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Optimizing of Granulation and Coating Process Parameters for Improved Dissolution and Content Uniformity in Oral Dosage Forms

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Abstract: *The optimization of the granulation and coating conditions is one of the most significant aspects of the production of high-quality oral doses. The variations in the granule properties, pill porosity and uniformity of the coating can profoundly affect the therapeutic outcome and safety of the patient. The present paper is dedicated to the design of a systematic quality by design (QbD)-based approach to the optimization of the conditions during the granulation, compression, and coating stages, in which the research analysis is aimed at the increased dissolution rates and content homogeneity of orally taken pills. An immediate-release tablet with API of BCS Class III is a case study that is presented in the paper. Design of Experiments (DoE) and key process parameters (CPPs) such as compression force, granule size, rate of coating spray and inlet air temperature were used to test dry granulation through slugging, pills pressing, and aqueous film coating. They were quantified with regard to predictive models as influencing factors in critical quality attributes (CQAs). The case study indicated that the strength of the granules was optimized with granulation and compression and the content variation was reduced to <10% and coating process modifications were made to achieve a better uniformity in the dissolution process, with error in prediction being <12% and adjusted 〖R〗^2of between 0.85-0.97 giving a strong scalable design space. The results show that a systematic optimization of the granulation and coating conditions has improved the dissolution, homogeneity and reproducibility of manufacturing, which provides useful information to the quality production of oral tablets.*

Keywords: Granulation optimization, Coating parameters, Oral dosage forms, Content uniformity, Dissolution rate, Quality by Design (QbD)

I. INTRODUCTION

The pharmaceutical manufacturing process involves a series of activities that are directed towards the production of safe, effective and quality drug products [1]. They involve production of solid oral dosage products, such as tablets and capsules, which form a significant part of industrial pharmaceutical operations due to their convenience of deployment, economic and wide treatment potential [2]. Only production of small-molecule drugs can be in numerous cases carried out at constant production lines, which offers a degree of flexibility in production scale and control of the process in comparison with the production of biopharmaceutical products.

The rate of dissolution and homogeneity of content are important characteristics of oral dosage that ensure the quality of the drug, and patient safety and therapeutic effects directly. Dissolution variance, or unexplored distribution of the active pharmaceutical ingredient (API) may lead to unpredictable drug release, under- or overdose, or undesired effect and, that is why the parameters of formulation and processing are to be adequately controlled [3][4].

These quality properties are achieved with the aid of the oral formulations that include granulation and coating processes. The process of granulation means the fine powder particles are transformed into bigger and uniform granules to make them easier to flow and minimize segregation in addition to a homogeneous distribution of the API [5][6]. The

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characteristics of granules, including their porosity and size dispersion, and mechanical strength determine the characteristics of drug dissolution, uniformity of content, and compaction characteristics. Coating process which includes film coating gives a functional surface to the tablet or granules so as to enhance stability, to mask a taste, to make the pills easier to swallow and to regulate the release of the drug.

Although it is important, the inconsistent size of particles, lack of uniform coating, poor flow, and inefficient drying may compromise the dissolution performance and uniformity of content [7]. Conventional optimization procedures in granulation and coating like the trial and error or one factor at a time (OFAT) techniques are tedious, time consuming and in most cases the outcomes are not reproducible. These constraints have made it mandatory to have a systematic method to identify and optimize key process parameters in order to improve product quality at all times.

This study is motivated by the necessity to enhance the performance of oral dosage forms through optimal parameters of the granulation and the coating. The study of how the primary process's critical factors affect dissolution behavior and content homogeneity is another area of concern, such as the properties of the granules, compression forces, and coating conditions. The aim is to develop an automated process of optimization that ensures high quality oral formulations that can be reproduced. This work has had significant contributions which include:

- **Identification of Critical Process Parameters:** The research process Cally identifies parameters of granulation and coating such as granule size, porosity, compression force, spray rate and inlet air temperature that produce maximum influence on the dissolution and content uniformity.
- **Optimization of Granulation and Coating Processes:** The parameters that are identified are utilized to optimize the granulation and coating conditions to optimize the flow of the granules, porosity of the pills and the monolayer formation. This reduces variability, enhances mechanical strength and offers reproducibility of production.
- **Enhancement of Dissolution and Content Uniformity:** The process changes in specific ways to improve not only API distribution and wettability but also coating coverage resulting in more rapid and predictable dissolution and enhanced content homogeneity, which satisfies the pharmacopeial requirements.
- **Practical Implications:** The results offer practical implications in pharmaceutical manufacturing which facilitates scalability, reproducibility and quality production of oral dosage forms.

