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Evaluation of Process Analytical Technology (PAT) In Monitoring Granulation Parameters for Improved Tablet Uniformity

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Abstract

Therapeutic efficacy and safety of pharmaceutical tablets largely depend on their uniformity and quality, especially during preclinical studies. This study will assess the use of Process Analytical Technology (PAT) to monitor granulation parameters in real time to enhance the consistency of tablets. During wet granulation, properties of the granules including particle size, moisture content, and bulk density are continuously measured using near-infrared spectroscopy (NIRS) and in-line particle size analyzers using animal-model-compatible formulations. GRS PAT granules are converted into tablets and examined concerning mass homogeneity, firmness, and friability and compared with non-PAT batches. Findings indicated that PAT-controlled production has led to a large decrease in the batch-to-batch variability resulting in tablets of uniform physical characteristics and mechanical strength. The statistical analysis revealed that batches approached by PAT is superior to conventional processes. The results indicate that the use of PAT in preclinical preparations improves process controls, variability, and stable tablet quality, which is a key to its usability as a standard method in early pharmaceutical development.

Key Words:

Process Analytical Technology, Pat, Granulation Parameters, Tablet Uniformity, Preclinical Formulations.

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1. INTRODUCTION

The process of making tablets is full of various steps such as granulation, drying, and compression[1]. Of them, the granulation process is a very important procedure, which directly affects the quality and consistency of the end-tablets[2]. Changes in granules properties (particle

size, moisture content and density) can cause variations in the weight of the tablet, uniformity of the content and dissolution properties. In preclinical trials, in particular[3], the quality of the tablet must be consistent to carry out animal-based pharmacological research reliably since the necessary dosage is paramount[4].

1.1. Background Information

The process of tablet manufacturing is complex and consists of a series of crucial steps such as granulation, drying, and compression[5]. Among them, the process of granulation is critical to the quality and evenness of the finished product. The characteristics of granules, including particle size, moisture content, flowability, and density, are important to downstream operations, including tablet compression, content uniformity, dissolution, and mechanical strength[6]. These properties may be subject to variability, causing variable pill weight, unequal distribution of drugs, effects on dissolution characteristics, and possible therapeutic inefficacy[7]. The consistency of tablet formulations is especially critical in preclinical research, and constancy of dosing in animal-based pharmacological testing is indispensable[8].

Process Analytical Technology (PAT) is a new method in the pharmaceutical industry that has facilitated real-time control and monitoring of the most important process parameters[9]. PAT incorporates analysis tools within the manufacturing facility, which enables the measurement of granule properties continuously and provides real-time feedback to adjust the conditions of the manufacturing process[10]. Such methods as near-infrared spectroscopy (NIRS), in-line particle size analysis, and moisture sensors help to obtain a complete understanding of the granulation process, and control granule properties accurately. Through active control of variability, PAT provides the opportunity to improve product quality, eliminate variations between batches and enhance efficiency within the manufacturing process[11].

1.2. Statement of the Problem

Granulation is a very variable and sensitive process even though progress has been made in the production of tablets and their quality assurance[12]. Traditional methods of quality control that are based on sampling and laboratory testing cannot be used to identify deviations during the granulation process. This can cause non-uniform granules and thus a tablet with variable weight, hardness, and friability. Such variances are especially paramount in preclinical preparations, where the accuracy and reproducibility of dosing have a direct impact on the validity of animal research[13]. Hence, the urgent need is related to methods that enable real-time monitoring and control of the granulation parameters to achieve high-quality and uniform tablets.

1.3. Objectives of the Study

The present study aims to evaluate the role of PAT in improving granulation and tablet uniformity, with a focus on preclinical formulations. The specific objectives are:

1. To assess the effectiveness of PAT tools in monitoring critical granulation parameters such as particle size, moisture content, and bulk density.
2. To evaluate the impact of PAT-guided process control on the uniformity, hardness, and friability of tablets.

3. To provide insights into optimizing preclinical, animal-compatible tablet formulations using real-time process monitoring.

2. METHODOLOGY

2.1. Research Design

This research utilized an experimental preclinical research design to determine the efficacy of Process Analytical Technology (PAT) in the measurement of granulation parameters and enhancement of uniformity in tablet production. Experiments are performed at controlled conditions in the laboratory via animal-model-compatible formulations. Its design is oriented towards real-time measurement of the important granulation parameters and how they affect the quality of tablets, allowing a systematic comparison of PAT-managed and standard processes.

2.2. Participants / Sample Details

- **Formulations:** A model drug is used to prepare three batches of granules by utilizing standard animal safe excipients, such as lactose and microcrystalline cellulose.
- **Batch Size:** A batch is 500 g granules in quantity to provide enough granules to monitor PAT and compress the final tablet.
- **Animal Considerations:** Tablets had been developed with specific attention to preclinical animal research; there is no human involvement. Preclinical safety standards are adhered to in all excipients and the processes.

2.3. Instruments and Materials Used

- **Granulator:** High-shear wet granulator for controlled and reproducible granulation.
- **PAT Tools:**
    - Real-time monitoring of moisture content by near-infrared spectroscopy (NIRS).
    - On-line particle size meter to continuously measure particle size.
    - Granulation Moisture sensors used to monitor the granule moisture.
- **Tablet Compression:** Rotary tablet press for consistent tablet formation.
- **Other Materials:**Standard pharmaceutical excipients (binders, fillers), solvents suitable to use in preclinical studies and animals, safe model drug formulations.

2.4. Procedure and Data Collection Methods

1. **Granulation Process:** The wet granulation is done in three different batches using similar process parameters like impeller speed, binder concentration and mixing time.
2. **PAT Monitoring:** During granulation, PAT tools continuously measured:
    - The particle size distribution.
    - Moisture content
    - Bulk density of the granules

3. **Process Adjustment:** In-process adjustments based on real-time feedback of PAT readings, such as:
    - Binder addition
    - Adjustments to mixing time.
4. **Tablet Compression:** Each batch of granules is pressed into tablets which are analyzed:
    - Weight uniformity
    - Hardness
    - Friability
    - Dissolution profiles (assuming applicable to preclinical standards)
5. **Data Collection:** All measurements are recorded in triplicate to ensure reliability, and raw data are systematically organized for statistical evaluation.

2.5. Data Analysis Techniques

- **Descriptive Statistics:** Mean and standard deviation are calculated for granule and tablet parameters.
- **Inferential Statistics:**
    - ANOVA is used to determine significant differences between batches monitored and not monitored with PAT.
    - Pearson correlation coefficient is calculated to determine associations between granulation parameters and metrics of uniformity of tablets.
- **Visualization:** Tablets, charts and graphs are used to present data in such a way that variability and batch-to-batch consistency are clear.

3. RESULTS

This section describes the results of this research on the use of Process Analytical Technology (PAT) in controlling the granulation parameters to achieve better uniformity of the tablet. Tables provide data about granule properties, physical characteristics of the tablet, and statistical comparison of properties of PAT-monitored and non-PAT batches.

Table 1 shows the granule characteristics measured via Process Analytical Technology (PAT) such as particle size, moisture content, and bulk density in three different batches of preclinical formulations.

Table 1: Granule Properties with PAT Monitoring

Batch	Particle Size (µm)		Moisture Content (%)		Bulk Density (g/cm³)	
	Mean	SD	Mean	SD	Mean	SD
1	320	12	4.5	0.3	0.65	0.02

2	315	10	4.3	0.2	0.66	0.03
3	318	11	4.4	0.3	0.65	0.02

The four batches are found to have a large standard deviation of 10-12 µm (Table 1), meaning that the particle size of the granules across the three batches are very similar and that the batches are not very different; also, the standard deviation is low. The moisture content is maintained at 4.3-4.5 with SD values of 0.2-0.3 indicating accurate control of moisture content during wet granulation. Batches also showed similar bulk density values (0.65–0.66 g/cm) with a small deviation, indicating homogeneous granule packing and flow characteristics. In general, the data indicate that tight control of vital granulation parameters could be achieved by implementing PAT monitoring, which favored greater uniformity and predictability of future tablet compression.

Table 2 provides an overall summary of the tablet uniformity parameters such as average weight, hardness, and friability of three batches of tablets that are manufactured using PAT-monitored granules.

Table 2: Tablet Uniformity Parameters

Batch	Average Weight (mg)		Hardness(N)		Friability (%)	
	Mean	SD	Mean	SD	Mean	SD
1	500	5	80	3	0.6	0.05
2	502	4	82	2	0.5	0.04
3	499	3	79	2	0.6	0.05

Table 2 shows that the three batches of tablets had the same weight, with the mean values falling within 499 mg and 502 mg, with low standard deviations (3-5 mg), indicating very good batch-to-batch consistency. The values of hardness are slightly different, with a small SD (23 N), suggesting that the tablets are of sufficient mechanical strength to be handled and packaged. The percentage of friability is low (0.5–0.6%) and SD values are 0.04–0.05% which indicated that the tablets did not chip or break easily during handling. In general, these findings indicate that PAT-based manipulation of granulation parameters is a successful approach to the manufacture of tablets with consistent physical characteristics and stable quality.

Table 3 shows the statistical analysis comparing the parameters of tablet uniformity between PAT-monitored and non-PAT batches such as tablet weight, hardness, and friability.

Table 3: Statistical Comparison of PAT vs Non-PAT Batches

Parameter	PAT		Non-PAT		p-value
	Mean	SD	Mean	SD	
Tablet Weight (mg)	500	4	510	12	0.02

Hardness (N)	80	2	75	5	0.03
Friability (%)	0.57	0.05	1.2	0.2	0.01

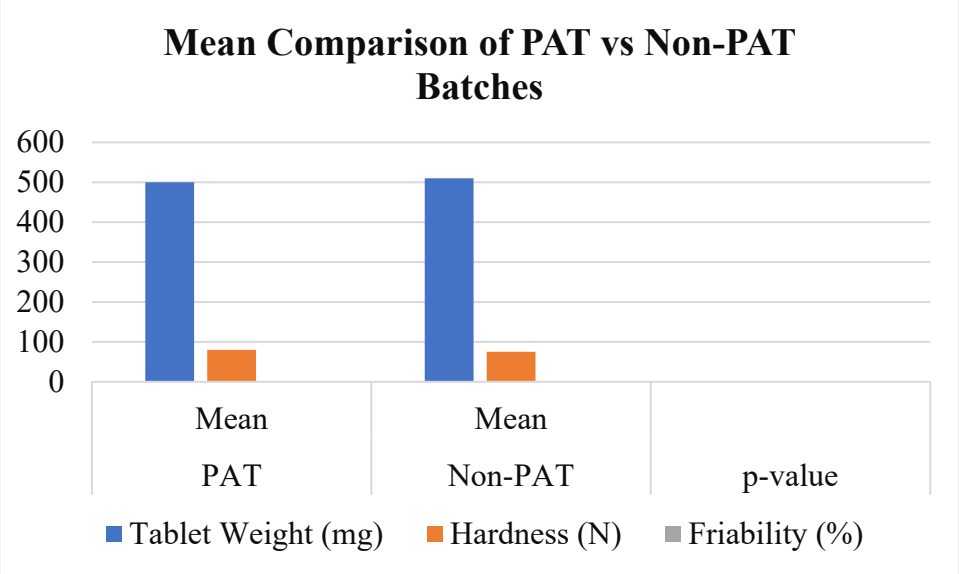

Figure 1: Mean Comparison of PAT vs Non-PAT Batches

Table manufactured under PAT monitoring had a much higher uniformity, as compared with non-PAT batches as indicated in Table 3. The mean weight of PAT batches of 500 mg and low SD of 4 mg compared to non-PAT batches with higher mean of 510 mg and relatively high SD of 12mg, which observed less control over weight variation. Likewise, the hardness is increased and uniform in batches of PAT (80 + 2 N) than non-PAT batches (75 + 5 N), indicating an increase in mechanical strength because of the granulation control. The friability of PAT-monitored tablets (0.57 ± 0.05%) is also significantly lower than that of non-PAT tablet (1.2 ± 0.2%), which is indicative of better chip and break resistance. All the p-values (less than 0.05) prove that the differences are statistically significant, and it is possible to conclude that PAT is very effective in improving the uniformity of the tablets and their quality.

4. DISCUSSION

The findings of the study are discussed in this section in the light of the available literature and preclinical pharmaceutical research. It not only emphasizes the effects of the application of Process Analytical Technology (PAT) on granulation parameters and uniformity of the tablet, but also explains the consequences of the obtained findings on preclinical formulations, and outlines the limitations on the research and the future research directions.

4.1. Interpretation of Results

Findings of this paper have revealed that use of Process Analytical Technology (PAT) contributes significantly to the uniformity and quality of tablets since it allows real-time monitoring of key granulation issues. Table 1 shows that the granule characteristics of particle size, moisture content, and bulk density fell within a small range in all batches. The standard deviations are low showing that PAT has been effective in reducing batch-to-batch variation in the granulating process. As a result, the weight, hardness, and friability of tablets manufactured using these granules are

consistent (Table 2), which proved that controlled granulation directly affects the quality of the final downstream tablet.

