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INTEGRATED APPROACHES OF PHARMACEUTICS AND PHARMACEUTICAL ANALYSIS IN MIXING PROCESS VALIDATION

Nancy Mohapatra[1*], Nibedita Pradhan[2], Aditya Patsani[3] and Chinmaya Sahoo[3]

[1*]Assistant Professor, Department of Pharmaceutical Analysis, Regional Institute of Pharmaceutical Science, Similipada, Angul, Odisha-759122.

[2]Assistant Professor, Department of Pharmaceutics, Regional Institute of Pharmaceutical Science, Similipada, Angul, Odisha-759122.

[3]Assistant Professor, Department of Pharmaceutics, The College of Pharmaceutical Sciences, Tamando, Janla , National Highway 16, Kalinga Vihar, Patrapada, Bhubaneswar, Odisha-751019.

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***Corresponding Author: Nancy Mohapatra**
Assistant Professor, Department of Pharmaceutical Analysis, Regional Institute of Pharmaceutical Science, Similipada, Angul-759122.
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ABSTRACT

Mixing validation is a crucial step in pharmaceutical industry since it is responsible for drug formulation consistency for therapeutic efficacy. Combining the disciplines of pharmaceutical analysis and pharmaceutics can provide a better and systematic understanding of the approaches and methods for mixing validation. The following paper discusses the main methods for integrated mixing validation, and their efficiency and applicability to find and eliminate inconsistencies in the pharmaceutical process. Further, the paper highlights the major challenges that are faced during this process, such as the variability of properties and the limitations of previously used methods to find mixtures inconsistencies, and explains the potential benefits that will be obtained as the results of the collaborative aspect. Finally, the importance of integrating the scientific disciplines in pharmaceutical analysis and pharmaceutics under this issue is considered taking into account the recent studies.

KEYWORDS: Mixing Process Validation, Pharmaceutics Integration, Pharmaceutical Analysis, Process Analytical Technology (PAT), Quality by Design (QbD).

INTRODUCTION

The validation of mixing processes in pharmaceutical manufacturing represents a key factor for the quality and consistency of a finished product. Homogeneous distribution of active and inactive ingredients contributes to

preventing product batch deviations that may lead to a reduced therapeutic effect or even adverse scenarios. An innovative workflow that integrates the fields of pharmaceutics and pharmaceutical analysis is intended to increase the confidence level associated with the validation process. The connection between formulation and accurate quantification results provides the possibility for improved control and monitoring. The combination of these two disciplines proves to bring evident benefits for the pharmaceutical industry, as it contributes to meeting the requirements of guidelines and regulations while enhancing the quality of pharmaceutical products. As the complexity and demands increase for the industry, reliance on knowledge and expertise at the interface between both disciplines brings the need for a control-oriented philosophy to complement the production of quality products to the forefront.

Overview of Mixing Process in Pharmaceutics

Mixing is an important unit operation during formulation development for any pharmaceutical products. It is the integral process to distribute components to achieve mix homogeneity in any dosage form to prevent from intra and inter unit variability of active pharmaceutical ingredient per unit. The specific mixing method like dry blending, wet granulation and high-shear depends on the formulation needs and physical characteristics of ingredient components. It is important to select appropriate process for mixing due to different reasons including safety aspects and drug efficacy. Non uniformity from content uniformity can lead to various outcomes of unknown half-effect and safety characteristics. In-process control parameters like bulk density and hardness of mixture can be the direct indicators for batch to batch consistency and thus during process development evolution it saves a lot during mixing monitoring stages (Vaja et al., 2021). Mixing validation is crucial in various aspect including but not limiting to solid dosage uniformity. Therefore, mixing can be also regarded as critical control point for product integrity and hence overall well being.

Nevertheless, there are still a few challenges preventing the accomplishment of drug uniformity during the process with a potential impact on the patient safety and the end product quality such as segregation, which is often encountered during discharging and transfer of the blend and may result in variability of drug content in different tablets (Jakubowska & Ciepluch, 2021). Moreover, there may be also incomplete blending due to particle size and density variations, such as sifting or fluidization, which may excite the demixing of components. Aspects like scale-up create additional challenges since the process parameters that guarantee effective mixing at a reduced scale do not necessarily predict the behavior in larger batches. Therefore, the knowledge about the variability sources must be incorporated in the development of such process by adjusting the mixing methods and coupling the control systems to reduce these inconsistencies and maintain drug content uniformity during the process (Jakubowska & Ciepluch, 2021). The integration of pharmaceutics and pharmaceutical analysis ensures precise and consistent drug formulation. Pharmaceutics contributes by optimizing mixing parameters such as particle size, flowability, and blending methods, while pharmaceutical analysis provides accurate evaluation using NIR, Raman, HPLC, and particle size analysis. Together, they enable real-time monitoring and control through tools like PAT and QbD. This integrated approach reduces variability, prevents segregation issues, and ensures uniformity across batches. By combining process understanding with analytical precision, manufacturers achieve higher product quality, regulatory compliance, and improved process efficiency shown in table-1.

Table 1: Integrated Approaches and Analytical Techniques for Mixing Process Validation.

Aspect	Pharmaceutics Perspective	Pharmaceutical Analysis Perspective	Integrated Outcome
Objective	Achieve homogeneity in active and inactive ingredients during formulation.	Quantitatively and qualitatively assess the uniformity of blends.	Enhanced product quality assurance and regulatory compliance.
Key Techniques/ Methods	Dry blending, wet granulation, high-shear mixing, Process Analytical Technology (PAT).	Near-Infrared (NIR), Raman Spectroscopy, HPLC, Particle Size Analysis (PSA), Blend Uniformity Tests (BUT).	In-line and real-time monitoring of blend uniformity, reduced sampling errors.
Critical Parameters	Particle size, density, flowability, mixing speed, time, and scale-up factors.	Statistical control limits, standard deviation, RSD, and content uniformity indices.	Real-time process monitoring and control of critical process parameters (CPPs).
Challenges	Segregation, incomplete blending, and scale-up inconsistencies.	Sampling error, analytical uncertainty, and method variability.	Improved control strategies through data-driven and model-based validation.
Tools for Integration	QbD, QbC, and PAT frameworks.	Chemometric modeling, machine learning, and computational analysis.	Predictive, risk-based, and adaptive process validation system.

It follows that poor mixing can affect not only batch-to-batch variability but also the performance, stability, and safety of the finished product. Failures in homogeneously distributing active pharmaceutical ingredients within the formulation can lead to heterogeneous dosages and suboptimal or toxic effects on the patients. Poorly mixed formulations can yield unsatisfactory results in terms of content uniformity and drug release, as APIs and excipients may aggregate or separate in such a manner that the dissolution and the drug absorption can be compromised (Buyukgoz et al., 2021). Such a failure can also induce physical or chemical instability in the drug product, triggering degradation or undesired interactions among APIs and excipients. Poor mixing practices can, therefore, seriously threaten the safety and well-being of patients and can potentially increase adverse reactions or therapeutic failures, undermining the public confidence in medicines as a reliable means of improving health and well-being (Buyukgoz et al., 2021).

Principles of Pharmaceutical Analysis in Mixing Validation

A multitude of analytical techniques have been developed and incorporated in the pharmaceutical analysis of blending uniformity, each capable of offering a unique insight into the homogeneity of a given blend. Spectroscopic techniques, including near-infrared and Raman spectroscopy, facilitate a rapid and non-destructive analysis of the blend through the identification of distinct molecular signatures corresponding to individual blend components. Chromatographic techniques, like high-performance liquid chromatography (HPLC), provide a quantitative analysis of the concentration of each separate ingredient within a given formulation, and are commonly employed for the confirmation of homogeneity on a more specific scale. Physical methods, such as particle size analysis (PSA) and blend uniformity tests (BUT), can also be used in conjunction with the above techniques to provide an understanding of factors such as segregation and dispersion, and resultant effects on the efficiency of the mixing process (Ermer & Nethercote, 2025). The selection of appropriate methodologies is of paramount importance in the analysis of blending uniformity, and must be complemented by rigorous method validation and performance verification in order to establish a solid analytical framework for the assurance of product quality throughout the pharmaceutical manufacturing process (Ermer & Nethercote, 2025).

