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AI-Based Prediction of Particle Size-Dissolution Relationships in Solid and Suspension Dosage Forms

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Abstract

Particle size distribution (PSD) is a critical quality attribute influencing dissolution, bioavailability, and manufacturability of pharmaceutical solid and suspension dosage forms. Traditional experimental approaches for particle size optimization and dissolution evaluation are time-consuming, resource-intensive, and often retrospective, limiting predictive capability. Recent advancements in artificial intelligence (AI) and machine learning (ML) offer transformative solutions by enabling data-driven prediction of PSD and its impact on dissolution behavior. Machine learning algorithms, including ensemble methods such as Light Gradient Boosting Machine (LightGBM) and artificial neural networks, can integrate formulation variables, process parameters, and analytical data to accurately predict particle size and polydispersity. These AI-based models facilitate early identification of critical formulation risks, support Quality by Design (QbD) principles, and reduce experimental workload. Moreover, coupling PSD predictions with dissolution modeling allows estimation of *in vitro* drug release profiles, particularly for poorly soluble drugs, without extensive repetitive testing. The integration of in-line and at-line particle size monitoring techniques with AI-driven models further enables real-time quality prediction and proactive process control. Despite these advantages, challenges remain in model interpretability, generalizability, regulatory acceptance, and dependence on high-quality datasets. Addressing these limitations through explainable AI, standardized validation, and robust data strategies is essential for broader industrial adoption. Overall, AI-based prediction of PSD–dissolution relationships represents a promising pathway toward knowledge-driven pharmaceutical development, offering accelerated formulation optimization, improved product quality, and alignment with regulatory and Pharma 4.0™ initiatives.

Keywords: Particle Size Distribution (PSD), Dissolution Prediction, Artificial Intelligence (AI), Machine Learning (ML), Quality by Design (QbD)

Introduction

Model-based strategies have become integral to modern pharmaceutical drug development, offering effective pathways to reduce development time, experimental cost, and raw material consumption while consistently achieving the desired product quality [1]. These approaches are strongly aligned with contemporary regulatory frameworks, particularly the Quality by Design (QbD) principles outlined in ICH Q8 and the evolving Pharma 4.0™ concept promoted by the International Society for Pharmaceutical Engineering (ISPE). Together, these paradigms encourage systematic understanding of materials, processes, and product performance through data-driven and knowledge-based methodologies [2]. In recent years, artificial intelligence (AI) and machine learning (ML) techniques have gained increasing attention within pharmaceutical research and development. Their application spans a broad spectrum of activities, including drug discovery, formulation design, and, to a lesser extent, manufacturing process optimization. These data-centric approaches have demonstrated significant potential to reduce experimental burden, leverage routinely collected development and manufacturing data and formalize prior knowledge into predictive models capable of supporting informed decision-making [3]. Particle size is widely recognized as a critical material attribute with a profound influence on both drug product performance and manufacturability. In solid and suspension dosage forms, particle size directly affects dissolution behavior, with smaller particles offering increased surface area and,

