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A General Review Article on Study of Pilot Plant Scale-Up Problems in Tablet Formulation

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Abstract: ***Scale-up in tablet manufacturing serves as an essential bridge between laboratory development and commercial production. During this transition, numerous challenges arise that can influence product quality, process reproducibility, and regulatory compliance. Common difficulties include variations in blending efficiency, granulation behavior, powder flow dynamics, compression characteristics, and resulting tablet properties such as hardness and friability [1][2]. Equipment design differences, altered process parameters, and changes in environmental conditions often cause deviations in critical quality attributes (CQAs), including dissolution, uniformity, and mechanical strength [2][3]. To address these issues, the application of Quality by Design (QbD), risk-based assessment, design of experiments (DoE), and Process Analytical Technology (PAT) is increasingly recommended [3][4]. Effective process validation and strong communication between formulation scientists and production personnel further support a successful scale-up pathway [5].***

I. INTRODUCTION

Pilot plant scale-up represents a crucial phase in pharmaceutical product development. It involves transferring a laboratory-optimized tablet formulation to larger batch sizes suitable for commercial manufacturing while ensuring consistency in quality, safety, and performance [6]. During this process, several challenges may emerge due to differences in equipment geometry, mixing dynamics, batch size, and environmental variations. Such changes can influence significant tablet attributes, including hardness, disintegration time, dissolution behavior, and content uniformity [8]. Overcoming these difficulties requires a structured strategy that incorporates risk evaluation, robust process optimization, and comprehensive validation protocols [9]. The implementation of quality management frameworks such as ISO 9001:2015 further supports seamless scaling and regulatory compliance, ensuring that the final product maintains the desired therapeutic performance [7].

Fig 1.1 ; Tablet Formulation during pilot plant scale-up Technique

A. Advantages of Identifying And Optimizing Problems During Pilot Plant Scale-Up

1) Enhanced Product Quality: Early detection of formulation or process-related issues helps achieve essential tablet quality attributes—such as hardness, friability, disintegration time, and dissolution profile—leading to consistent therapeutic performance and reduced batch-to-batch variability [10].

2) Improved Process `Robustness: Optimizing the process at the pilot scale strengthens manufacturing reliability by reducing sensitivity to minor variations in raw materials or operating conditions. This ensures smooth transfer to commercial-scale equipment [11].

3) Reduction in Batch Failures: Troubleshooting scale-up challenges prevents costly failures at the production stage. Addressing granulation, blending, or compression issues beforehand minimizes rework, wastage, and batch rejections [12].
4) Cost Efficiency : Resolving operational and formulation challenges at the pilot stage avoids expensive corrections during commercial manufacturing. This leads to savings in raw materials, labor, energy, and regulatory documentation [10,13].
5) Better Regulatory Compliance: A well-optimized pilot-scale process naturally aligns with cGMP principles and regulatory expectations. Proper scale-up documentation and validated processes reduce the likelihood of compliance-related challenges [13].
6) Optimization of Critical Process Parameters (CPPs): Critical parameters—such as blending duration, granulation solvent quantity, drying temperature, and compression force—can be fine-tuned at pilot scale, ensuring consistent product performance [11].
7) Accurate Prediction for Commercial Scale-Up: Pilot-scale experimentation provides valuable insight into how the formulation will behave in production-scale machinery, which shortens development timelines and ensures efficient technology transfer [12].
8) Reduction of Technical and Processing Risks: Identifying risks related to flow, lubrication, binder distribution, and mechanical strength enables the implementation of preventive measures before full-scale production begins [10].