Moreover, sound and appropriate sampling strategies and statistical methods are critical for the success of mixing process validation. In order to represent the blend uniformity accurately and limit the errors associated with heterogeneity or local segregation of the powder mass in the mixing vessel, representative sampling is necessary. Sampling using thief probes is still one of the most widely used approaches in the industry; however, the sampling procedure should be carefully developed to ensure that the retrieved sample is truly representative for the entire batch (Crouter & Briens, 2019). The retrieved data then will be subjected to a thorough statistical analysis to calculate content uniformity, identify outliers and evaluate the mixing end points with improved confidence. Use of statistically sound methods will increase reliability of the validation data and improve the process control and the evidence delivered for compliance with regulatory requirements for product quality and consistency (Crouter & Briens, 2019).

Moreover, the analysis of results obtained by analytical techniques is crucial for process scientists to verify blend homogeneity and detect potential problems during the production of pharmaceutical batches. The performance of analytical data is evaluated on how well they indicate the blend uniformity of constituents using quantitative indices of batch uniformity such as standard deviation, relative standard deviation and range. When the results exceed threshold value or unexpected variability is observed across different regions analyzed, the behavior is systematically investigated, as it may indicate that the constituents are not adequately blended, segregated or disturbed by the equipment. The use of modern analytical software and statistical methods, and the added capability of computational techniques, for example, machine learning to detect non-obvious trends or outliers in an extensive and complex data, improves the sensitivity and reliability of the analysis (Akash & Rehman, 2025). By applying appropriate methodologies to analyze statistical data, it allows process scientists not only to confirm blend homogeneity, but also to quickly identify possible issues, allowing accidents in the production of pharmaceuticals (Akash & Rehman, 2025).

Integrated Approaches: Combining Pharmaceutics and Analysis

The mixing validation framework established in the pharmaceutical industry rests on the technicallysound integration of methodologies from the multidisciplines of formulation science and analytical chemistry. Understanding the properties of materials (eg particle size, flowability) and pairing that with high-tech analysis creates a control strategy that implies, measures and assesses critical-process parameters during the manufacturing method. The inclusion of contemporary protocols installing the Process Analytical Technology (PAT) suites (eg near infrared spectroscopy, Raman spectroscopic methods), enables in-line observation of the blend uniformity deviations during processing of solid dosage forms (Kim et al., 2021). This integrated strategy also improves the quality of the Design by Quality (QbD) approach with process verification replacing exclusive terminal testing. It advances the proactive detection and correction of problems with impacts on performance in the final product. Ultimately, it adds to process reliability and expeditious resolving of uncertainties that can focus on deviations with pharmaceutical industry expectations (Kim et al., 2021).

The integration of PAT tools together with deep understanding of formulation could help in systematic identification and prevention of blending failures at the initial stages of the manufacturing processes. Near-infrared spectroscopy (NIRS) offers continuous assessment of blend uniformity and allows operators to track the segregation events, due to changes in particle size or flow during the subsequent transfer steps that may not be captured using traditional end-point tests. Meanwhile, the utilization of data on important formulation-related factors, such as excipient choice, segregation particle shapes and morphology help formulation scientists to adjust any modification of the process

parameters or the blend composition to reduce potential demixing and improve process robustness. In one of the studies it was presented that such combined analytical and formulation-based approaches can effectively reduce the potential repeatability issues resulted from the blending segregation during critical process steps especially while the material is transferred from hoppers to die filling (Jakubowska & Ciepluch, 2021). The coordinated approach outlined above support proactive measures not only to fight the content uniformity failures but also result process efficiency improvement while adhering to high quality requirements.

In addition, interdisciplinary interaction of formulation scientists and analytical chemists provides crucial benefits in terms of mixing process validation. Their collaboration opens up opportunities to address complex manufacturing issues in an integrated manner, combining expertise on material behavior and precise measuring techniques. It facilitates accessing subtle inhomogeneities in blends quickly through a cohesive approach integrating standard analytical methods with innovative computational data processing techniques, such as machine learning algorithms and cloud computing systems (Akash & Rehman, 2025). Teams may also readily modify process design and analytical techniques on-the-go based on shared knowledge, resulting in adaptive processes that are robust to variations, ultimately delivering consistent quality in each batch (Akash & Rehman, 2025). Finally, such an integrated approach may foster advancement in continuous innovation and product development in process control and scientific assessment in the pharmaceutical manufacturing industry (Akash & Rehman, 2025).

Regulatory Perspectives on Mixing Process Validation

From the regulatory perspective, the mixing process validation is tightly evaluated by the US FDA and EMA. Both agencies aligned on the basic principles of quality assurance as batch consistency, process reproducibility and appropriate control on each manufacturing step. Source (Deeks, 2021) reports mentioned that US FDA recommendations are focused on systemic process validation guided with analytical evidences, while EMA encourages similar recommendation but minor differences in documentation and process outlook could be seen based on the historical regulatory setup. Further examples also provided for multinationals manufacturers to take note of separate requirements whereby apart from above common basic principles, differences could be seen in data representation or the analytical techniques (Deeks, 2021) accepted. Hence, compliance with regulatory expectations required the need of viewing not only on generalize principle but also on further details on how these principles are viewed and adapted accordingly.

Moreover, Quality by Design (QbD) is a systematic approach ensuring that innovative pharmaceutical formulation and evaluation are harmonized to achieve continuously meet dynamic regulatory expectations. QbD encourages early identification of critical quality attributes (CQAs) and critical process parameters (CPPs), enabling embedding robust analytical methodologies along with process design controls throughout development and, consequently, consistent meeting of product specifications. This harmonious approach assists in regulatory submissions wherein documentation embodies processes knowledge, risk analysis and evidence-based rationales from formulation and analytical perspectives (Su et al., 2019). In this regard, it is worth noting that the QbD approach is well aligned with recent modern concepts, such as Quality-by-Control (QbC) wherein the model-based approaches' and on-line monitoring towards its real-time applicability enhance the continuous quality control and process facilitation concepts. Thus, QbD is not limited to regulatory requirements only but also establishes a bridge of pharmaceutics and pharmaceutical

analysis disciplines to strengthen data-driven, science-focused culture in pharmaceutical manufacturing (Su et al., 2019).

In addition, risk assessment tools also play an integral role to identify critical process parameters (CPPs) during mixing process validation and closely associated with regulatory requirements as these tools (FMEA, HACCP) review each step to determine where any deviation from the product/process set limits could have a substantially detrimental impact on product quality or safety. Manufacturers adopt monitoring systems that focus controls on such variables where there is a high likelihood of failure and the consequences are severe. Effective regulatory monitoring of these steps extensives the scope of processes /parameters /tests / controls. For API drug products, or for parenterals and sterile products, put forth additional steps might include HEPA filtration efficiency studies and smoke studies to know operational excellence or process knowledge, to identify or manage risk at initial stage (Baseman, 2020). In conclusion, risk assessment tools are strongly recommended to focus for proactive improvements over entire processes without compromising the state of validation work (as per changing regulatory requirements).

Case Studies in Integrated Mixing Validation

One example of the successful implementation of integrated pharmaceutics and pharmaceutical analysis is the validation of the continuous mixing technology (CMT) device by a Discrete Element Method (DEM) model. The study showed the successful calibration of the cohesive contact model for the powders by combining the results of the compression and shear cell tests with the results of the numerical simulation. Here, the calibration results integrated provided a stronger link from the material property measurements of the physical powder bulk to the numerical model (Toson et al., 2021). With the predictive DEM simulation of the residence time distribution (RTD) in the CMT, the results obtained were validated against that from physical experiments conducted using tracer spike tests, thereby ensuring the reliability and accuracy of the DEM model. With the method described, the reduction of the physical experiments provided additional insight into the process, allowed significant time savings, and at the same time, no loss in the formulation understanding was recorded. Based on this example, it can be seen that integrated knowledge of formulation, model development, and analysis creates a strong link toward the understanding of the mixing process and allows its optimization. The implementation of DEM simulation together with the physical validation and experimentation of the CMT provides a strong example of such collaboration based on the effective use of both pharmaceutics and its analysis toward process control (Toson et al., 2021).

Finally, some key takeaways from this case study were highlighted related to the challenges during continuous mixing validation and the success of implemented solutions. The researchers have found the challenges during powder behavior characterization, mainly obtaining the particle cohesion and flow parameters to simulate and model the material behavior realistically. The application of a complete physical characterization methodology, including the compression and the shear cell tests, had allowed the calibration of the Discrete Element Method (DEM) with specific parameters of the material, improving the model fidelity and information content. Also, confidence in RTD validation predictions was gained by direct data comparison of the simulation and experimental tracer spike results with similar behavior. The co-relation found from these two sources added value to the confidence of the developed process model and its predictive capabilities (Toson et al., 2021). The integration of all these approaches allowed for less dependency on resource-intensive experiments (Toson et al., 2021). Data-centric modeling and validation methods have proven

their capability to optimize the pharmaceutical mixing processes, along with the importance of experimental data submission and acceptance (Toson et al., 2021).

This integration represents a significant advancement in process and product quality in the blend of formulation know-how with analytical modeling. The study shows how commercial techniques are used in an extensive analytical characterization of the materials to predict the behavior and performance of the process in the development of methods (Buyukgoz et al., 2021). The use of simulation avoids unnecessary experiments, which are often costly in time and resources while achieving a high adjustment to the real behavior of the processes. This shortens the development times and increases the knowledge of the process that allows a better adjustment of mixer and critical process parameters. For example, in unique content uniformity determinations, it was possible to demonstrate with experimental data and simulation that the correct mixer configuration provided acceptable drug levels in dosage units. As a result of the identification of problems such as agglomeration through measurement and other analytical techniques, the manufacturers can keep the processes stable and avoid losses of efficacy and reliability in the process. An effort that reinforces the knowledge gained with this collaborative and integrated validation method it’s worth it (Buyukgoz et al., 2021).

Advances in Technology for Mixing Process Validation

The latest innovations in technologies are changing the mixing process validation in the pharmaceutical field mainly by utilizing real-time process monitoring and advanced data analytic tools. The mechanistic modeling approaches like Discrete Element Method (DEM) enables researchers to accurately simulate complicated unit process operations such as blending and granulation, which includes a specific model to improve process control and predictive capabilities. The key material properties of the constituent particles, as well as their interaction parameters, are incorporated in mechanistic models within a simulation platform, which allows detailed specification of a material's movement and distribution within the equipment (Yeom et al., 2019). In addition, the branded data analytic applications together with real-time sensor networks provides implication to the process performance metrics to continuously assist operators in detecting and correcting process excursions during manufacturing. Together, these innovations pave the way for the pharmaceutical mixing process validation methodologies to shift from time-consuming end specification tests, which are dependent on retrospective analysis, toward more proactive and data-supported validation strategies based on observation and practical calculations from validated mechanistic models (Yeom et al., 2019).

Finally, automation and digitalization are becoming more and more important to increase the precision and reproducibility of the mixing validation procedures. Automated processes allow for the complex mixing conditions, defined protocols to be controlled without variability due to the operator influence, defects and/or human mistakes and compliance to the fixed acceptance parameters before, during and after each process. Digitized systems can exactly monitor the processing parameters like mixing speed, temperature, time and allow for immediate troubleshooting to maintain the homogeneity and quality of the batch data through the entire process. In this manner, manufacturers are able to keep product specification in accordance with the existing international standards and guidelines like those provided by International Council for Harmonisation Q6A; where for stability during the product shelf-time both limits at release and acceptance criteria are determined to preserve the integrity and craftsmanship of the desired product (Manger, 2019). Through automation and digital data management, pharmaceutical industries initiate the process validation with more reliable, reproducible solutions and establish, reinforce appropriate documentation and

compliance requirements and systems that meet the demanding expectations of the present-day industry (Manger, 2019).

Future perspectives on the role of pharmaceutics and pharmaceutical analysis in process validation are likely to focus on the advantages of the integration of alternative testing strategies, particularly in vitro ones. With the evolution of in vitro methodologies, their development and standardization are expected to lead to more streamlined validation, with less dependency on traditional in vivo models that are often resource demanding (Bas et al., 2021). 3Rs' advocacy is likely to have a broader impact on the adoption of new in vitro strategies, with consequent gains in development and regulatory acceptability timelines. Following inter-laboratory validation and standardization, new methodologies could tie into enhanced reproducibility and reliability to predict the success of mixing processes in different manufacturing scenarios (Bas et al., 2021). The trends foreseen for this area are aligned with the pursuit of an ethically and economically sustainable future for validation methodologies, capable of integrating innovative pharmaceutical science and customized analytical approaches. Recent advances such as Discrete Element Method (DEM) modeling, automation, and real-time monitoring have transformed pharmaceutical mixing validation, enabling predictive and data-driven control. Regulatory agencies like the FDA and EMA emphasize evidence-based, reproducible processes supported by frameworks such as Quality by Design (QbD) and Quality by Control (QbC). Case studies, including continuous mixing technology validation, demonstrate how integrating formulation knowledge with analytical modeling reduces experimental workload while maintaining accuracy. Future trends point toward in vitro validation and ethical, sustainable testing methods. Despite ongoing challenges like limited resources and technical expertise, collaborative and interdisciplinary approaches continue to enhance process robustness, regulatory compliance, and overall product quality shown in table-2.