This conclusion can also be supported by the statistical comparison with non-PAT batches (Table 3). The substantial differences ($p < 0.05$) in the properties of tablets (weight, hardness, and friability) suggests that standard granulation without real-time measurements provides more variation and may lead to inaccurate dosages and mechanical damage. Adjustments in PAT, including the ability to add a binder in controlled amounts and smaller mixing periods, helped to achieve increased process control and better results.

4.2. Comparison with Existing Studies

The use of PAT in large-scale industrial pharmaceutical production has been stated as having beneficial effects in the past. It is shown that the use of near-infrared spectroscopy (NIRS) and particle size measurements enhanced the reliability of the granulation process[14], whereas another emphasized the value of PAT in minimizing the vagaries of weight and friability of tablets throughout the wet granulating process[15]. The study applies these findings to the preclinical animal based formulations where it is stressed that even minor sized experimental batches can be of benefit due to the ability to provide real time monitoring of the processes. The observed homogeneity of granules and tablet properties here support the overall generality of application of PAT in vastly different scales and formulations.

4.3. Implications of Findings

The findings of this study have several practical implications:

1. **Enhanced Reliability in Preclinical Studies:** Reproducible tablet properties through controlled granulation also plays an important role in animal-based pharmacological research. This is also reliable in delivering constant preclinical data minimizing variation of experimental results.
2. **Resource Optimization:** The real time monitoring minimizes istage by enabling corrections to deviations made on-the spot in the granulation process. This reduces the amount of batch rework or loss.
3. **Better Product Quality:** The quality of Tablets manufactured under PAT screening is less variable, they have enhanced mechanical strength and reduced friability enhancing the possibility of safer and more efficient delivery of drugs.

4.4. Limitations of the Study

Although the research is proven to be effective, it is worth noting that it has the following limitations:

- Only a drug with a single model and three batches are tested. Generalization of the results needs to be done in larger studies involving a variety of drugs and batch sizes.
- Only these three granulation parameters, viz. particle size, moisture content and bulk density are observed. Influencing factors like temperature fluctuation, viscosity of the binder or pores in the granules are not incorporated.

- The investigation with preclinical, small-scale preparations as well as the extrapolation to large-scale commercial production can also need further validation.

4.5. Suggestions for Future Research

Future analyses might also consider the possibility of using PAT in preclinical and industrial applications:

- Multiple Drug Formulations: PAT Assessment Multiple Drug Formulations: Testing on a range of model drugs with varying physicochemical characteristics to determine its applicability.
- Advanced PAT Tools: Use enhanced PAT tools, to provide a more detailed real-time analysis (raman spectroscopy, interlocking non-infrared, near-infrared chemical imaging).
- Scale-up Studies: PAT-enabled granulation Assessing the scalability of PAT-enabled granulation to large batch sizes and production lines.
- Integration with QbD: Systematic process optimization with regulatory compliance by incorporating PAT with Quality by Design (QbD) concepts.

5. CONCLUSION

5.1. Summary of Key Findings

The paper shows that Process Analytical Technology (PAT) is very useful in measuring the parameters of the grainulation process to help increase the uniformity of the tablet in a clinical formulation. When using PAT tools like a near infrared spectroscopy (NIRS) and in-line particle size analyzers, the properties of the granules such as particle size, moisture content and bulk density remained constant throughout a batch. Tablets manufactured using PAT-observed granules had a similar weight, good hardness and low friability, and significant changes toward better properties are observed relative to non-PAT batches. These results prove that real-time control and modifications during the granulation reduce the batch-to-batch fluctuation and positively affect the quality of the tablets.

5.2. Significance of the Study

PAT when used in preclinical tablet formulations offers a number of valuable advantages. It also guarantees reliable and reproducible tablet properties, essential in producing uniform animal-based pharmacological certainties. PAT also maximizes resource utilization, minimizes istage and enhances the overall optimization of the process through minimizing variation and potential error in the granulation process. These benefits highlight the potential of PAT as a typical instrument to improve quality management in early-stage pharmaceutical research.

5.3. Final Thoughts and Recommendations

It concludes that PAT is an effective strategy to manage key granulation variables and consistently generate identical tablets during preclinical trials. Further studies are encouraged to be conducted exploring how it can be combined with more sophisticated tools of analysis, scale up studies as well as multiple drug formulations as a way of further confirming its effectiveness in various contexts. The use of PAT in conventional preclinical development of formulations could lead to a

great deal of enhancement in the reliability, reproducibility, and quality of pharmaceutical tablets eventually leading to the development of more efficient and effective drugs.

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