WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Process Analytical Technology in Pharmaceutical Manufacturing of Oral Solids with Applications of Artificial Neural Networks – A Concise Review

Sanket Ratnaparkhi [a]*, Dr. Pankaj Mandape [a], Chandrakant Wadile [a], Divyanka Bodas [a], Denish Dighore [a]

[a] *Formulation, Research and Development, Micro LabsLimited, Mumbai, Maharashtra*

A B S T R A C T

Industry 4.0 is revolutionizing production by adopting digitalization, automation, and big data, with the objective of achieving interlocked systems, sovereign decision-making, and intelligent factories. Machine learning methodologies, including artificial neural networks (ANN), have surfaced as effective instruments for tackling associated computational challenges. The pharmaceutical industry has also benefited from these improvements, as the Process Analytical Technology (PAT) project has facilitated real-time process analysis and enabled science- and risk-based flexible production. This approach enables quicker and more economical production, simultaneously minimizing waste and thereby reducing the environmental footprint. This article seeks to evaluate the potential of artificial neural networks in the context of process analytical technology to facilitate the modernization of pharmaceutical manufacturing. A systematic evaluation of the current state of artificial neural networks (ANNs) is conducted concerning the predominant production processes of solid pharmaceutical goods, highlighting potential research gaps and future initiatives. This review may facilitate the advancement of machine learning methodologies in therapeutic fabrication and ultimately support the establishment of intelligent manufacturing systems with automated quality assurance.

Keywords: Artificial neural networks, machine learning, process analytical technology, Industry 4.0, Real time release testing

1. Introduction

1.1 Industry Revolutions

Originally unveiled at the 2011 Hannover Fair, Industry 4.0 became officially recognised in 2013 as a German strategic initiative to play a leading role in sectors that are now transforming the manufacturing industry. The contemporary trend of automation technology in the industrialized sector is known as Industry 4.0. Industry 4.0 is the fourth industrial revolution, which combines quickly developing technologies like robotics, artificial intelligence (AI), the internet of things (IoT), and sophisticated computing to fundamentally alter the production landscape. Production systems that are autonomous, self-organizing, and integrated are hallmarks of Industry 4.0. If Industry 4.0 is the future, then Industry 1.0 is the starting point of the modern pharmaceutical industry. Herbal or plant remedies have been used as medicines for as long as civilization has existed. Significant advances in the formulation and processing of materials for medicinal application have only occurred in the past 200 years. Commercial-scale equipment capable of crushing, milling, blending, and pressing greater amounts of medications replaced the manual processing of botanical, mineral, and animal-derived materials in Industry 1.0 (1) During the 19th century, the dye and chemicals business or independent pharmacies were the two main sources of larger-scale medication manufacture using non-electrical power-driven machinery. (2) The pharmaceutical business, which has experienced great expansion over the past century, was established in the 19th century as a result of this shift from laboratory-scale to wholesale drug production. However, several of the earliest devices from the first industrial revolution, such tablet presses and pneumatic mills, are still in widespread use today.

Electricity and early electronic devices, as well as assemblage with preset controls that integrated basic automation and process controls, made it possible for manufacturers to define fundamental process parameters during the second industrial revolution, or Industry 2.0. This showed up in the pharmaceutical manufacturing sector as electronic machine-based crushing, milling, blending, and tablet pressing, which enabled larger-scale production and—most importantly—better process and quality control. Nevertheless, most process controls were restricted to static, pre-established settings that only permitted passive control techniques and process performance monitoring. Innovations in Industry 2.0 directly resulted in devices like contemporary tablet presses that can consistently make more than a million tablets per hour. (3) It is arguable that a large portion of the pharmaceutical manufacturing sector still functions according to the Industry 2.0 paradigm.

The advancement and accessibility of computers and communication expertise, including networked computing, the internet, and wireless infrastructures, made possible the third industrial revolution, or Industry 3.0. Higher levels of process and equipment automation made possible by these technologies

made it possible to implement ideas like active control and continuous manufacturing in the pharmaceutical industry. The development of more complex control strategies and improved process and product quality were made possible by human-computer interfaces. Better tracking of production-related factors and metrics was made possible by remote sensing and monitoring, which also decreased the requirement for human operators on the manufacturing floor. While some businesses have already fully embraced Industry 3.0, the pharmaceutical sector is still mostly in the process of doing so. One method that has been widely used in other industries is continuous manufacturing, which transfers materials created at each stage of the process immediately and constantly to the next stage for additional processing. The pharmaceutical sector has been slower to embrace continuous production for a variety of reasons. (4) Consequently, the pharmaceutical sector has yet to attain consistent six sigma production capacity, which is characterized by less than 3.4 errors per million opportunities and is typical of other industries. (5) Advanced process analytical technology (PAT), which promises to offer process and product quality data in near real time, was introduced to the pharmaceutical manufacturing industry during the third industrial revolution. Model-based or Quality by Design (QbD) procedures, which seek to regulate target product quality profiles within a specified set of quality criteria, were also improved by Industry 3.0. More technological developments are necessary to obtain deeper process knowledge and real-time analytics, which will more broadly enable real-time release testing with high levels of product quality assurance, particularly for biotechnology products, in order to fully realize the potential of PAT and QbD. It is evident that additional effort is required to enhance process control and reliability, as quality problems account for roughly two thirds of medicine shortages. However, Industry 3.0 is making it possible to gain a much better grasp of how to collect, process, and safeguard vast volumes of data related to pharmaceutical manufacture.

Industry 4.0, representing the fourth industrial revolution, integrates advanced developed technologies to facilitate autonomous, self-organizing manufacturing systems that function independently of human intervention. The experience acquired in the automated and digital context of Industry 3.0 facilitates the extensive transition to Industry 4.0 within pharmaceutical manufacturing. While Industry 3.0 focused on the rapid development of individual operations and tools, Industry 4.0 aims to enhance entire manufacturing systems and infrastructures. The progression from basic data collection to digital maturity involves a transformation of data. Initially, raw data is gathered from manufacturing processes. This data is then analyzed to produce information, which is further enhanced into knowledge through contextualization, potentially aided by artificial intelligence. Ultimately, this process culminates in actionable wisdom that informs decision-making through insightful contributions. (Fig. 1) This knowledge underpins autonomous systems and cyber-physical machines, which are governed by computer algorithms and possess capabilities for self-optimization, decision-making, remote operation, and adaptive control.