B. Application Of Problem Identification During Pilot Plant Scale-Up

1) Determination of Critical Quality Attributes (CQAs): Pilot-scale work helps define the physical and mechanical attributes—such as hardness, dissolution, friability, and uniformity—that must be controlled for optimal tablet performance [14].
2) Drug–Excipient Compatibility Evaluation: Compatibility studies at the pilot level help detect possible stability issues, such as degradation or phase changes caused by interactions between the drug and excipients [15].
3) Optimization of Granulation Parameters: Adjusting binder concentration, moisture levels, mixing time, and granulation rate helps achieve suitable granule flow, compressibility, and uniformity [16].
4) Assessment of Equipment Performance During Scale-Up: Pilot-scale trials reveal performance differences between laboratory and production equipment, allowing modifications to blending speed, impeller force, or compression pressure [17].
5) Troubleshooting Content Uniformity Issues: Design of Experiments (DoE) is often employed to identify factors influencing drug distribution and prevent segregation during blending or transfer [18].
6) Implementation of PAT Tools: Using real-time monitoring tools—such as NIR moisture analyzers—enhances control over granulation and drying, ensuring better consistency across batches [20].
7) Optimization of Compression Parameters: Adjusting compression force, dwell time, and tooling type helps reduce tablet defects like capping, chipping, or lamination [20].
8) Environmental Control: Monitoring humidity, temperature, and airflow helps avoid issues such as sticking, picking, and moisture-induced instability during processing [21].

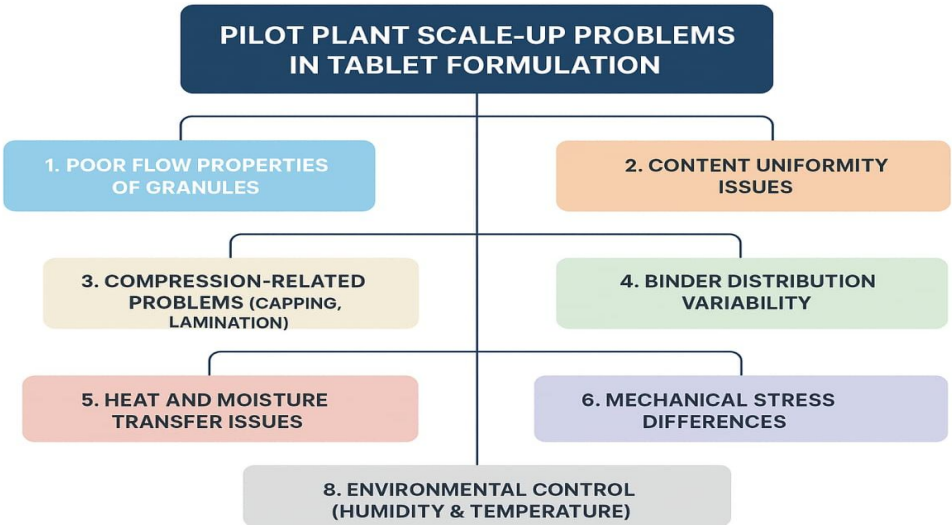

Fig 1.2 Pilot Plant Scale-up Problem in tablet Formulation

C. Types Of Pilot Plant Scale-Up Problems In Tablet Formulation

1) Formulation-Related Challenges

These issues arise from the physical and chemical characteristics of the drug substance and excipients:
Drug–Excipient Incompatibility: Can lead to chemical degradation or altered bioavailability [22].
Particle Size Variability: Impacts flowability, content uniformity, and dissolution behavior [22].
Moisture Sensitivity: Causes poor compressibility and may result in stability concerns during drying or storage [22].

2) Process-Related Challenges

Problems that emerge because of changing process dynamics during scale-up:
Granulation Difficulties: Adjustments in wet or dry granulation may cause uneven granule size and strength [23][24].
Mixing and Segregation: Larger batch volumes may reduce blend uniformity [24].
Drying Inefficiencies: Non-uniform drying results in inconsistent moisture distribution and variable tablet hardness [23].

3) Equipment-Related Challenges

Scale-up introduces equipment differences that affect product quality:
Compression Force Variability: Larger tablet presses may generate weight inconsistencies [22][24].
Equipment Geometry Differences: Alter the flow pattern and mixing efficiency of powders [24].
Shear and Speed Variations: Influence granule structure, blend behavior, and tablet characteristics [24].

4) Stability-Related Challenges

The stability profile may change when batch size increases:
Thermal Stress During Drying: Larger batches retain heat longer, affecting the stability of heat-sensitive APIs [25].
Exposure to Humidity: Leads to moisture uptake, changes in dissolution, or physical degradation [25].