A. Organization of the Paper

The paper is organized in the following way: Section II outlines granulation methods, such as dry and wet. Section III is devoted to the coating processes, film coating, process parameters. Section IV provides a case study where QbD-based framework is used to optimize granulation and coating. Section V is the literature review, identifies gaps in the recent research and finally, Section VI gives conclusions and future research with recommendations.

II. GRANULATION IN ORAL FORMULATIONS

The process of granulation, which involves the expansion of particles by agglomeration, is a crucial unit operation in the manufacturing of pharmaceutical dosage forms, namely tablets and capsules. Large agglomerates known as granules are created during the granulation process from tiny fine or coarse particles [8]. Granules are made to improve the final product's uniformity of the active pharmaceutical ingredient (API), increase the blend's density so that it takes up less volume per unit weight for better flow, have a narrow particle size distribution for content uniformity and volumetric dispensing, have enough fines to fill in the spaces between granules for better compaction and compression properties, and have enough moisture and hardness to avoid breaking and dust formation during the process. Overview of Tablet Manufacturing Processes is shown in Figure 1.

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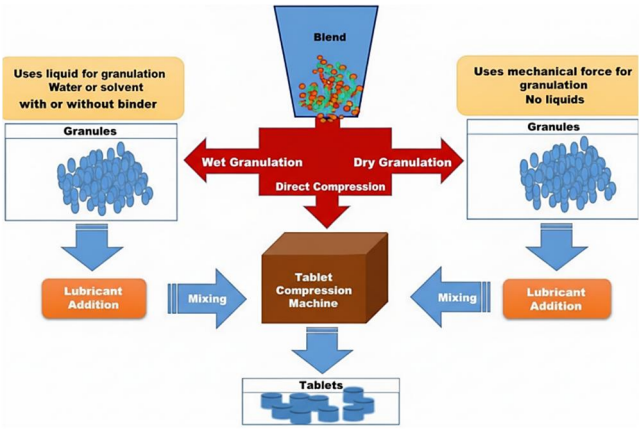

Fig. 1. Schematic Overview of Tablet Manufacturing Processes

A. Classification of Granulation

There are two broad categories into which the granulation process may be split up, depending on the technique employed to promote the agglomeration of powder particles, dry granulation and wet granulation.

1) Dry Granulation

In pharmaceutical production, dry granulation is a moisture-free method that compresses powdered particles into granules. It has benefits such shielding active medicinal ingredients and formulations from moisture-induced deterioration. Slugging is used in the dry granulation process to create tablets, particularly when the components are moisture-sensitive or cannot tolerate high temperatures [9]. This process, also known as dry granulation, pre-compression, or twofold compression, entails the production of big tablets called slugs, which are then crushed using pressure rollers or a mesh screen. After being combined with lubricants, the granular slugs are crushed into tablets.

2) Wet Granulation

The pharmaceutical and nutraceutical industries frequently use wet granulation to improve flowability, compressibility and dosage uniformity of the powder. The characteristics of the granules, including the density and the size distribution are a by-product of the coexisting process of nucleation, agglomeration, and breakage [10]. The nucleation starts with the binder wetted powder bed to form initial granules. Agglomeration is achieved by collisions of the granules, augmenting size and consolidation. Breakage is caused by larger and weaker granules breaking under shear and impact loads which form fines that re-enter the process. Formulation properties and process operating conditions have an effect on these mechanisms in Figure 2.

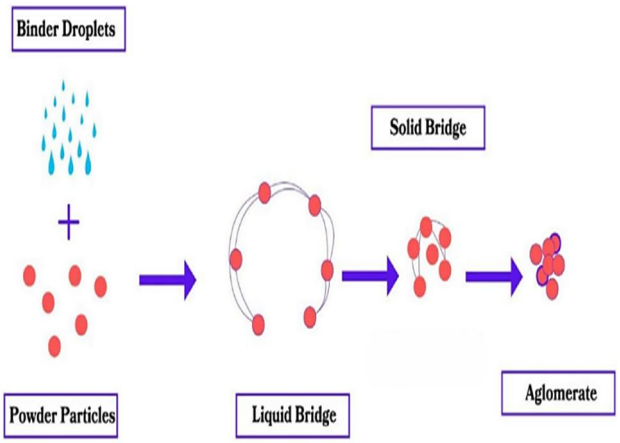

Fig. 2. Mechanisms of the Wet granulation [11]

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A. Granulation Effects on Bioavailability and Content Uniformity

Granulation has been shown to heavily affect essential quality attributes of a pharmaceutical product, such dissolving behavior, uniformity of content and overall therapeutic performance. The granulation will then be managed accordingly to ensure consistency of production and higher bioavailability.