consequently, enhanced dissolution rates that may improve bioavailability. However, particle size reduction can also introduce manufacturing challenges, such as poor flowability, reduced compressibility, increased risk of segregation, and variability in content uniformity and mechanical strength of final dosage forms. In suspension systems, inappropriate particle size distributions may further contribute to sedimentation, caking, and dose non-uniformity, underscoring the need for precise particle size control [4]. Traditionally, particle size characterization has relied on off-line analytical techniques such as sieve analysis, laser diffraction (LD), and microscopy. While these methods are well established, they are often time-consuming, operator-dependent, and unsuitable for real-time process monitoring and control. As the pharmaceutical industry increasingly adopts Process Analytical Technology (PAT) tools and continuous manufacturing (CM) platforms, there has been a clear shift toward in-line and at-line particle size measurement techniques [5]. Technologies such as spatial filtering velocimetry (SFV) and focused beam reflectance measurement (FBRM) enable real-time monitoring; however, each technique presents inherent limitations. LD typically assumes spherical particles and may provide misleading size distributions for non-spherical systems, while FBRM reports chord length distributions that do not always directly correlate with true particle size [6]. These analytical constraints complicate the establishment of robust particle size–performance relationships. Dissolution testing plays a pivotal role throughout pharmaceutical development, from early formulation screening to batch release and lifecycle management. Dissolution behavior is considered a critical quality attribute, particularly for poorly soluble drugs and complex dosage forms [7]. Despite its importance, conventional dissolution testing remains resource-intensive and retrospective in nature, offering limited predictive capability during formulation development and process optimization. The integration of QbD and PAT concepts has created a demand for predictive tools capable of linking material attributes, such as particle size distribution, to dissolution performance in a proactive and knowledge-driven manner [8]. The convergence of AI, ML, and machine vision presents a promising opportunity to overcome these challenges. ML algorithms are well suited to handle complex, high-dimensional datasets and can uncover non-linear relationships between particle size characteristics and dissolution behavior that are often overlooked by traditional statistical approaches. By integrating particle size data obtained from off-line or in-line analytical techniques with formulation, process, and dissolution data, AI-based models can enable accurate prediction of dissolution profiles for both solid and suspension dosage forms. Such predictive frameworks support rapid formulation optimization, reduced experimental workload, and enhanced process understanding. This article explores the application of AI-based modeling approaches for predicting particle size–dissolution relationships in solid and suspension dosage forms. Emphasis is placed on the role of machine learning in integrating particle size analytics, dissolution performance, and manufacturing considerations within a QbD and PAT-enabled development framework. The potential of these approaches to accelerate pharmaceutical development, improve product quality, and support regulatory-aligned, data-driven decision-making is critically discussed [9].

AI & Machine Learning in PSD Prediction

Particle size distribution (PSD) is a critical quality attribute influencing dissolution, stability, and bioavailability of pharmaceutical dosage forms, particularly suspensions and poorly soluble solid products [10]. Traditional trial-and-error approaches for controlling PSD are time-consuming and resource-intensive. Recent studies have demonstrated that artificial intelligence (AI) and machine learning (ML) techniques offer powerful alternatives for predicting PSD based on formulation and process variables. Machine learning models such as Light Gradient Boosting Machine (LightGBM), artificial neural networks (ANNs), and deep learning frameworks (e.g., Keras-based models) have been successfully applied to predict mean particle size and polydispersity index (PDI) in pharmaceutical suspension formulations [11].

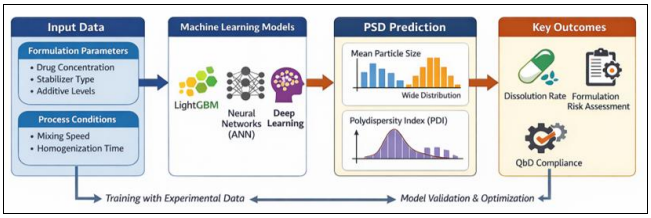

Fig 1: AI & Machine Learning in PSD Prediction

These models utilize formulation parameters (drug concentration, stabilizer type and concentration) and process conditions (mixing speed, homogenization time) as inputs to generate accurate PSD predictions. Among the evaluated algorithms, ensemble learning methods such as LightGBM demonstrated superior predictive performance due to their ability to handle nonlinear relationships and complex interactions between formulation variables [12]. Neural network–based models further improved prediction accuracy when large and diverse datasets were available, highlighting the importance of data quality and model training in pharmaceutical AI applications [13]. AI-based PSD prediction enables early identification of critical formulation risks and supports Quality by Design (QbD) principles by linking material attributes and process parameters to final product quality. Accurate PSD prediction is particularly important for suspension dosage forms, where particle agglomeration and size variability directly affect dissolution rate and content uniformity [14]. Furthermore, the integration of AI models with experimental data reduces development timelines and minimizes experimental failures. However, challenges remain related to model interpretability, regulatory acceptance, and the need for robust external validation before routine industrial implementation [15]. Overall, AI and machine learning represent transformative tools for PSD prediction, providing a foundation for advanced modelling of downstream performance attributes such as dissolution behavior in both solid and suspension dosage forms [16].

AI Models Linking Particle Size Distribution (PSD) to Dissolution

Particle size is a well-established determinant of dissolution and absorption behavior, particularly for poorly soluble drugs belonging to Biopharmaceutics Classification System (BCS) class II. Variations in particle size distribution (PSD) can lead to significant changes in dissolution rate, making

PSD a critical quality attribute for many pharmaceutical products [17]. Consequently, there is a growing need for predictive dissolution models that can estimate *in vitro* drug release behavior based on PSD and related material attributes [18]. Recent studies demonstrate that dissolution rates can be successfully predicted by integrating experimentally determined PSD data into mathematical frameworks such as population balance models (PBMs). These models describe particle-level phenomena including nucleation, growth, aggregation, and breakage, which collectively influence dissolution kinetics [19].

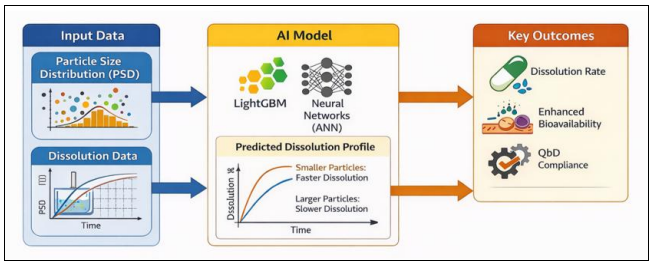

Fig 2: AI Models Linking Particle Size Distribution (PSD) to Dissolution

When PSD is used as an input parameter, PBMs enable reliable prediction of dissolution profiles without extensive repetitive dissolution testing. Advances in artificial intelligence (AI) and machine vision have further strengthened this approach by enabling real-time measurement of component-specific PSD in powder blends [20]. The PSD data obtained through AI-based object detection techniques can be directly linked to dissolution prediction models, allowing *in vitro* dissolution profiles of dosage forms such as capsules and tablets to be estimated in real time. Experimental results have shown a clear correlation between particle size and dissolution behavior, where smaller particles dissolve more rapidly while larger particles exhibit slower dissolution [21]. The performance of these integrated AI–PSD–dissolution models have been validated using similarity and difference factors, demonstrating acceptable agreement between predicted and experimental dissolution profiles. This confirms the robustness and reliability of AI-enabled dissolution prediction strategies [22]. By combining in-line PSD measurement with predictive modeling, these approaches represent a significant advancement in pharmaceutical process analytical technology (PAT), enabling proactive quality control and reducing reliance on traditional, time-consuming dissolution testing. Overall, AI-driven models linking PSD to dissolution offer a promising pathway toward real-time quality prediction, enhanced process understanding, and more efficient pharmaceutical product development and manufacturing [23].

Machine Learning for Particle Size Development

Machine learning (ML) techniques are increasingly being recognized as effective tools for predicting particle size outcomes during pharmaceutical product development. Particle size is a critical quality attribute that plays a major role in determining dissolution behavior, bioavailability, and overall product performance [24]. The ability of ML models to learn complex relationships between formulation variables and process conditions makes them particularly well suited for particle size prediction tasks. Recent studies have demonstrated the successful application of ML-based regression models to predict final particle size in processes such as spray drying. These models utilize key formulation and processing parameters including feed concentration, inlet temperature, atomization conditions, and solvent composition as input variables [25].

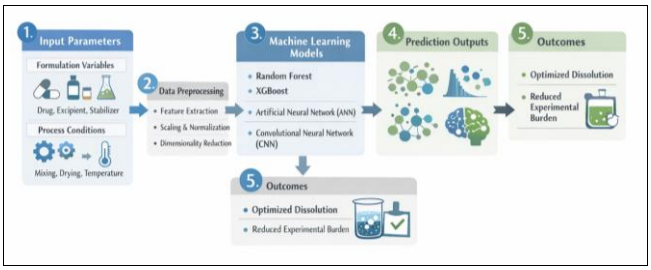

Fig 3: Machine Learning for Particle Size Development

By training on experimentally generated datasets, ML algorithms are able to establish robust correlations between processing conditions and particle size outcomes. Among the various modeling approaches evaluated, ensemble-based algorithms have consistently shown superior predictive accuracy compared to traditional linear regression methods. This improved performance is attributed to their capacity to capture nonlinear interactions and multivariate dependencies inherent in pharmaceutical manufacturing processes. Model performance is commonly assessed using statistical indicators such as the coefficient of determination (R^2) and root mean square error, which confirm the reliability of ML-based predictions [26]. Despite these advantages, the predictive capability of ML models is highly dependent on the size, diversity, and quality of the training dataset. Limited data availability can restrict model accuracy, and extrapolation beyond the defined experimental design space remains a significant challenge [27]. Nevertheless, ML-driven particle size prediction offers substantial benefits by reducing experimental workload, accelerating development timelines, and supporting quality-by-design (QbD) strategies through proactive control of particle size during pharmaceutical manufacturing [28].

Emerging Trends and Limitations

The application of artificial intelligence and machine learning (ML) in pharmaceutical formulation and analytical development has expanded rapidly in recent years. These data-driven approaches are increasingly being used to predict critical quality attributes, particularly particle size distribution (PSD) and polydispersity index (PDI), by correlating formulation composition and process parameters [29]. Advances in ML algorithms, supported by growing experimental datasets, have significantly enhanced the accuracy and reliability of PSD prediction models. Among the various modeling approaches, ensemble learning techniques such as Light Gradient Boosting Machine (LightGBM) have shown superior predictive performance across diverse datasets [30]. The integration of ML tools with formulation and process variables represents a promising strategy to accelerate pharmaceutical development, reduce experimental burden, and support quality-by-design (QbD) initiatives [31]. These trends indicate a shift toward more predictive, data-centric approaches in pharmaceutical analysis and manufacturing. Despite these advancements, several limitations hinder the widespread adoption of ML-

based models in pharmaceutical applications [32]. Model performance remains highly dependent on the size, diversity, and quality of available datasets. Inadequate or imbalanced datasets can lead to reduced prediction accuracy, particularly for certain manufacturing techniques such as antisolvent precipitation [33-37]. Additionally, many ML models exhibit limited generalizability due to formulation-specific or process-specific training data. Another major challenge is the interpretability of complex ML models, which continues to be a concern for industrial implementation and regulatory acceptance [38-40]. Black-box modeling approaches may conflict with regulatory expectations for transparency and scientific understanding. Furthermore, the lack of standardized datasets and the need for external validation present additional barriers to routine implementation in regulated environments. Addressing these challenges through improved data strategies, model interpretability, and regulatory alignment will be critical for the future integration of AI-driven predictive models in pharmaceutical analysis [41-46].

Conclusion

Artificial intelligence–based modeling approaches represent a transformative advancement in understanding and predicting the complex relationship between particle size distribution (PSD) and dissolution behavior in both solid and suspension dosage forms. As particle size remains a critical quality attribute influencing dissolution, bioavailability, manufacturability, and product stability, the ability to predict its impact using data-driven methods offers substantial advantages over traditional empirical and trial-and-error approaches. The application of machine learning techniques, including ensemble learning methods, artificial neural networks, and deep learning frameworks, has demonstrated strong potential for accurately predicting PSD based on formulation composition and processing parameters. When integrated with dissolution modeling strategies, these AI-driven approaches enable reliable estimation of dissolution profiles, particularly for poorly soluble drugs and complex dosage forms. The incorporation of real-time or in-line PSD data through PAT tools, combined with AI-based predictive models, further strengthens the capability to achieve proactive quality control and enhanced process understanding.AI-enabled prediction of particle size–dissolution relationships aligns closely with Quality by Design (QbD) principles and supports regulatory expectations for systematic, science-based pharmaceutical development. By reducing experimental burden, minimizing development timelines, and enabling informed decision-making within the design space, these models facilitate more efficient formulation optimization and manufacturing robustness. In suspension systems, where PSD directly governs dissolution rate, sedimentation behavior, and dose uniformity, AI-driven predictive frameworks offer particular value for ensuring consistent product performance. Despite the demonstrated benefits, challenges remain in terms of data availability, model interpretability, generalizability, and regulatory acceptance. The performance of AI models is inherently dependent on high-quality, diverse datasets, and the use of complex “black-box” algorithms may limit transparency and confidence in regulated environments. Addressing these limitations through improved data strategies, incorporation of explainable AI techniques, standardized validation practices, and closer alignment with regulatory guidance will be essential for broader industrial adoption.Overall, AI-based prediction of PSD–dissolution relationships represents a promising pathway toward more predictive, efficient, and knowledge-driven pharmaceutical development. Continued integration of machine learning with PAT, continuous manufacturing, and mechanistic modeling approaches is expected to further advance real-time quality prediction and control. As these technologies mature, AI-driven frameworks are poised to play a central role in enabling next-generation pharmaceutical manufacturing under the Pharma 4.0™ paradigm.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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