Table 2: Advances, Regulatory Expectations, and Case Study Highlights.

Category	Key Highlights	Impact/Outcome	References
Technological Advances	Discrete Element Method (DEM), automation, digitalization, real-time monitoring.	Shift from end-point testing to proactive, data-supported validation.	Yeom et al. (2019); Manger (2019)
Regulatory Frameworks	FDA & EMA guidelines emphasize process reproducibility and evidence-based control. QbD & QbC approaches integrate formulation and analytical aspects.	Improved documentation, risk assessment, and regulatory compliance.	Deeks (2021); Su et al. (2019); Baseman (2020)
Case Study Example	Continuous Mixing Technology (CMT) validation using DEM simulation.	Demonstrated integration of formulation data and analytical modeling; reduced experimental effort while maintaining high accuracy.	Toson et al. (2021)
Future Trends	In vitro validation methods, ethical testing (3Rs), data-driven decision-making.	Sustainable, reproducible, and efficient validation practices.	Bas et al. (2021)
Challenges and Solutions	Limited resources, instrument access, technical expertise gaps.	Interdisciplinary collaboration, training, lifecycle analytical validation.	Ermer & Nethercote (2025); Sánchez-Paternina et al. (2019)

Challenges and Limitations

Notwithstanding, the complete implementation of pharmaceutics and pharmaceutical analysis into mixing validation faces considerable obstacles even today, due to numerous technological limitations and reasons outlined above. Resources are frequently constrained, mostly, by insufficient access to advanced analytical instruments and qualified

personnel, ultimately leading to inability to establish and maintain cutting-edge monitoring systems across all production sites. There are persistent technical issues, mostly, associated with insufficient separation of process errors from sampling and analytical stages, which introduces additional noise in blend variability and complicates process control (Sánchez-Paternina et al., 2019). As an example, using variographic calculations highlighted that minimum possible error for obtained drug concentration can positionaly significantly exceed routine near-infrared spectroscopy method accuracy, meaning existed uncertainty during validation procedures. Such results findings prove that further methodology and process approaches are still required to accurately separate error causes, improve appropriate resource facilitation, and achieve proper pharmaceutics and analytical systems integration throughout mixing validations (Sánchez-Paternina et al., 2019).

Practical solutions to such problems should, therefore, be centered on relevant organizational and technological improvements, which would ease transitions between pharmaceutics and pharmaceutical analysis. The creation of interdisciplinary teams with organized communication structures could help overcome false assumptions and tensions built upon the lack of certain technical know-how and be instrumental for the reconciliation of varying expertise and competence gaps. There could be reasonable implementation of lifecycle validation of analytical methods, which could involve specific procedures for selecting analytical methods, the practice of ongoing governance of data-related processes, and validation of the analytical methods during development and routine manufacturing (Ermer & Nethercote, 2025). Alongside these processes, continuous training and educational programs directed on development of professionals in the field can enable organizations to source their own technical know-how in state-of-the-art instruments and advancements in analytical methodologies. Moreover, the commitment to adopting risk assessment and data integrity protocols assisted by teams of competent personnel across varying disciplines could further develop professional ties and build an infrastructure for dealing with reliable and efficient mixing validations (Ermer & Nethercote, 2025).

CONCLUSION

Pharmaceutics and pharmaceutical analysis integration in mixing process validation become key factor for product and regulatory quality assurance in pharmaceutical industry. Through this multidisciplanry perspective it is possible to accurately focus on critical variables control and risk management related to blending homogeneity, segregation and process variations. Timely deviations detection supported by analytical methodologies and formulation sciences save the potential loss of therapeutic effectiveness and product recall or significant economic loss. Enhanced documentation compliance becomes possible to achieve through continuous process and product verification and control characterisation that best meet current regulations requirements. By integrating formulation and pharmaceutical analytical sciences it become possible to improve robustness and reproducibility of manufacturing processes assuring patient safety and confidence in product quality.

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