5) Quality Control & Validation Challenges

Issues observed during routine quality assurance:
Batch-to-Batch Variability: Differences in hardness, dissolution, and physical properties may arise during scale-up [26].
Process Validation Issues: Establishing reproducibility becomes more complex at larger scale [26]

II. CONTENT UNIFORMITY ISSUES

Content uniformity is a critical requirement to ensure each tablet contains the correct amount of active pharmaceutical ingredient (API). During scale-up, achieving and maintaining uniform distribution becomes more challenging due to increased batch size, equipment geometry, and powder flow complexities.

A. Segregation Due to Differences in Particle Size and Density

API and excipients often vary in density, shape, or size. While small laboratory-scale batches mix well, larger pilot-scale batches exhibit:
Increased particle movement
Settling of heavier drug particles
Upward movement of lighter excipients
Fine particles adhering to equipment surfaces
These factors create zones enriched or depleted in API, resulting in variable content uniformity across tablets [27].

B. Uneven Distribution in Large Blending Equipment

In large-scale mixers—such as bin blenders, octagonal blenders, or double-cone blenders—mixing efficiency generally decreases because of:
Different mixing geometry
Slower blade or vessel rotation
Reduced mixing energy
Longer residence time

This can lead to poor API dispersion and localized concentration gradients throughout the batch [28].

C. Segregation During Material Flow and Compression

Even after blending, segregation often occurs during:
Hopper feeding
Transfer from blender to compression machine
Flow into feed frames and dies
Differences in particle flow properties intensify segregation, especially at higher machine speeds. As a result, individual tablets may show inconsistent drug content [29].
Impact of Content Uniformity Failure
Therapeutic Issues: Under- or over-dosing may affect patient safety and efficacy.
Regulatory Failure: Non-compliant batches are rejected.
Economic Loss: Increased rework, wastage, and production delays.

III. COMPRESSION-RELATED PROBLEMS: CAPPING & LAMINATION

Tablet compression defects frequently occur during scale-up due to changes in compression force, dwell time, and material properties.

A. Capping

Definition: The top or bottom portion of a tablet separates or breaks away after ejection.
Scale-up causes:
Excessive compression force, leading to trapped air inside granules [27]
Higher compression speeds → shorter dwell time and weaker bonding [27]
Elastic recovery of certain excipients like microcrystalline cellulose [28]
Improper moisture content (too high or too low) [29]

B. Lamination

Definition: Tablet splits into layers, often horizontally.
Scale-up causes:
High-speed compression causing insufficient particle consolidation [27]
Wide particle size variation producing density differences [28]
Uneven binder distribution leading to weak bonding [29]
Entrapped air due to inefficient deaeration [29]
Solutions During Scale-Up
Optimize compression force and turret speed [27]
Maintain consistent granule size distribution [28]
Adjust granule moisture to ideal levels [29]
Improve binder concentration and mixing strategy [29]

IV. BINDER DISTRIBUTION VARIABILITY

Binder ensures granule cohesion and tablet strength. Uneven binder distribution leads to a mixture of weak and over-wet zones, which affects flow, compressibility, and uniformity
Why Problems Increase During Scale-Up
Larger equipment geometry creates dead zones and uneven movement [27].
Spray distribution issues in wet granulation cause binder to reach only parts of the powder bed [28].
Differences in residence time lead to over-processed or under-processed regions [29].
Higher mechanical energy input alters granule wetting behavior [27].
Consequences
Variable granule strength → affects hardness and friability [27]
Weight and thickness variation in tablets [27,28]

Altered disintegration and dissolution rates [28]
Greater risk of compression defects like capping [27,29]
Poor content uniformity, especially for low-dose APIs [29]
Detection and Control
Granule size distribution and friability testing [27]
Hardness/tensile strength testing across batch [28]
PAT tools such as NIR or Raman for binder and moisture detection [29]
Monitoring torque and power consumption in granulation [27]
Mitigation Strategies
Optimize granulator design and fill volume [27]
Adjust spray nozzle type, spray pattern, and rate [28]
Maintain binder solution viscosity and temperature [28]
Use DoE for controlled scale-up [29]
Post-granulation blending or sieving (when necessary) [27]

V. HEAT AND MOISTURE TRANSFER ISSUES

Heat and moisture distribution are often non-uniform during drying, granulation, and compression in large-scale operations.
Causes During Scale-Up

A. Larger Batch Volumes

Heat penetration becomes slower
Inner layers retain moisture
Outer layers become overdried [27,28]

B. Equipment Geometry Differences

Fluid bed dryers, tray dryers, and ovens exhibit airflow maldistribution
Dead zones develop where drying is incomplete [27]

C. Airflow and Temperature Variation

Insufficient airflow results in moist pockets
Excess airflow causes surface overdrying [28,29]

D. Insufficient Moisture Monitoring

Manual sampling in large batches is less accurate
Real-time moisture uniformity is harder to maintain [29]
Consequences
Uneven granule hardness and flowability [27]
Capping, lamination, or sticking during compression [28]
Chemical degradation due to high moisture or heat [1]
Increased fines or agglomeration affecting flow [28]
Strategies to Resolve Heat & Moisture Issues
Optimize drying parameters: airflow, temperature, agitation [27]
Use advanced dryers (vacuum, microwave-assisted) [28]
Implement PAT moisture sensors for real-time control [29]
Conduct multi-point sampling during drying cycles [29]

VI. MECHANICAL STRESS DIFFERENCES

Mechanical stress increases during scale-up because of larger equipment size, longer processing times, and greater shear/impact forces.

Why Mechanical Stress Increases
Large high-shear granulators deliver more impact and shear per unit mass [27,29]
Longer mixing times cause particle attrition and fines [28]
Higher impeller or roller speeds modify granule structure [29]
High compression speeds increase risk of tablet defects [29]
Consequences of Increased Mechanical Stress
Excessive fines, leading to poor flow and inconsistent filling [27]
Polymorphic or amorphous transformations of APIs [30]
Reduced compressibility and altered tablet hardness [29]
Equipment clogging or sticking due to fines buildup [28]
Strategies to Control Mechanical Stress
Use geometric and kinematic scaling principles (e.g., constant tip speed) [27]
Monitor granule properties regularly (PSD, crystallinity) [28,30]
Avoid unnecessary overprocessing—utilize PAT endpoints [29]
Use low-shear transfer systems like vacuum conveyors [30]

Fig 1.3 Problem causing during tablet formulation

VII. EQUIPMENT SCALING ISSUES

Equipment differences between laboratory, pilot, and production scales are one of the most frequent sources of variability during tablet scale-up. As batch size increases, equipment geometry, mechanical design, and operational behavior change significantly, often altering the performance of the formulation.
Key Factors Contributing to Equipment Scaling Problems

A. Geometry and Design Variations

Smaller laboratory equipment is designed for precision, while larger machines used in pilot plants have different:
Bowl or chamber shapes
Impeller-to-bowl ratios
Mixing patterns
Dead zones
For example, when high-shear granulators are scaled up, the impeller design and chopper configuration may no longer provide identical shear distribution across the batch [27].

B. Mechanical and Operational Differences

At larger scales, equipment usually operates with:
Higher impeller speed
Greater torque and power input
Longer or variable cycle times
These changes can lead to over-granulation, under-mixing, or excessive particle breakage [27,28].

C. Scale-Dependent Flow & Mixing Dynamics

Powder flow behavior changes with scale. Larger vessels often exhibit:
Slower blending efficiency
Reduced axial mixing
Broader residence time distribution (RTD) [29]
This results in non-uniform binder distribution or blend segregation.

D. Heat & Mass Transfer Limitation

Dryers and granulators at commercial scale often show:
Uneven airflow
Hot or cold spots
Moisture gradients [30]
This affects granule hardness, flowability, and compressibility.

E. Control System Limitations

Lab-scale equipment has precise controls for:
Temperature
Speed
Pressure
Pilot-scale systems may respond more slowly, making it harder to maintain critical process parameters (CPPs) consistently [29]
Effects of Equipment Scaling Issues
Non-uniform granule size and density [27]
Altered tablet hardness, weight, and dissolution profile
Increased risk of defects such as capping or lamination
Higher batch rejection rates and lengthy troubleshooting periods [29]
Changes in moisture distribution leading to stability problems [30]
Strategies to Overcome Equipment Scaling Challenges

1) Geometric and Kinematic Similarity

Use principles such as maintaining:
Constant tip speed
Similar bowl-to-impeller ratio
Matching airflow patterns [27]

2) Use of Design of Experiments (DoE)

DoE helps predict how changes in machine parameters affect product attributes and identifies the optimal operating window [28].

3) Developing Scale-Down Models

Smaller equipment designed to mimic large-scale behavior helps identify issues before full-scale batches [29].

4) Integration of PAT Tools

NIR, moisture analyzers, and torque sensors provide real-time data during scale-up [30].

5) Collaboration with Equipment Manufacturers

Understanding equipment-specific dynamics can significantly reduce trial-and-error during scale-up [29].

VIII. ENVIRONMENTAL CONTROL (HUMIDITY & TEMPERATURE)

Environmental conditions directly affect the performance of powders, granules, and tablets. Their impact becomes much more significant when scaling from small laboratory batches to larger pilot or production-scale operations.
Why Environmental Control Becomes Critical During Scale-Up

A. Powder Moisture Sensitivity

Many APIs and excipients absorb or lose moisture depending on the surrounding humidity.
Consequences include:
Sticking or picking during compression
Poor powder flow
Altered tablet hardness [27]

B. Temperature-Dependent Binder Behavior

Binder solutions change viscosity with temperature;
High temperature → lower viscosity → faster penetration
Low temperature → thicker binder → uneven wetting [28]
This leads to variability in granule size and strength.

C. Compression Stage Sensitivity

High humidity can cause sticking and picking, while low humidity may result in brittle tablets and increased likelihood of capping [29].

D. Drying and Granulation Instability

Variations in environmental temperature or humidity affect:
Drying uniformity
Moisture retention
Granule strength [30]
If air entering equipment is not controlled, previously optimized processes become unstable.
Consequences of Poor Environmental Control
Variability in tablet hardness and weight [28]
Degradation or transformation of sensitive drugs
Segregation due to moisture-induced clumping
Inconsistent binder activation and distribution [29]
Challenges Specific to Scale-Up
Larger facilities require robust HVAC systems
Increased heat generation from equipment
Frequent human movement causing humidity fluctuations
Localized “micro-environments” inside large equipment [30]
Strategies for Effective Environmental Control
A. Controlled Manufacturing Areas
Maintain validated temperature and humidity ranges (e.g., 30–50% RH for most products) [28].
B. Real-Time Monitoring
Use multiple sensors across the manufacturing floor and inside processing equipment [29].
C. Conditioning of Raw Materials
Store and equilibrate raw materials in controlled environments before use [27].
D. Process Adjustments
Modify:
Lubrication levels
Compression force
Inlet air conditions to compensate for environmental variations [30].

IX. CASE STUDIES

These case studies illustrate real-world problems encountered during tablet formulation scale-up and the practical solutions applied.

A. *Case Study 1: Capping and Lamination in Direct Compression Tablets*

During scale-up from a 10-kg batch to a 50-kg batch, severe capping and lamination were observed. According to Singh & Kumar (32), the increased compression speed reduced dwell time, leading to insufficient deaeration. Additionally, magnesium stearate was over-mixed, weakening particle bonding.

Corrective Actions:

Reduced turret speed

Shortened lubrication time

Implemented pre-compression

These measures eliminated the defects (32).

B. *Case Study 2: Content Uniformity Failure in Wet Granulation*

A 5-kg formulation scaled to 25-kg failed content uniformity testing. According to Gowthamarajan & Singh (33), the change in impeller-to-chopper geometry led to improper binder distribution and excessive fines.

Solutions:

Matched specific power input

Implemented wet-mass screening

Switched to a bin blender for final mixing

These changes restored uniformity (33).

C. *Case Study 3: Coating Defects During Scale-Up*

A coating batch increased from 20-kg to 60-kg resulted in picking, roughness, and color variation. Shah (34) attributes this to higher spray rates, poor mixing in larger pans, and humidity fluctuations.

Remedies:

Adjusted spray rate

Optimized inlet air temperature\

Improved humidity control

These modifications solved the coating-related issues (34).

D. *Case Study 4: Dissolution Failure After Compression Scale-Up*

A BCS Class II drug showed slower dissolution after scaling up to a rotary press. Bansal (35) reports that higher compression force reduced tablet porosity, hindering dissolution. Lubricant distribution also varied at scale.

Corrective Measures:

Lowered compression force

Adjusted dwell time

Added additional disintegrant intragranularly

Dissolution returned to acceptable levels (35).

E. *Case Study 5: Non-Uniform Drying and Degradation in Fluidized Bed Dryer*

A moisture-sensitive drug degraded during pilot-scale fluid bed drying. Gad (35) explains that airflow maldistribution and hot zones caused uneven drying.

Solutions Implemented:

Improved airflow distribution

Implemented temperature ramping

Used NIR moisture sensors

This enhanced drying uniformity and reduced degradation.

X. FUTURE PERSPECTIVES IN PILOT PLANT SCALE-UP OF TABLET FORMULATION

The future of tablet scale-up processes is shifting towards advanced, data-driven, and automated systems. These advancements will improve product consistency, reduce development time, and minimize risk during scale-up.

A. Integration of Quality by Design (QbD) and PAT Tools

Emerging scale-up strategies emphasize the use of QbD principles supported by modern Process Analytical Technology (PAT) tools such as:
Near-Infrared (NIR) spectroscopy
Raman analyzers
Real-time moisture sensing instruments
These tools allow early identification of Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs), enabling proactive control of process variability and reducing dependence on trial-and-error approaches [37].

B. Adoption of Continuous Manufacturing (CM)

Continuous manufacturing is expected to replace or supplement traditional batch processes. CM provides:
Improved uniformity
Better process control
Reduced material wastage
Faster scale-up with fewer equipment-dependent issues
Common scale-up problems—such as blend segregation and granule variability—are significantly minimized in continuous systems [38].

C. Digital Twins and AI-Based Process Prediction

Advanced computational technologies, including AI/ML algorithms and digital twins, will help predict:
Granule growth
Flow behavior
Tablet hardness
Dissolution performance
These models can simulate scale-up conditions before running pilot trials, reducing development time and improving reproducibility [39].

D. Advanced Equipment Design and Automation

Next-generation pilot plants will utilize:
Sensor-integrated mixers and granulators
Automated feedback controls
Smart monitoring systems
These technologies will automatically adjust parameters such as speed, airflow, temperature, or compression force to maintain optimal conditions and reduce operator variability [40].

E. Sustainability and Improved Environmental Control

Future manufacturing systems will incorporate:
Energy-efficient HVAC systems
Better humidity and temperature regulation
Low-waste, eco-friendly processes
Tightly controlled environments help minimize humidity-related tablet defects like sticking, capping, and poor flow [41].