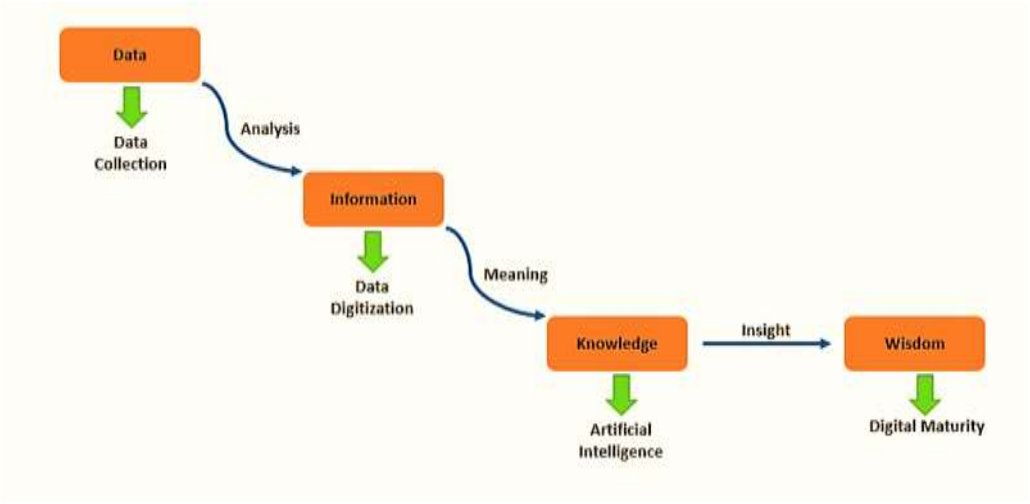


Fig. 1 The stages of data transformation on the path to realizing Industry 4.0.

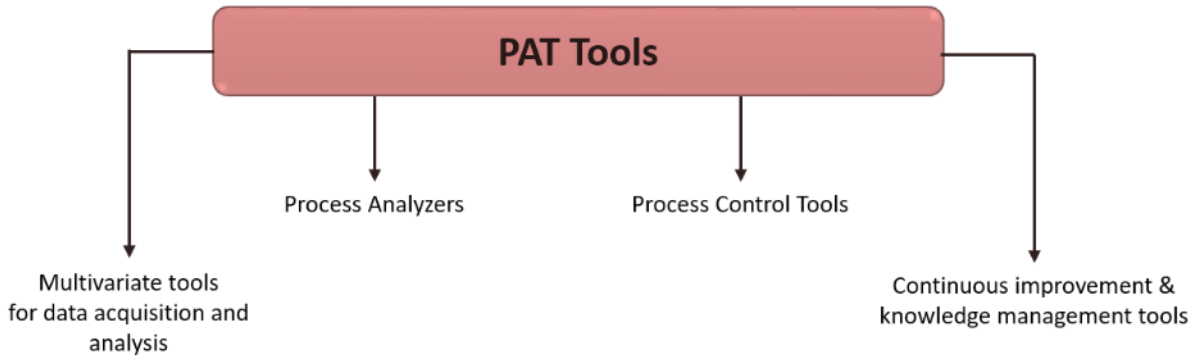
1.2 Process Analytical Technology(PAT) with ANN (6)

The Quality by Design (QbD) and Process Analytical Technology (PAT) frameworks also encourage modernization in the pharmaceutical sector. In order to establish the design space under which the quality is satisfactory, the QbD highlights the importance of understanding the product and process, including critical material attributes and critical process parameters that have a significant impact on the critical quality attributes of the product and process. According to FDA, PAT is considered to be a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality. By highlighting the necessity of real-time dimensions of the CQAs and CPPs using in-process sensors, together with the suitable data analysis techniques and control approach, the PAT project also intends to promote science- and risk-based production.

PAT consists of two parts: a strategy for implementing regulations that will allow for innovation, and a collection of scientific ideas and instruments that encourage innovation.

Designing and creating well-understood procedures that will reliably guarantee a predetermined quality at the conclusion of the manufacturing process is one of the PAT framework's intended objectives. These practices might lower quality and regulatory risks while increasing efficiency, and they would be in line with the fundamental principle of quality by design. A reduction in production cycle times through the use of PAT tools and controls, the prevention

of rejects, scrap, and reprocessing, real-time release testing, and increased automation to improve automation safety and reduce human errors are likely to result in quality, safety, and/or efficiency gains. These gains will vary depending on the process and the final product. PAT tools are used to comprehend processes for quality assurance, manufacturing, and scientific risk-managed pharmaceutical improvement. These tools include the following: (Scheme 1.)



Scheme 1. Process Analytical Technology tools.

a. Multivariate Tools for Design, Data Acquisition and Analysis:

Curative products and processes represent intricate multi-factorial systems from physical, chemical, and biological viewpoints. Numerous development strategies exist for identifying optimal formulations and processes. The knowledge gained from these development programs serves as the basis for product and process design. This awareness base supports and justifies flexible regulatory pathways for innovation in manufacturing and post-approval changes. A understanding base is most beneficial when it encompasses scientific understanding of relevant multi-factorial relationships (e.g., between formulation, process, and quality attributes) and provides a framework for evaluating the applicability of this knowledge across various scenarios (i.e., generalization). The benefit can be attained by employing multivariate mathematical techniques, including statistical design of experiments, response surface methodologies, process simulation, and pattern recognition tools, alongside knowledge management systems. The applicability and consistency of knowledge represented through mathematical relationships and models can be evaluated using statistical assessments of model predictions. Methodological experiments grounded in statistical principles such as orthogonality, reference distribution, and randomization offer effective approaches for identifying and analyzing the effects and interactions of product and process variables. Conventional one-factor-at-a-time experiments fail to consider interactions between product and process variables.

Experiments done during product and process development can serve as building blocks of knowledge, evolving to assist more complexity during the product's lifetime. Data from structured experiments helps to build a knowledge system about a certain product and its related processes. This information, together with data from other development projects, can help to create a complete institutional knowledge base. Data mining allows the discovery of useful patterns for future development projects by means of expanding this institutional knowledge base in terms of variable range and data density. By improving process simulation model creation, experimental databases help to accelerate ongoing learning and lower general development time. Used properly, these techniques help to find and evaluate process and product variables possibly critical for performance and quality. The tools can measure their effects on product quality as well as find possible failure causes and mechanisms.

b. Process Analyzers:

Process analysis has progressed notably in recent decades, driven by a growing recognition of the importance of gathering process data. The industrial factors influencing productivity, quality, and environmental impact have facilitated significant progress in this domain. The evolution of available tools has transitioned from primarily univariate process measurements, including pH, temperature, and pressure, to instruments that assess biological, chemical, and physical attributes. Some process analyzers offer non-destructive measurements that yield information regarding the biological, physical, and chemical characteristics of the materials under processing. These measurements may be:

- At-line: Measurement conducted with the sample extracted, quarantined, and analyzed near the process stream.
- On-line: Measurement conducted by diverting the sample from the manufacturing process, with the possibility of returning it to the process stream.
- In-line: A measurement technique in which the sample remains within the process stream, potentially employing either invasive or non-invasive methods.

The measurements obtained from these process analyzers do not require absolute values of the property in question. The capacity to assess relative variations in materials prior to (e.g., within a lot, between lots, from various suppliers) and during processing would yield valuable insights for process regulation. A flexible process can be developed to handle the variety of the materials during processing. This strategy can be implemented and validated when variations in quality attributes and additional process information are utilized to regulate the process (e.g., feed-forward and/or feedback). The

installation of process analyzers on existing production equipment should occur post-risk analysis to guarantee that it does not negatively impact process or product quality.

c. Process Control Tools

Process monitoring and control techniques aim to observe the condition of a process and actively adjust it to sustain a desired state. Strategies must include the characteristics of input materials, the capability and dependability of process analyzers in measuring important qualities, and the attainment of process endpoints to guarantee the consistent quality of output materials and the final product. The design and optimization of medication formulations and manufacturing processes under the PAT framework may encompass the following steps, although the chronology may vary:

- Recognize and quantify essential material and process characteristics pertinent to product quality.
- Develop a process measurement system to provide real-time or near real-time (e.g., on-, in-, or at-line) monitoring of all relevant qualities.
- Establish process controls that allow for modifications to maintain oversight of all essential features.
- Establish mathematical correlations between product quality characteristics and metrics of essential material and process attributes.

Within the PAT agenda, a development endpoint is not a predetermined period; instead, it signifies the attainment of the desired material attribute. This, however, does not imply that process time is disregarded. A range of permissible process durations (process window) is expected to be attained during the manufacturing phase and should be assessed, with strategies for mitigating substantial deviations from acceptable process durations to be formulated.

Where PAT encompasses the complete manufacturing process, the proportion of in-process components and end products assessed during production may significantly exceed the levels now attained by laboratory testing. Multivariate Statistical Process Control can be effective and advantageous for maximizing the benefits of real-time measurements. Effective judgments must be grounded in comprehension of processes and the forecasting and regulation of pertinent process/product characteristics. This is a method to ensure compliance with the CGMP regulations, namely control methods that validate the efficacy of the manufacturing process (21 CFR 211.110(a)).

d. Continuous Improvement and Knowledge Management

Continuous learning via data acquisition and analysis throughout a product's life cycle is essential. This data can support the justification of proposals for post-approval modifications. Methods and information technology systems that aid in knowledge acquisition from these databases are beneficial for manufacturers and can enhance scientific collaboration with the Agency.

Opportunities must be recognized to enhance the applicability of pertinent product and process knowledge in regulatory decision-making. A knowledge base is most advantageous when it encompasses scientific comprehension of pertinent multifactorial relationships (e.g., between formulation, process, and quality attributes) and provides a method to assess the applicability of this knowledge across various scenarios (i.e., generalization). The current information technology infrastructure renders the construction and maintenance of this knowledge base feasible.

1.3 Artificial Neural Networks(ANN)

Artificial intelligence (AI) is the branch of computer science focused on developing software that can execute complex, intelligent computations like to those performed by the human brain. It encompasses methodologies, instruments, and systems designed to replicate human approaches to logical and inductive information acquisition, as well as cognitive processes for problem-solving. AI advancements can be classified into two primary groups. The first encompasses methods and systems that replicate human experience and derive conclusions from a predetermined set of rules, exemplified as expert systems. The second encompasses systems that simulate brain function, such as artificial neural networks (ANNs). Artificial Neural Networks (ANNs) are digital representations of the human brain, computer algorithms engineered to replicate the information processing mechanisms of the human brain. Artificial Neural Networks acquire knowledge through experiential learning with suitable exemplars, akin to human learning, rather than through programming. Neural networks acquire knowledge by identifying patterns and relationships among data. The brain is an exceptional instrument for pattern identification. Upon observing a pen, we recognize it as such because biological neurons in a specific region of our brain have encountered a comparable input pattern previously and have associated that distinct pattern with the term 'pen'. Our brain comprises billions of linked neurons, enabling us to learn and recognize an almost infinite array of input patterns. (7)

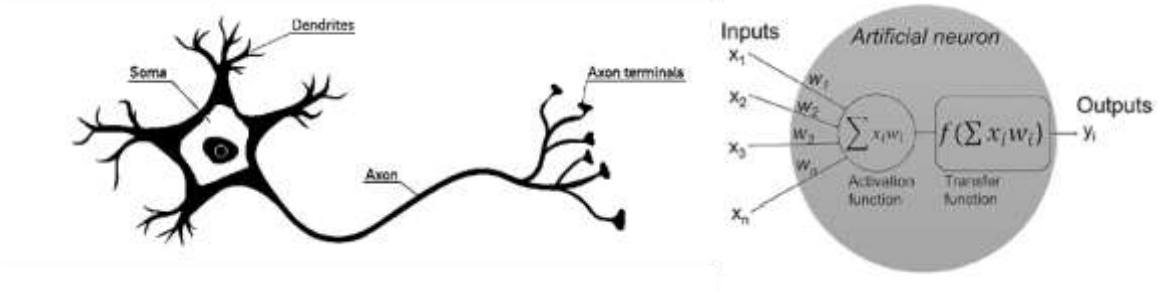


Fig. 2 Human neuron and an artificial neuron.

An artificial neural network is a computational model inspired by biological systems, composed of numerous individual units, known as artificial neurons, interconnected by coefficients (weights) that define the neural architecture. They are also referred to as processing elements (PE) due to their function of processing information. Each processing element possesses weighted inputs, a transfer function, and a singular output. PE is fundamentally an equation that equilibrates inputs and outputs. Artificial Neural Networks (ANNs) are referred to as connectionist models since the connection weights embody the system's memory. Artificial networks, despite their sophistication, remain far inferior to the creative capabilities of the human brain. The human brain is exceedingly intricate, and regrettably, numerous intellectual activities remain poorly understood. Artificial Neural Networks (ANNs) can handle vast quantities of data and generate predictions that are occasionally remarkably precise. This does not render them intelligent in the conventional 'human' sense, so the phrase computer intelligence may more accurately describe these systems. (7)

2. Active Ingredients Developments in Pharmaceutical Manufacturing

2.1 Synthesis

The synthesis of carbon-based compounds is the initial phase in pharmaceutical production for generating the active pharmaceutical ingredient (API). Method monitoring and control can be employed in both uninterrupted and batch operations to sustain a stable state, ascertain endpoints, or optimize operational conditions. Artificial Neural Networks (ANNs) are utilized in optimizing process considerations to enhance reaction outcomes and effectiveness, as well as to characterize non-linear correlations between spectroscopic data and the targeted factors via black-box multivariate modeling. The influence of process factors (i.e., time, temperature, enzyme quantity, molar ratio) on the yield of enzymatic production of betulinic acid ester can be characterized using a feedforward artificial neural network (ANN), utilizing 21 training experiments. Among the learning algorithms compared—quick propagation, incremental backpropagation (BP), batch BP, and the Levenberg-Marquardt algorithm—speedy propagation demonstrated the greatest strength.

Numerous studies have addressed the optimization of synthesis via artificial neural networks (ANNs). Valizadeh et al. utilized a multilayer perceptron (MLP) to improve glucosamine extraction from chitin, considering three variables: acid concentration, acid solution to solid ratio, and reaction duration. The constructed network was evaluated against the outcomes of genetic algorithm (GA) and unit cloud optimization tactics, which exhibited superior model fitting compared to the MLP model; however, the ANN excelled during validation. Deep reinforcement learning, utilizing RNN, was employed to optimize four two-component reactions (12). The method systematically identified the ideal flow rate, voltage, and pressure for the microdroplet reactions, employing fewer iterations than alternative black-box optimization systems. Optimization constructed on artificial neural networks (ANN) could be executed in conjunction with a computational fluid dynamics (CFD) model, which served as the source of training data, maximizing numerous parameters such as conversion, selectivity, and yield in butadiene synthesis. An RNN could substitute a genuine plant model (14) or a state-space model (15) in control algorithms. This may enhance the prediction of process dynamics in a model predictive control (MPC) for continuous pharmaceutical synthesis, as it substantially reduces computational demands relative to mechanistic models. Furthermore, the ANN can significantly benefit from the data-abundant context of PAT-supported manufacturing. While the aforementioned examples indicate that API synthesis could significantly benefit from ANN modeling, the findings primarily rely on historical data rather than PAT data. Several instances in the literature demonstrate the assessment of inline or online PAT measurement utilizing ANNs. Using a multilayer feedforward network with 15 calibration samples, Fourier transform infrared (FT-IR) spectroscopic observations assessed the amounts of glucose and glucuronic acid during a fermentation process. The artificial neural network (ANN) outperformed the conventional partial least squares (PLS) regression. An artificial neural network model based on UV-Vis spectra acquired from an immersion probe concurrently assessed phenol and chlorophenols (17). The spectra for network training were condensed using principal component scores.

2.2 Crystallization

Crystallization is essential in linking API synthesis with formulation processes by yielding solid crystalline API, significantly influencing the end product's yield, purity, manufacturing ability, and bioavailability. PAT sensors, including ATR-IR and UV probes, are utilized to monitor solute concentration, while focused beam reflectance (FBR) and in situ minute measurements, such as particle vision and measuring (PVM), can provide information on crystal size and count. Machine learning can predict the crystallization results based on prospective process data. Velásco-Mejía et al. constructed ANN and GA models with data from 54 industrial batch crystallizations (19). Nine descriptors were employed to model crystal density as the consequence, leading to the identification of the most crucial parameters and, following optimization, a significant enhancement in the product. The design space of a cocrystallization process was examined using 25 experimental runs and four response variables (20). By utilizing operating variables (including temperature, supersaturation, agitation speed, and seeding characteristics) as inputs for the artificial neural network, a more precise prediction of the crystal growth rate can be achieved compared to various non-linear regression methods (21).

Artificial Neural Networks (ANNs) have been employed to extract information from data-intensive Process Analytical Technology (PAT) instruments, such as in-line microscopic pictures. A ResNet CNN has demonstrated efficacy in categorizing crystals identified in PVM images, achieving over 98% accuracy in contamination classification (22). This in-line technique can aid in detecting traces of unwanted polymorphs and, consequently, can be employed in feedback control to enhance product purity. Additionally, the growth rate may be forecasted by assessing the particle size distribution by CNN-based in-line image analysis (23). FBRM measurements yield chord length distribution as particle size data, which, in conjunction with solid concentration, can serve as input for a layer RNN (24) to compute the crystal size distribution (CSD). Szilágyi and Nagy (25) exhibited an alternative methodology: A neural network was able to quickly and directly convert two-dimensional CSD (needle-shaped crystals) to segment dimension

distribution and aspect ratio distribution. This was essential for facilitating the utilization of FBRM and PVM as quantitative direct feedback control instruments inside a population balance model (PBM)-based control framework, given that the results of the PBMs and the analytical sensors are not directly comparable. The proposed method achieved a calculation speed six times faster than direct conversion, which may be critical for real-time applications. Öner et al. (26) emphasized that predominantly historical data were utilized for model building. A completely automated laboratory crystallization system has been constructed in their study, incorporating temperature and FBRM sensors and utilizing an RBF network. The training was conducted in real-time, utilizing a reference batch alongside in-line acquired data and an evolving data strategy. The network was revised as fresh experimental data became available. Notwithstanding the limited data, the control technique demonstrated resilience to many perturbations, such solvent impurity, seed size, or impeller speed. This methodology is relevant even in the absence of extensive historical data or comprehensive process comprehension.

3. Stages in Pharmaceutical Manufacturing

3.1 Blending Process

Due to wear, excessive blending over extended periods of time can alter the particle size and size distribution. These modifications to the intermediate products' characteristics, like assay, content homogeneity, and dissolution, might have a significant impact on the final products' quality. Inspection of the quality attributes, such as particle size, particle-size distribution, and blending consistency, is therefore required throughout the process. Additionally, real-time monitoring should be used in this process to take into account CPPs like blender speed and duration.

The current offline analysis uses sampling and process halting to assess blending homogeneity. Nevertheless, the majority of PAT tools are time-consuming, damaging, and frequently interfere with sampling. Therefore, PAT tools can be utilized in the blending process to manage CPPs through real-time monitoring to ensure CQAs and to nondestructively measure IQAs and process performance in real-time. (6) The accurate implementation of powder mixing essentially guarantees the uniform scattering of components in the production of solid dosage forms. Machine learning approaches have been utilized on several occasions to facilitate the real-time analysis of API concentration during the blending process and to forecast the performance of powders in diverse settings. Since the 2000s, it has been demonstrated that forecasting the API concentration of powders using artificial neural networks (ANNs) based on near-infrared (NIR) spectra is as effective as partial least squares (PLS) regression. Furthermore, artificial neural networks can forecast the necessary duration to attain a uniform combination. Tewari et al. (29) employed NIR spectroscopy, artificial neural networks, and several multivariate data analysis techniques for at-line blending endpoint detection. El-Hagrasy et al. used an InSb imaging camera to track the blending process while installing NIRS probes at six distinct points within a V-blender to test the homogeneity of powder blending. Offline NIRS and UV-VIS measurement data were employed as a reference method, and the blending homogeneity was measured by varying the blending time of the blending process. To acquire correct data, the measured data were preprocessed using SNV, MSC, and second-order differentiation to eliminate linear baseline shifts. (30) Moreover, these strategies may prove beneficial for regulatory purposes in the future. Artificial Neural Networks can also be utilized to analyze data when the impacts of specific variables manifest after a temporal delay. The blend composition exiting the continuous blender may be forecasted by a recurrent neural network, functioning as the digital twin of the blender, utilizing the system's residence time distribution and the mass flow pace of the source material streams (31). Results similar to a residence distribution of time model can be obtained from a non-linear self-correcting network with exogenous inputs.

3.2 Granulation

Granulation is a particle enlargement method that is vital for enhancing process ability and significantly affects the quality of the end product, such as content uniformity and dissolution. Granulation is executed using either wet or dry methods, such as high-shear, fluidized bed, roller compactor systems, or the increasingly prevalent continuous solution of twin-screw wet granulation (TSWG). For over 25 years, ANN models have been developed to forecast product quality based on the process characteristics of fluidized bed (32-35), high-shear wet (36), and dry granulation (37, 38). Meng et al. assessed the size and form changes, physical characteristics, and composition of the granules during twin-screw granulation using NIRS, Raman spectroscopy, and 3D high-speed imaging cameras. Granule characteristics, including size, porosity, density, and flowability, were quantitatively predicted using NIRS, while granule shape and size were tracked in real time using Eyecon 3D imaging. Additionally, the homogeneity of the medication content and the granules' solid-state transition were assessed using Raman spectroscopy. According to this work, the PAT tool can accurately and precisely estimate granule properties under a range of operational situations. (39) Acevedo et al. used NIRS on a roller compactor to track the ribbon density. The PCA model created using the spectrum from in-line monitoring during the roller-compaction process demonstrates that the ribbon's physical change may be identified and qualitatively examined. (40)

Moreover, the scaling of wet and fluid bed granulation processes was also enhanced by artificial neural networks (41–43). Korteby et al. (44) shown that the relative significance of the independent input variables of the ANN model may be ascertained by a fluid hot-melt granulation process in conjunction with the Garson equation. The particle size of the binder was determined to have the most significant influence on the attributes of the finished granules, succeeded by binder viscosity grade and binder content. The ANN integrated the benefits of first-principles and data-driven modeling by elucidating the impact of variables, but its development was considerably simpler than that of a first-principles model. In dry granulation, the granule size distribution post-milling (45), ribbon friability (37), and ribbon density (46) might also be anticipated. Utilizing artificial neural networks (ANN) to model granule quality in continuous granulation was feasible, as evidenced by the calculation of d10, d50, and d90 values based on the liquid-to-solid ratio, screw speed, screw configuration, and material throughput. It has been proposed that ANN models may be utilized for the MPC of the process. Moreover, artificial

neural networks (ANNs) can be amalgamated with additional data processing methodologies, such as Kriging or finite volume schemes, to formulate hybrid models that optimally merge the advantages of both approaches. Consequently, ANNs can also be included into more intricate systems. The adaptability of artificial neural networks enables efficient processing of many signal types. For example, thermocouples may also function as Process Analytical Technology (PAT) instruments. Reddy et al. employed online monitoring to regulate the intermediate product's temperature, wetness, and moisture content using Raman spectroscopy. PLS was used as a multivariate tool to create a calibration model. Consequently, it was established that the intricacy of altering particle shape based on the CPP influences medication solubility throughout processing. This suggests that wet granule monitoring is a crucial component of the clinical stage, and that utilizing a PAT instrument to regulate it is an effective quality-control technique. (51) Huang et al. used the FBRM C35 in a high-shear granulator to measure the size and quantity of particles in real-time utilizing an inline monitoring method. (52)

3.3 Compression and Coating

In the majority of pharmaceutical production procedures, tableting produces the discrete units of the final product. It is imperative that every tablet administered to the patient adheres to stringent quality standards. The emergence of predictive modeling and PAT technologies significantly aids in accomplishing this objective. One of the initial considerations in formulating a tableting process is the behavior of the compressed powder combination within the tablet press. The blend's flowability must be sufficiently high to ensure that each time the die is filled, a nearly similar mass of powder is transferred into it. Wahl et al. used an NIRS probe installed on the tableting press's powder-feed frame to examine the homogeneity of the powder content. To accurately forecast the composition of the powder, they employed the DoE. Additionally, they used a UV-VIS light spectrometer to measure the standard of drug content. The UV-VIS and in-line NIRS measurements were found to be in agreement. To look for significant process abnormalities, like as elevated drug content in the powder, the authors ran a PCA of the spectrum. (53) Critical material attributes (CMAs), including the type and particle size of diluent, the kind of glidant, bulk density, Carr’s compressibility index, and parameters of Kawakita’s equation (54–56), were employed using various machine learning algorithms based on the outcomes of a design of experiments (DoE) comprising 30–50 configurations.

Capping, defined as the impulsive detachment of the tablet's upper layers, signifies a noteworthy quality issue in subsequent handling (e.g., film coat and packing) and must be prevented. Belič et al. (57) forecasted the capping propensity using neural networks and incoherent logic, considering the particle size of the tableted powder and the parameters of the tablet press. They determined that the procedure enhances making improvement markedly more than conventional trial and error methods. During the development of a dosage form, extensive datasets are generated that facilitate the establishment of design spaces within the Quality by Design (QbD) framework through the application of appropriate mathematical techniques. Zawbaa et al. (58) employed a hybrid approach integrating artificial neural networks with variable selection algorithms to identify the manufacturing parameters that most significantly affect the porosity and tensile strength of tablets. The variable selection results revealed that compaction pressure was the predominant influence. These investigations demonstrated that artificial neural networks (ANNs) are effective in delineating the design space and forecasting the process ability of the powder and the quality of the tablets based on critical material attributes (CMAs); however, the tableting phase remains deficient in implementations of PAT-based ANN models. The Critical Quality Attributes (CQA) of the final tablets are affected by both the tableting process and the preceding manufacturing procedures, as well as the characteristics of the raw ingredients.

4. Characterization of Final Product

4.1 Content Uniformity and Assay

The content uniformity (CU) of final products or intermediates is an often examined critical quality attribute (CQA) that must adhere to specific restrictions. Spectroscopic PAT instruments are extensively employed to quantify the active pharmaceutical ingredient content in solid dosage forms to achieve these objectives. Even so, linear quantifiable approaches are not always applicable for assessing multivariate data. In such instances, artificial neural networks may offer a means to achieve a validated calibration approach. Habitually, UV-Vis spectroscopy is employed to analyze assays, and artificial neural networks (ANNs) have been utilized multiple times to enhance the quantification of various active pharmaceutical ingredients (APIs), even in trace levels. Nonetheless, it is a detrimental practice that is incompatible with the PAT principle. Conversely, vibrational spectroscopy, such as Raman and NIR spectroscopy, serves as a valuable in-line, non-destructive technique for the categorization of solid samples. Only one study has been identified that quantifies the active pharmaceutical ingredient (API) using Raman spectroscopy and artificial neural networks (ANN), which examined commercial tablets and capsules comprising diclofenac sodium. PLS, principal component regression (PCR), and counter-propagation artificial neural networks (CP-ANN) approaches were examined, with the latter integrating unsupervised and supervised learning. Although PCR generally produced greater mistakes, PLS and CP-ANN demonstrated equivalent outcomes for both tablets and capsules. A relative standard error of validation of 2.6–3.5% for tablets and 1.4–1.7% for capsules was achieved, demonstrating a strong connection with reference data for saleable formulations. NIR spectroscopy is a more prevalent approach, although the significant overlap among the signals of the components. Numerous APIs have been analyzed by ANNs, including paracetamol, caffeine, ciprofloxacin, aspirin, and phenacetin (27, 63, 64).

It can be concluded that for the measurement of API concentration in solid samples, artificial neural networks significantly enhanced outcomes compared to linear multivariate approaches, such as partial least squares regression, using an equivalent number of calibration samples. An additional prospective application of artificial neural networks (ANN) could involve forecasting analyte quantities from process data, independent of spectroscopic measurements, thereby actualizing the Real-Time Release Testing (RTRT) idea. For instance, the quantity of ascorbic acid in nutraceutical goods could be estimated based on physicochemical parameters, including pH, specific gravity, and viscosity (65). The artificial neural network, functioning as the soft sensor, yielded a regression coefficient of 0.92 for quantification.

4.2 Tensile Strength and Friability

The suitable resistance is a critical quality attribute (CQA) of the tablets, influencing subsequent processes such as coating and packaging, and is primarily defined by tensile strength (TS) or friability (FR). Nonetheless, these features are not readily quantifiable using existing PAT methods. Efforts have been undertaken to monitor the TS via NIR spectroscopy, wherein alterations in the baseline may correspond with tablet hardness, thus facilitating the development of a real-time approach (66, 67). The ideal WT-ANN architecture was developed, resulting in a satisfactory approximation of tablet hardness that surpassed the exactitude of the linear PLS regression model.

In a different study (68), PLS and ANN evaluated theophylline tablet resistance similarly at the lowest set point, while ANN performed better for tougher tablets. Modeling the TS and FR in accordance with their CMAs and CPPs is an alternate strategy. In order to forecast TS and FR as outputs, Bourquin (69) showed an ANN network that used the weight ratio of four ingredients, dwell time, and compression force as inputs. While the ANN model showed a low correlation for friability (R^2=0.413), the expected TS showed a significant parallel with the observed values (R^2=0.753). There is a clear tendency toward overfitting, which could have been lessened by using a larger training dataset. The impact of the kind and amount of lubricant (magnesium stearate, sodium stearyl fumarate) and filler (microcrystalline cellulose, HPMC, crospovidone/PVP) in combination with several active medicinal substances was examined using an ensemble artificial neural network. Within the range of 30 to 60 N, the crushing strength was predicted in (71) with an error of less than 0.1 N. Neural networks may also incorporate information on tablet properties and tableting processes, such as tablet compression rate, diameter, weight, height, porosity, radial sound velocity, and compression force (72). Six different machine learning algorithms, including four artificial neural network techniques, were used in (73) to predict the tablets' tensile strength, total compression work, detachment work, and expulsion work by varying the polymer kinds and concentrations.

4.3 In Vitro Dissolution

In vitro dissolution testing serves as a critical measure of product quality, knowingly contributing to the research, development, and routine quality control of drug products. The tests must be conducted using standardized instruments and involve labor-intensive and time-consuming methods. Thus, an RTRT approach, which has also been examined in relation to ANNs, could provide significant advantages. Most studies on artificial neural networks related to dissolution prediction primarily focus on optimizing formulations to achieve the desired dissolution properties. In this context, various ANN structures, including MLP, Elman networks, and RNNs, have demonstrated applicability. Furthermore, a number of process variables, including the effect of retarded polymer in tablets, tableting force of compression, and crushing strength, have been modeled. When the impact of CMAs/CPPs on dissolution is seen in the PAT data, PAT tools can be used to forecast dissolution. PLS regression analysis of NIR spectra predicted dissolution, highlighting the importance of tablet composition, moisture content, compression strength, and mixing shear forces. Pawar et al. used at-line NIR spectroscopy in a continuous direct compression process in which the dissolution was simultaneously impacted by the API content, compression rate, feed frame speed, and blender speed (82). The capacity of Raman chemical maps to non-destructively forecast dissolution has been demonstrated recently (84). The chemical map makes it possible to determine the components' geographical distribution and CSD in addition to the tablets' chemical makeup. However, the speed of the chemical mapping needs to be further decreased in order to use it as a PAT technique.

The application of a single PAT tool may not consistently suffice. Artificial Neural Networks (ANNs) facilitate the integration of diverse Process Analytical Technology (PAT) sources and enable data processing for a stand-in dissolution model. Our group was the first to demonstrate the integration of Raman and NIR spectra for an extended-release tablet formulation using an artificial neural network. The data-fused ANN models demonstrated superior performance compared to both the PLS modeling results and the models developed using only a single PAT sensor (85). Artificial Neural Networks (ANNs) can be developed utilizing not only spectroscopic data but also incorporating supplementary process data within the ANN, such as the recorded compression force and CSD data. Additionally, support vector machines and an ensemble of regression trees were evaluated; however, artificial neural networks yielded the highest accuracy. The concept can be extended to accommodate various numbers and types of input data, potentially enhancing the carrying out of projecting dissolution models within an RTRT framework.

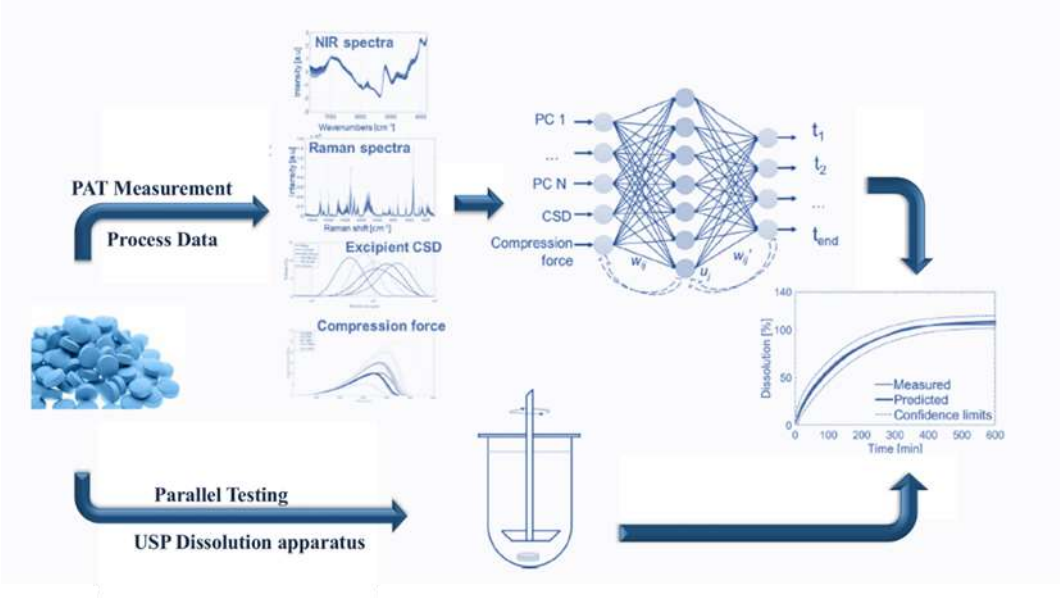


Fig. 3 Neural network-based prediction of in vitro dissolution utilizing PAT data

5. Digital Transformation

Upon reviewing the current applications of artificial neural networks in pharmaceutical manufacturing processes, two primary categories of research can be identified. The application of artificial neural networks (ANNs) first is for non-linear relapse in the assessment of analytical sensor data and other to establish a relationship between arbitrary inputs and results parameters. Table 1. presents a summary of the studies in which the developed models utilized PAT data or where the input was directly obtainable during a process.

Table 1. Application of Neural Networks for (Potential) PAT purposes in some process steps of pharmaceutical manufacturing

Studied process/product	PAT data used in ANN	Dataset	ANN Type	Predicted Output	Ref.
API synthesis					
Glucose fermentation	FT IR	15 Samples	FF-BP	Glucose and glucoronic acid conc.	(16)
Oxidative coupling of phenols	UV-Vis	16 Samples	PC ANN	Kinetic rate constants and reaction order	(88)
Crystallization	Conc., Temp.	Simulation data from PBM	FF-BP	Future process response, temp. profile optimization	(89)
Batch crystallization					
Powder Blending	Near IR	32 Calibration samples	FF-BP	Paracetamol, diphenhydramine conc. prediction	(27)
Compound powdered drug					
Phenoxymethylpenicillin powder	Near IR	66 Calibration samples	FF-BP	API Content Prediction	(28)
Granulation	Microwave spectroscopy, Near IR	Compacted ribbon samples, various settings	FF-BP	Prediction of granule density, moisture content, API content	(90)
Acetaminophen MCC blend roller compaction					
Dry granulation of MCC Mannitol mixture	Compaction force, roll speed	161 experiments	FF-BP	Prediction of granule density	(45)

Compression coating **Tablet compression**	Compression force	Tablets produced with 209 settings	FF-BP with optimization	Prediction of tablet porosity and tensile strength	(58)

According to the Pharma 4.0 idea, digitalization is expected to grow significantly over the next several years since it can improve manufacturing's clarity, litheness, proficiency, output, and quality (91). According to the authors of (92) from Novartis Global Drug Development, a pioneer in the digitization of pharmaceuticals, historical operational data could be a useful tool for assessing the company's capacity. At the moment, accessing this data takes a long time and is unreliable and fragmented. Digitalization platforms, exemplified by Novartis's "Nerve Live" platform, can facilitate the collection, cleaning, and analysis of valuable data. Centralized and accessible databases (data lakes) can be established to compile raw materials' attributes, process parameters for each unit operation, and various PAT measurements relevant to the manufacturing process, as depicted in Fig. 4.

Digitalization presents various challenges for pharmaceutical companies and initiates changes across business, operational, and technological dimensions (93). The role of data scientists and information technology (IT) personnel is increasingly important as new competencies and resources become necessary. It is essential to establish cross-functional teams, address cybersecurity concerns, and prioritize standardization for long-term compatibility (91). Several chapters in the handbook address the digital transformation of laboratories, including analytical, research, and solid-state labs, offering a foundational knowledge base on central concepts and practical implementation guidance. Information management tools such as the Electronic Laboratory Notebook (ELN), Laboratory Information Management System (LIMS), and Enterprise Resource Planning (ERP) are introduced. Additionally, principles of cybersecurity, communication protocols, data and modeling technologies, reporting, and the creation of FAIR (findable, accessible, interoperable, reusable) data are examined.(94, 95)

Many of these concepts can also be applied to the operations of laboratories and manufacturing facilities within pharmaceutical companies. Siemens's commercially available cloud-based open IoT operating system, MindSphere (93), and Novartis's "Nerve Live" platform (92) are examples of this IT system's industrial implementation. MindSphere unites disparate devices within a cloud platform, integrates several data sources and information management tools, and guarantees the best possible data protection and storage—all of which are critical for pharmaceutical businesses.

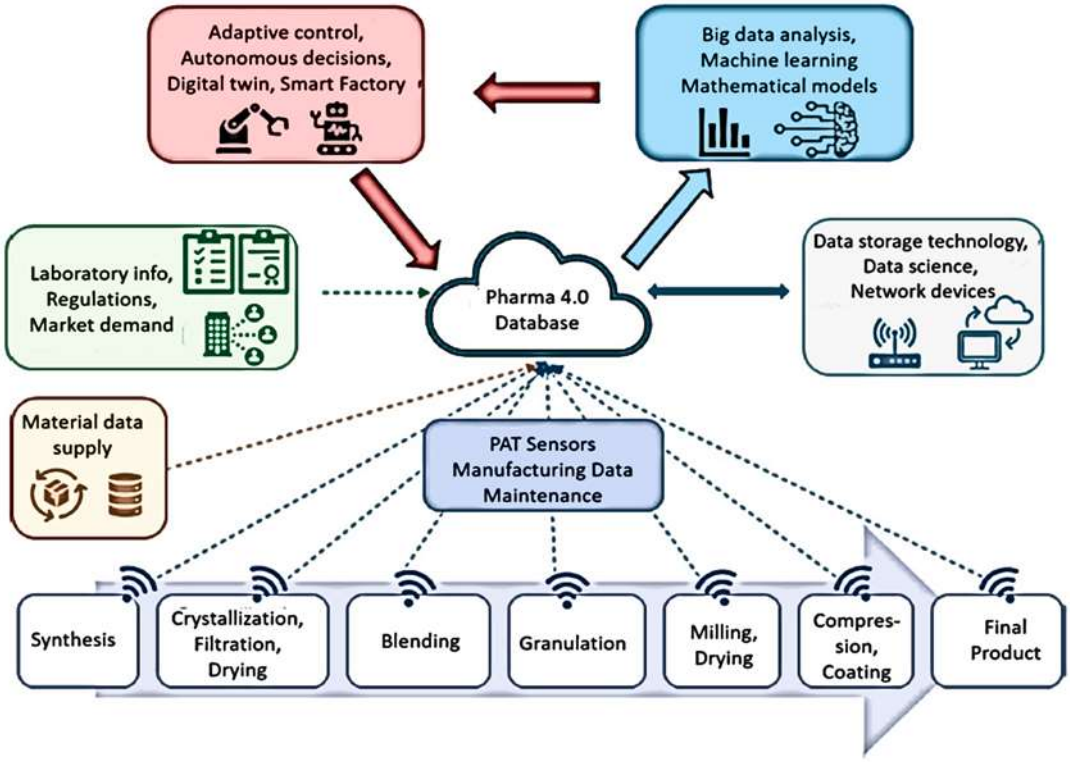


Fig. 4 Digitization in context of Artificial intelligence models for PAT in the Pharma 4.0

The use of artificial neural networks (ANN) with real-time pharmaceutical production data and integrating several process phases is still limited, according to published research articles. Pharmaceutical corporations can gain a substantial competitive edge by putting such platforms into place, which could make it more difficult to publish these findings. Furthermore, the widespread adoption of autonomous smart manufacturing and digital transformation depends on both academic and industrial research. The importance of time-series neural networks, which could be examined in more detail, and the adaptation and real-time training capabilities of neural networks for continuously growing data also require more research. Furthermore, the scientific and chemical understanding of the research, development, and manufacturing processes of therapeutic products must not be replaced or compromised by an AI black-box model. This can be achieved, for example, by using hybrid mathematical models to integrate physical-chemical process knowledge into the automated platform.

6. Conclusion

Machine learning techniques, including artificial neural networks, have become crucial data analysis tools for processing large datasets and implementing Industry 4.0 concepts. This paper aims to evaluate the preparedness of pharmaceutical manufacturing by reviewing the application of artificial neural networks (ANNs) in the context of process analytical technology (PAT). In conclusion, artificial neural networks (ANNs) have been evaluated for various functions in prevalent manufacturing processes; however, their application in real-time process analytical technology (PAT) remains limited. Future directions and research gaps have been identified. Thus, artificial neural networks may play a crucial role in the development of smart, autonomous pharmaceutical manufacturing systems in the future. This approach facilitates faster and more cost-effective production while reducing waste, thereby lessening the environmental impact. Additionally, automated systems can decrease human exposure to hazardous processes or substances, such as hormones or cytostatics. The implementation of advanced manufacturing technologies associated with Industry 4.0 presents challenges to the existing regulatory framework, as most regulations were established within the context of Industry 2.0 and traditional batch manufacturing practices. The U.S. FDA has initiated a process to identify and implement necessary modifications in the regulatory framework to facilitate the adoption of new technologies. New policy and regulatory topics associated with Industry 4.0 encompass the management of data-intensive environments, the developing concepts of process validation for advanced manufacturing systems, and the regulatory oversight of post-approval changes for these systems. International regulatory convergence will be useful in encouraging industry adoption of new manufacturing technologies.

REFERENCES

1. Anderson S, editor. Making medicines: a brief history of pharmacy and pharmaceuticals. Pharmaceutical Press; 2005.
2. Kremers E, Sonnedecker G, Urdang G. Kremers and Urdang's History of pharmacy. Amer. Inst. History of Pharmacy; 1986.
3. Swarbrick J. Pharmaceutical process validation. Nash RA, Wachter AH, editors. New York, NY: Marcel Dekker; 2003 May.
4. Lee SL, O'Connor TF, Yang X, Cruz CN, Chatterjee S, Madurawe RD, Moore CM, Yu LX, Woodcock J. Modernizing pharmaceutical manufacturing: from batch to continuous production. Journal of Pharmaceutical Innovation. 2015 Sep;10:191-9.
5. Lawrence XY, Kopcha M. The future of pharmaceutical quality and the path to get there. International journal of pharmaceutics. 2017 Aug 7;528(1-2):354-9.
6. FDA. U.S. Department of Health and Human Services, Food and Drug Administration. Guidance for Industry: PAT – a framework for innovative pharmaceutical development, manufacturing, and quality assurance. 2004.
7. Agatonovic-Kustrin S, Beresford R. Basic concepts of artificial neural network (ANN) modeling and its application in pharmaceutical research. Journal of pharmaceutical and biomedical analysis. 2000 Jun 1;22(5):717-27.
8. Zupan J, Novič M, Li X, Gasteiger J. Classification of multicomponent analytical data of olive oils using different neural networks. Analytica Chimica Acta. 1994 Jul 11;292(3):219-34.
9. Zurada J. Introduction to artificial neural systems. West Publishing Co.; 1992 Jan 1.
10. Moghaddam MG, Ahmad FB, Basri M, Rahman MB. Artificial neural network modeling studies to predict the yield of enzymatic synthesis of betulinic acid ester. Electronic Journal of Biotechnology. 2010 May;13(3):3-4.
11. Valizadeh H, Pourmahmood M, Mojarrad JS, Nemati M, Zakeri-Milani P. Application of artificial intelligent tools to modeling of glucosamine preparation from exoskeleton of shrimp. Drug development and industrial pharmacy. 2009 Apr 1;35(4):396-407.
12. Zhou Z, Li X, Zare RN. Optimizing chemical reactions with deep reinforcement learning. ACS central science. 2017 Dec 27;3(12):1337-44.
13. Gbadago DQ, Moon J, Kim M, Hwang S. A unified framework for the mathematical modelling, predictive analysis, and optimization of reaction systems using computational fluid dynamics, deep neural network and genetic algorithm: A case of butadiene synthesis. Chemical Engineering Journal. 2021 Apr 1;409:128163.
14. Wong WC, Chee E, Li J, Wang X. Recurrent neural network-based model predictive control for continuous pharmaceutical manufacturing. Mathematics. 2018 Nov 7;6(11):242.
15. Baranilingesan I. Optimization algorithm-based Elman neural network controller for continuous stirred tank reactor process model. Current Science. 2021 Apr 25;120(8):1324-33.
16. Franco VG, Perín JC, Mantovani VE, Goicoechea HC. Monitoring substrate and products in a bioprocess with FTIR spectroscopy coupled to artificial neural networks enhanced with a genetic-algorithm-based method for wavelength selection. Talanta. 2006 Jan 15;68(3):1005-12.
17. Hasani M, Moloudi M. Application of principal component-artificial neural network models for simultaneous determination of phenolic compounds by a kinetic spectrophotometric method. Journal of hazardous materials. 2008 Aug 30;157(1):161-9.
18. Gao Y, Zhang T, Ma Y, Xue F, Gao Z, Hou B, Gong J. Application of PAT-based feedback control approaches in pharmaceutical crystallization. Crystals. 2021 Feb 24;11(3):221.

19. Velásco-Mejía A, Vallejo-Becerra V, Chávez-Ramírez AU, Torres-González J, Reyes-Vidal Y, Castañeda-Zaldivar F. Modeling and optimization of a pharmaceutical crystallization process by using neural networks and genetic algorithms. Powder Technology. 2016 May 1;292:122-8.

20. Shaikh R, Shirazian S, Walker GM. Application of artificial neural network for prediction of particle size in pharmaceutical cocrystallization using mechanochemical synthesis. Neural Computing and Applications. 2021 Oct;33:12621-40.

21. Vasanth Kumar K, Martins P, Rocha F. Modelling of the batch sucrose crystallization kinetics using artificial neural networks: comparison with conventional regression analysis. Industrial & engineering chemistry research. 2008 Jul 16;47(14):4917-23.

22. Salami H, McDonald MA, Bommarius AS, Rousseau RW, Grover MA. In situ imaging combined with deep learning for crystallization process monitoring: application to cephalexin production. Organic process research & development. 2021 Jul 1;25(7):1670-9.

23. Chen S, Liu T, Xu D, Huo Y, Yang Y. Image based measurement of population growth rate for l-glutamic acid crystallization. In2019 Chinese Control Conference (CCC) 2019 Jul 27 (pp. 7933-7938). IEEE.

24. