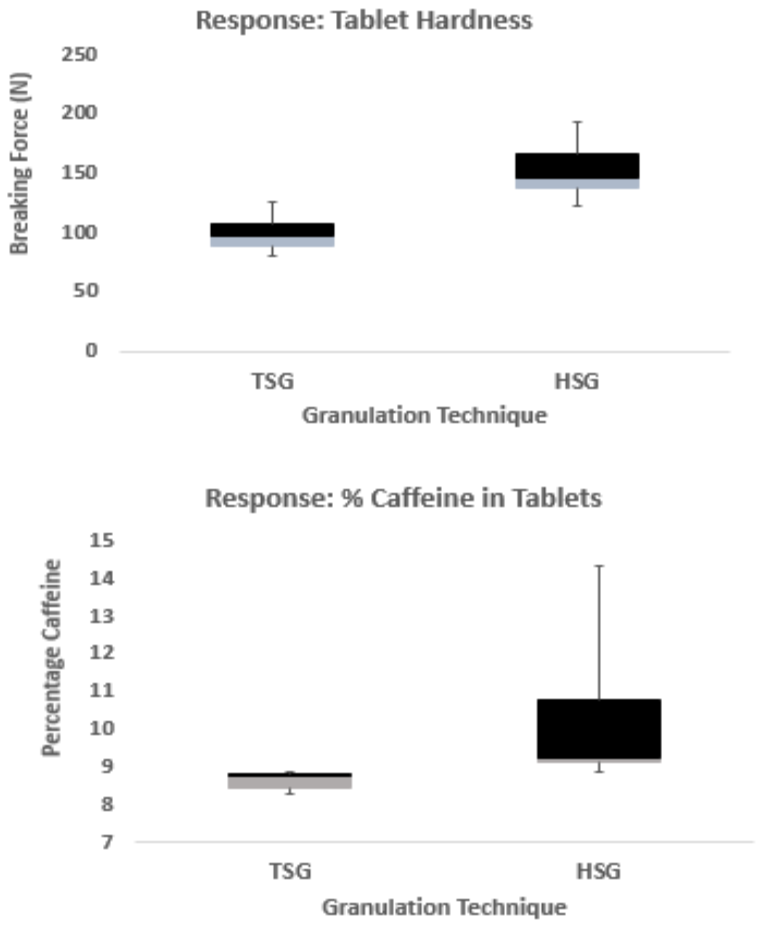


Fig 4.3: Box plot for (a) tablet hardness (b) Caffeine % in tablets for TSG and HSG.

4.2 Conclusion

In this thesis, a four component low-dose formulation consisting 8% (w/w) Caffeine was premixed and used for producing granules in two different granulation equipment. The aim of the study was to understand the relationship between the process parameters and the attributes of granules and tablets produced by both these techniques, with the objective of reaching a rational conclusion about the robustness of the two techniques. It is important to understand that these two methods of granulation are intrinsically different, and a comparison of the two processes at mechanistic & fundamental level is difficult. However,

the approach in this study has been to compare the robustness of the two methods, rather than the two methods itself.

Process optimization for TSG and HSG presented expected results. The design space for the operation of the TSG is wide, allowing a huge scope for varying parameters at multiple levels to achieve good quality granules and tablets. The HSG on the other hand offers a smaller window for optimized operation, however operation of the HSG in the optimized design space would allow us to produce granules and tablets of desired CQAs. Reproducibility and reliability is a serious quality concern in the pharmaceutical manufacturing. With such large margins of variations in the measured responses, it is safe to presume that the granule and tablet attributes in HSG were found to sensitive to changes in the granulation conditions explored in this study. This would present a serious issue of non-uniformity and inconsistency within batches.

To conclude, continuous granulation using the TSG was found to be robust and reliable technique for this formulation. Granule and tablet attributes were found to within limits and decently insusceptible to the severe changes in processing conditions.

4.3 Future Research Opportunities

The dissertation was conducted to establish and compare the robustness of a continuous twin-screw granulator with a high-shear batch granulator using a Design of Experiments approach. Extreme operation conditions of TSG were explored and compared with HSG. Given the noteworthy performance of the TSG, extended experimentation in the design space identified would shed more light on the capabilities and limitations of the granulator. Having identified the critical parameters governing the granulation process and the product quality, further investigation of these parameters is highly recommended. The distribution

of the API and excipients in the tablet is the most critical factor governing the tablet CQAs. It is indeed a key factor to be considered in blending and granulation operations. A study focused on the distribution of API in the different granule size classes would provide a deeper insight into producing high-performing tablets. Another opportunity to extend and support the findings of this study would be compare the granules and tablet CQAs produced in the optimized design spaces of both the equipment for this formulation and study how material properties of a different formulations would affect the same.

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