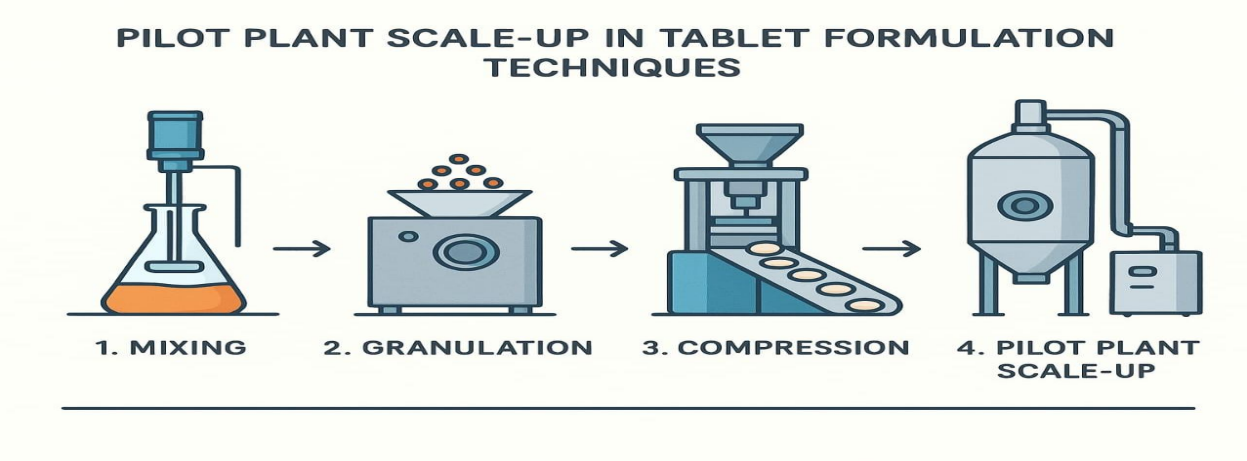

Fig 1.4 ; pilot plant scale-up problem In Tablet Formulation Technique

XI. RESULTS

A. *Changes in Granule Properties During Scale-Up*

The transition from pilot to commercial scale often alters granule size distribution due to differences in impeller geometry and shear energy. This results in increased fines or harder granules, which directly impacts flowability, blend uniformity, and tableting performance [42,43].

B. *Non-Uniform Drying and Moisture Distribution*

Large-scale drying equipment—such as industrial fluid bed dryers—typically removes moisture unevenly across the batch. This leads to variable moisture levels that influence compressibility, tablet hardness, and dissolution characteristics [42,43].

C. *Blend Segregation and Content Uniformity Issues*

Differences in blender design and fill level during scale-up cause either over-blending (generating fines) or under-blending (poor uniformity). Additional segregation often occurs during material transfer [44].

D. *Tablet Defects at Higher Scale*

During compression, changes in powder flow and machine settings may lead to capping, lamination, weight variation, or hardness inconsistency. Rotary tablet presses at scale operate at high speeds, causing shorter dwell time and greater variability [43].

E. *Variation in Dissolution and In-Vitro Performance*

Larger-scale operations can alter tablet density, porosity, or coating uniformity, resulting in noticeable differences in dissolution behavior. These variations must be controlled or justified to meet regulatory expectations [45,46].

XII. DISCUSSION

A. *Causes of Scale-Up Challenges*

1) Equipment Geometry Differences: Scaling does not preserve hydrodynamic conditions like shear fields or power-per-unit-volume, affecting granulation and compression behavior [42,43].
2) Residence Time Distribution (RTD): Larger equipment creates broader RTDs, leading to uneven processing zones [44,45]
3) Heat and Mass Transfer Inefficiencies: Poor drying uniformity directly influences moisture content, granule growth, and binder activation [42].

B. *Impact on Critical Quality Attributes (CQAs)*

Content Uniformity: Variability during blending or transfer especially affects low-dose formulations.
Mechanical Properties: Differences in granule porosity and density impact hardness, friability, and disintegration.
Dissolution Profile: Variations in hardness or coating thickness alter in-vitro performance and require bridging studies [45].

C. Control Strategies for Successful Scale-Up

1) Quality by Design (QbD): Identifies CPPs and CQAs and establishes a design space for robust operation [43,47].

2) Mechanistic Modeling: Using principles like constant energy input and dimensional analysis helps maintain consistency during scaling [43].

3) PAT Tools: Real-time sensors (NIR, torque meters, particle size analyzers) detect deviations early [44,45].

4) Regulatory Guidance: Following SUPAC-IR and ICH Q8 guidelines ensures regulatory acceptance and minimizes post-approval challenges [46].

XIII. CONCLUSION

The study of pilot plant scale-up in tablet formulation highlights the complex challenges encountered when transitioning from laboratory-scale development to full-scale commercial manufacturing. Success depends on a comprehensive understanding of the physicochemical properties of the API and excipients, as well as the influence of equipment design and process parameters [48]. Major challenges include maintaining uniform blending, optimizing granulation conditions, and achieving consistent tablet hardness and dissolution across all batch sizes [49].

The integration of Quality by Design (QbD), risk-based approaches, and the use of Process Analytical Technology (PAT) offers a systematic framework for identifying and controlling Critical Process Parameters (CPPs) and ensuring product quality [50,51]. Adherence to regulatory guidelines such as ICH Q8 further strengthens process reliability and compliance [52]. Future advancements in automation, continuous manufacturing, and digital modeling will likely simplify scale-up procedures and enhance consistency, leading to safer, more efficient pharmaceutical production systems.

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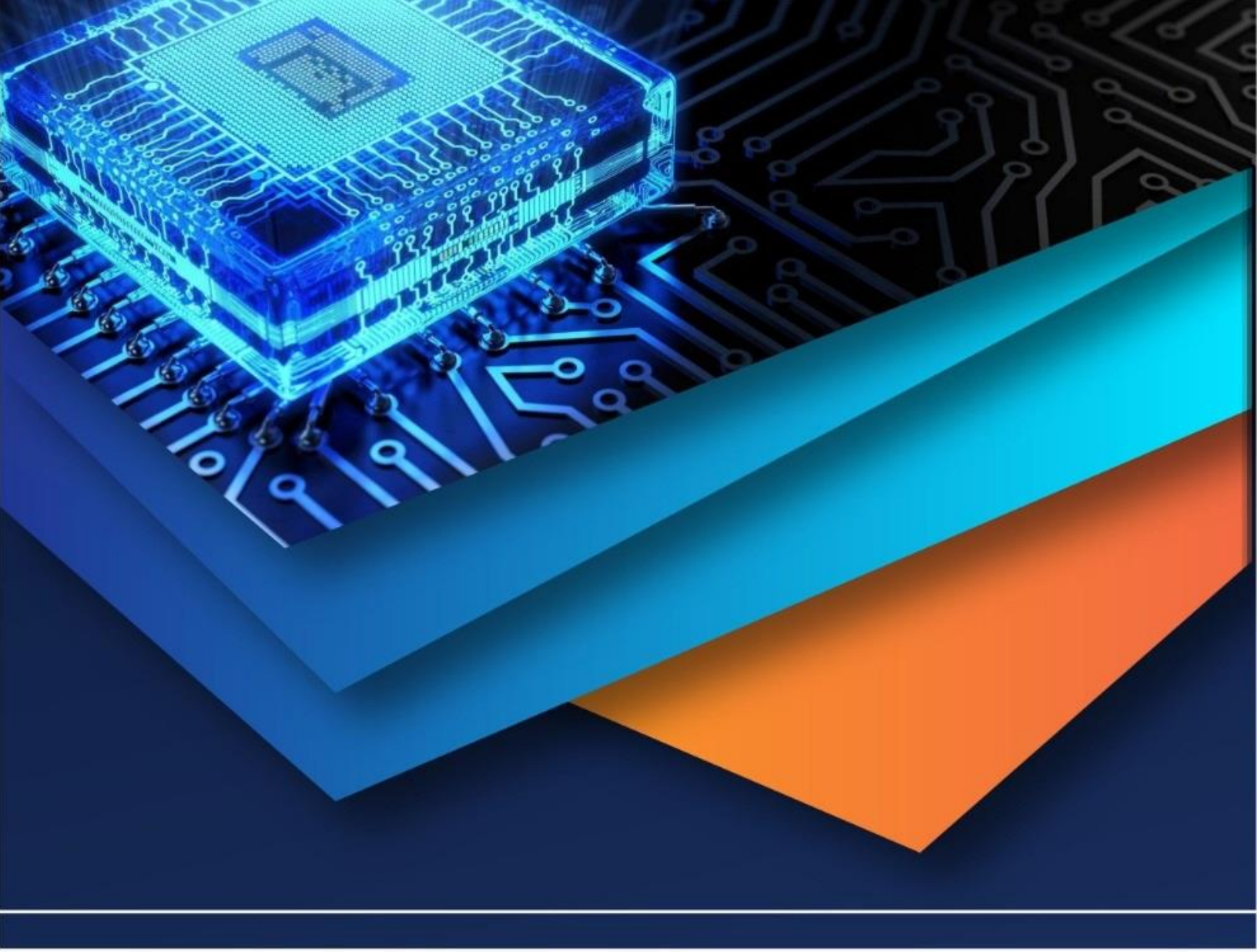

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