- **Improved Dissolution Rate:** The porosity and surface morphology of granules can be controlled and it enhances the active pharmaceutical ingredients' (APIs') low solubility [12]. The increased surface area of the substance also helps in faster reaction to the dissolution media and the higher wettability is required to achieve better dispersion and absorption that translates to more predictable and reliable release of the drug.
- **Enhanced Wettability and Content Uniformity:** The wet granulation process involves hydrophilic binders that change the granulometry of the materials so that they can strongly absorb aqueous media. This increases dissolution of low inherent wettability APIs. In addition, granulation enables uniform spreading of the API across every granulation and other contents in the dosage form being randomly varied.
- **Reduced Sticking and Capping:** Fine powders attach to equipment used in tablet manufacturing that causes such defects as picking, lamination or capping. More binding and larger granules are easier to predict their flow and are not likely to adsorb to processing equipment. Not only does it enhance manufacturing efficiency but it also helps bring about uniformity in the weight of the tablet and the content.
- **Enhanced Stability and Mechanical Robustness:** Granulation has the ability to contain APIs in larger granules and shield them against environmental influences, e.g. moisture or oxygen [13]. Such physical protection enhances the stability over time and stability of dissolution profile throughout storage and handling. In addition, the homogeneous and strong granules are not affected by compressing and their homogeneity in the end dosage form is preserved.

To conclude, the process of granulation increases bioavailability, dissolution, content uniformity, and mechanical strength. Optimization of parameters of granulation yields effective, high-quality and reproducible dosage forms.

III. COATING IN ORAL FORMULATIONS

The process of coating a desirable dosage form, such as a tablet or granule, with an exterior dry film to achieve certain goals, including concealing flavour or protecting against external conditions, is known as coating. A polyhydric alcohol, gums, resins, waxes, flavourings, colouring compounds, and plasticizers can all be found in the coating substance. Polymers and polysaccharides were primarily utilized as coating materials in the contemporary age, along with additional excipients including colours and plasticizers. To ensure that the coating is stable and long-lasting, several care must be taken throughout the application procedure [14]. This method may extend its shelf life, cover up its bitter flavour, and provide a smoother coating that is easier to swallow. Coatings can even be used to regulate the active ingredient's release. Site-specific coated dose formulations are possible. The coating keeps medications that are sensitive to acid from harming the gut. By regulating the tablet's rate of dissolving, the medication release rate in the gastrointestinal tract (GIT) might be managed.

A. Film Coating

A thin layer of a polymer substance is covered with oral solid dosage forms, including as particles, granules, and tablets, in a process known as film coating. The thickness of the coating might vary from 20 to 100 µm [15]. A variety of parameters, including the composition of the core tablet and coating liquid, process conditions, and coating equipment, influence the end product's pharmaceutical quality in the multivalent process of film coating tablets. Tablets are most frequently coated via a side-ventilated, perforated pan coater. Its airflow mechanism, which uses a perforated pan, guarantees quick and constant drying conditions. Because water has a poor evaporation capacity, aqueous film coating equipment must have a high drying efficiency.

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B. Factors Affecting Coating Quality

To achieve a consistent, flawless, and high-quality coating, it is essential to have control over the crucial elements when choosing the coating method. The key factors are listed below:

- **Spray air flow rate:** The impact of airflow rate on the coating process has not received much attention in previous pan coater research, despite the fact that process air is a crucial component in the production of pharmaceuticals [16]. The drying efficiency of the coating unit and the quality of the coated tablets are said to be impacted by the perforated pan coater's flow rate and airflow. By raising the input airflow rate, the tablet bed temperature rises linearly, boosting the coating unit's evaporative capacity and removing tablet overwetting issues. Nevertheless, it finds that the inlet airflow has no effect on the coating composition's homogeneity or efficiency.
- **Solid content and viscosity:** The viscosity of the coating solution is influenced by the quantity of polymers present. Using a high molecular weight polymer or a high polymer concentration in the coating solution increases its viscosity. A coating solution with a high solid content makes tablets heavier more quickly, but it can also make it harder to transfer a viscous coating liquid. To increase the temperature and decrease the viscosity, the coating solution may be heated if needed [17].
- **Inlet Air Temperature:** Inlet air temperature regulates the drying of the coating material. Higher temperatures cause rapid drying that cause cracks or peeling and low temperatures cause tacky uneven coating. The correct temperature can also be important to guarantee uniform drying, proper adhesion and finishes to the surface.
- **Atomization Pressure:** Atomization pressure is defined as the force applied in order to spray the coating solution in fine drops. A uniform coating layer is formed as a result of proper atomization. The pressure is low leading to big droplets and uneven coverage whereas excessive pressure may lead to overspray and wasting of material [18].
- **Pan/Drum Speed and Pressure:** Tumbling rate and exposure of the spray to the particles depends on the speed and the internal pressure of the coating pan or drum. Adequate speed means that the coating is evenly applied. Excessively fast speed can destroy the particles and excessively slow can create uneven coating and time-consuming processing.

C. Effect on Dissolution and Uniformity

The coating procedure has a great effect on the dissolution character and homogeneity of the end product. Lack of control of process parameters may result in drug release variations, coating thickness and mechanical properties. The variables that have a significant influence on the dissolution rate and uniformity include over wetting, drying efficiency, and surface properties.

- **Oversetting and Uneven Drying**: Oversetting of the substrate experienced because of excessive application of coating solution or due to uneven drying. This may cause agglomeration, streaking or uneven deposits, which cause dissolution rates to vary. Certain parts of the product dissolve more quickly or slowly with respect to bioavailability [19]. To minimize such effects, it is necessary to maintain the balanced rate of spray and controlled drying.
- **Temperature and Drying Efficiency**: There are fundamental factors that concern the temperature of the inlet air and the coating solidification in solvent evaporation and coating solidification. Slow drying process leaves a sticky sort of coating which will tend to have defects but a quick drying process can cause cracks or brittle surfaces. The two extremities negatively impact on dissolution consistency. Optimized temperature ensures that the entire solvent is removed and coating integrity is ensured.
- **Surface Uniformity and Mechanical Strength**: A uniform coating layer enhances mechanical strength and dissolves uniformly [20]. Even finishes reduce the possibilities of chipping, peeling or the irregular disintegration. Appropriate atomization, pan or drum speed and pressure ensure that all particles or tablets receive an even coating, which increases the physical strength and dissolution properties.

To summarize, it is necessary that these parameters are regulated in order to achieve reproducible dissolution, high uniformity of the product and uniform therapeutic performance.

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IV. CASE STUDY: QBD-BASED GRANULATION AND COATING OPTIMIZATION

The case study demonstrates that an immediate-release oral tablet has been designed using a Quality by Design (QbD) framework to design the granulation and coating processes. The impact of critical process parameters on dissolution performance and content uniformity was experimented upon through the assistance of systematic experimental design and statistical modelling [21]. To maximize granulation and compression parameters to maximize the homogeneity of the granules and porosity of the tablets, but to maximize the uniformity of the film formation, which did not decrease the drug release, the coating parameters were filtered. Pilot and commercial-scale batches were used to establish a solid design space and understand the processes better without treatment modification of the formulation, and predictive models were developed and validated.

A. Methods & Materials

In this section, the procedure and the materials used in the experiment described that are selected to be employed in the case study. The model used to model the experiment was the Quality by Design (QbD) principles that focus on systematic experimentation, reproducibility, and aspects of industry.

Materials

The research was carried out on an immediate-release tablet that contained a BCS Class III API (high solubility and low permeability) because it is sensitive to process changes which may influence the dissolution. The excipients were of pharmaceutical quality and included colloidal silicon dioxide (glidant), magnesium stearate (lubricant), croscarmellose sodium (super disintegrant), and microcrystalline cellulose (filler/binder). It was a cellulose-derived, plasticizer-based, aqueous film coating that was ready-to-use. Before experiments, the powders were refined so that they were uniform and behaved in a consistent manner:

- **Pre-Blending and Powder Preparation**: The API and excipients were sifted and mixed under controlled circumstances in order to attain uniformity. The last phase of blending involved addition of the lubricant to avoid excessive lubrication.
- **Dry Granulation by Slugging**: Dry granulation was done by slugging in a rotary tablet press. Compression force was considered as an important parameter, and the resulting slugs were milled to obtain granules, which were held aside per condition.
- **Tablet Compression**: The granules were pressed in tablet cores with fixed tooling. The force of compression was adjusted according to the experimental design but other factors were maintained constant.
- **Film Coating Procedure**: Tablet cores were film-coated in a perforated pan coater with a dispersion in aqueous. Pilot-scale and laboratory experiments were done to test the process parameters, and no difference was observed in the constant increase in coating weight between the batches.

B. Quality by Design Framework and Risk-Based Approach

This study used Quality by Design (QbD) strategy that integrated risk analysis and a systematic experimental approach to assure product quality was designed into the process [22]. There were critical quality attributes (CQAs) (especially those influencing mechanical integrity and dissolution), and possible critical processes parameters (CPPs) in granulation, tableting and coating were identified by the use of prior knowledge and initial risk assessment.

This evaluation led to the selection and evaluation of granulation (slugging) and tableting compression forces as CPPs on a Design of Experiments (DoE) basis and the screening of coating parameters on a Plackett-Burman design basis. This integrated strategy has enabled in determining the essential variables, gauging their influence on CQAs, and a sound scientifically based design space.

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C. Experimental Design

The experimental research was performed in two consecutive steps: optimization of dry granulation and tablet compression, and screening of the coating process parameters. The slugging and tableting forces were studied under a multilevel factorial design in the granulation/compression phase, and were chosen as a key determinant of granule integrity, tablet porosity, content uniformity, and dissolution performance. During the coating step, the Placket Burman (PB) screening design was applied to test various parameters such as the rate of spray and the inlet air temperature liberalistic ally and to determine which of the above parameters had maximum effect on the dissolution uniformity and the end quality of the tablet.

D. Model Assessment

The statistical performance indicators such as adjusted coefficient of determination (R2 adj), level of reliability, and prediction error analysis were used to assess the adequacy and predictive capacity of the developed QbD models [23][24]. The impact of coating and granulation/compression operations on dissolving performance and content uniformity were measured using different models. Granulation, compression and coating models with the evaluated CQAs, adjusted R^2 (0.85–0.97), prediction error (<8–12%) and the reliability level are given in the Table I, showing the accuracy of the model, its consistency and performance measurement parameters.

TABLE 1: OVERALL PREDICTIVE MODEL PERFORMANCE SUMMARY

Model Category	Evaluated CQA	R^2adj Range	Prediction Error	Reliability Level
Granulation models	Content uniformity	0.85–0.90	<10%	Acceptable
Compression models	Dissolution rate	0.90–0.97	<8%	High
Coating models	Dissolution uniformity	0.88–0.92	<12%	Acceptable–High

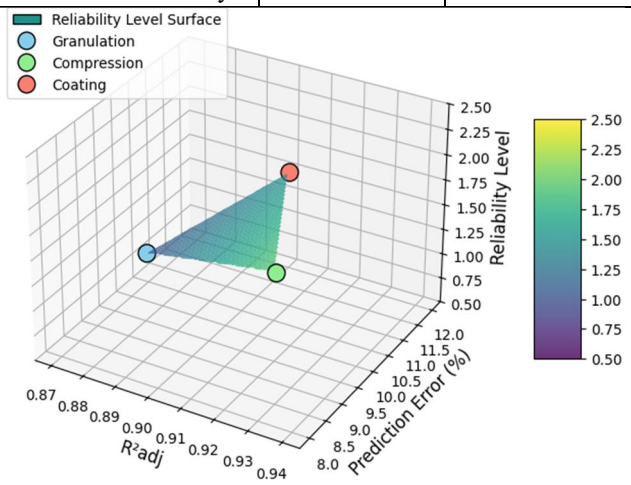

Fig. 3.3D Visualization of Predictive Model Performance

A 3D representation of the output of three pharmaceutical process models Granulation, Compression, and Coating using quantitative measurements of important quality attributes as illustrated in Figure 3. Adjusted R^2 (R^2adj) on the X-axis which is between 0.85 and 0.97 is a measure of predictive accuracy. Y-axis indicates the error of prediction (%) of each of the models (<8-12%), and Z-axis shows the level of reliability, Acceptable (1) and High (2). The resulting smooth colourful surface is an interpolation of reliability levels among R^2adj, and values of prediction error with each point distinguished as a model. The colorbred and legend make the distinction between the surface and individual model performances obvious, allowing one to directly compare the accuracy, error, and reliability.

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E. Key Findings

The major results of this research are the crucial role of the parameters of granulation, compression, and coating on the dissolution performance and uniformity of the content. The significant findings of the research are as follows:

- Granulation (slugging) compression force had a great influence on granule strength and content homogeneity through the segregation and homogeneity of the blend.
- Tableting compression force was the most important variable that determined tablet porosity that directly affected dissolution rate and disintegration behavior.
- Variation in dose was minimized and uniformity of contents were enhanced even without changing the formulation by optimization of granulation conditions.
- Coating spray rate in turn exerted an eminent effect on dissolution uniformity, though the higher the rate, the greater the variability owing to over wetting of the tablet.
- The temperature of the inlet air during coating enhanced efficiency of drying and uniformity of coating, which resulted in consistent dissolution profiles.
- The QbD-based statistical models had acceptable or high predictive capability and aided in the creation of a strong, scalable design space.

V. LITERATURE REVIEW

The literature emphasizes the breakthroughs in granulation and the optimization of coating and focuses on the process parameters, material properties, and modelling techniques to enhance the quality of the tablet, its dissolution and its manufacturing stability.

NK, Shinde and Mane (2024) describe the manufacturing method, but involve Sifting, Dry Mixing, Wet Granulation, Drying, Sizing, Mixing, Blending, Capsule Filling, Packing, and evaluation of process difficulties at critical points. The paper has Critical Process Parameters (CPPs) to these steps which are tested in a manufacturing optimization experiment. Critical Quality Attributes (CQAs) that are observed are, Blend Uniformity, Water Content, physical properties of the blend, capsule parameters, and Dissolution, Dosage Unit Uniformity, Assay, Degradation Product, and Microbial Examination tests [25].

Ram Munnangi et al. (2024) studied how the TSMG process can be optimized to produce immediate-release tablets with Ibuprofen (IBU) and Acetaminophen (APAP). They hypothesized that amorphous IBU would be a better dissolver whereas crystalline APAP would be stable. Their study compared different elements that influenced the processability and dissolution by maintaining the processing temperatures lower than the melting points of all the materials except IBU. The results demonstrated a 32-fold increase in IBU's solubility in 0.1 N HCl, confirming the amorphous transition of IBU and the stability of APAP. Osmotic agents were introduced to achieve a considerable improvement in tablet break up and the final formulation with increased IBU release; 12.5% improved to 20% on dissolution tests [26].

Jena and Jat (2024) design a dose form of hyperphenylalaninemia treatment by the immediate-release dosage of sapropelic dihydrochloride. They involve a pre-formulation drug-excipient compatibility study, a prototype, the optimization of the prototype by using dissolution tests and optimization. Strategic choice of excipients was designed to be pharmaceutically equivalent to Kuvan and the changes included the use of LH 21 as a binder and the absence of anhydrous dibasic calcium phosphate. The feasibility trial focused on bioequivalence and stability besides the identification of high-risk stages in the tablet manufacturing process through processes such as top spray fluid bed granulation and roller compaction [27].

Chen et al. (2023) examined the relationship between coating uniformity and tablet flow dynamics using a computational model that combines a ray-tracing technique with discrete elements. Their findings demonstrated that the flow pattern was altered as the coating pan's periphery speed increased, from the slumping to the attracting pattern, and decreased the coefficient of variation in the weight of each inter-tablet coating to 1.0, increasing the easy of uniformity. However, homogeneity was lost as the coefficient increased to 2.0 above the higher speeds. The experiment demonstrated the significance of the difference in speeds between tablets and optimization of nozzle positions and the impact of the shape

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and placement of baffles in generating desired coating patterns at lower velocities, and thus the fact that the manners in which the tablet flows and the uniformity of the resulting coating are linked [28].

Jaspers et al. (2022) review the surge in roller compaction as an enhancement method chosen to conduct dry granulation in the process of producing oral solid dosage. Thee though a way easier and less cumbersome, suffers a disadvantage in less compactness in the granules in comparison to ungranulated powders. The authors introduce a novel approach that is the addition of super disintegrants intra-granularly that addresses loss of compatibility in granules based on anhydrous lactose. The process softens the granules, such that during the compressing of the pills, the particles would be much easier to break and surface area of the lactose to be expanded in order to create a stronger bond, which leads to increased pill strength. The article brings to focus the significance of super disintegrants to perfecting formulae of dry granulation [29].

Liu et al. (2021) examines a high-speed process of tablet film coating in continuous production under the Box-Behnken design. It investigates at how factors like temperature, suspension spray rate, and intake air flow rate affect the outcome (output air temperature, humidity, coating efficiency, moisture content, and uniformity). The statistical models showed that these variables are significant in all the process responses. Monte Carlo simulations were used to develop a design space on the probability of failure with the independent variables being moisture content (less than 3.5%), and uniformity (weight standard deviation less than 4 mg of 200 mg tablets) and independent validation showed the design space effective at improving quality by design in pharmaceutical manufacturing [30].

The Table II is a systematic comparison of the previous research based on the processes, parameters, results, strengths, and weaknesses to determine the unaddressed gaps that inform the optimization of the granulation and coating parameters in oral formulations.

TABLE 2: SUMMARY OF LITERATURE ON GRANULATION AND COATING PARAMETERS AFFECTING TABLET QUALITY

Authors	Study on	Key Parameters Investigated	Key Findings	Advantages	Limitations
NK, Shinde & Mane (2024)	Wet granulation–based capsule manufacturing	CPPs across sifting, dry mixing, wet granulation, drying, blending, capsule filling	Optimized manufacturing process consistently met CQAs including dissolution and dosage uniformity	Comprehensive evaluation of CPPs and CQAs across the entire manufacturing process	Lacks detailed analysis of individual granulation parameters; coating process not included
Ram Munnangi et al. (2024)	Twin-screw melt granulation (TSMG)	Drug melting behavior, excipients, disintegrants, processing temperature	Amorphous conversion of ibuprofen significantly enhanced solubility and dissolution	Demonstrates effective dissolution enhancement for poorly soluble drugs	Coating parameters and content uniformity were not evaluated
Jena and Jat, (2024)	Immediate-release tablet formulation	Blending, roller compaction, and top spray fluid bed granulation; excipient selection, intragranular/extragranular ratios, particle size	Optimized formulation achieved uniformity, dissolution, stability; CQAs met with process adjustments	Uses DoE & OFAT; links granulation parameters to dissolution and content uniformity	Coating not included; focused on immediate-release tablets, not film-coated or extended-release
Chen et al. (2023)	Tablet pan coating	Pan speed, tablet flow regimes, baffle design	Rolling and cascading flow	Provides mechanistic	Dissolution behavior and

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			regimes significantly improved coating uniformity	understanding of coating uniformity and scale-up relevance	upstream granulation effects were not studied
Jaspers et al. (2022)	Dry granulation (roller compaction)	Superdisintegrant placement, granule hardness	Intragranular superdisintegrants improved tablet compactibility	Addresses a key limitation of dry granulation	Dissolution and dosage/content uniformity were not investigated
Liu et al. (2021)	Continuous tablet film coating	Air temperature, spray rate, and inlet air flow rate	Established design space for coating uniformity using QbD	Strong application of DoE and QbD in continuous coating	Granulation effects and dissolution performance not directly evaluated

VI. CONCLUSION AND FUTURE WORK

Despite the effectiveness of the QbD-based optimization in the enhancing granulation and the coating processes, several limitations still remain. The case study points out that predictive model creation and assessment of various critical parameters of processes may be computationally expensive and time-consuming particularly in large-scale production. Besides, though the study was conducted on dissolution, content uniformity and granule integrity, other aspects like long term stability, moisture sensitivity and variability in raw material properties were not entirely covered. The other shortcoming is that the simulation of the processes of coating does not fully replicate the complexities of manufacturing in the world, including the uneven flow of pills, variability in pan loading, or changes in the environment. More research is required on the integration of the real-time process monitoring and process analytical technology (PAT) to improve predictive accuracy and reduce variation in the manufacturing process. The dissolution, mechanical strength, and stability could be balanced at the same time through the use of multi-objective optimization approaches. Further scale and predictive advantages can be achieved with hybrid model techniques that combine QbD and machine learning. Moreover, by conducting trials based on the case studies to validate the optimization strategies at varying formulations and production scale, one will be guaranteed increased applicability. Such undertakings will help in coming up with strong, high quality oral dosage forms with predictable therapeutic behavior and regulatory compliance.

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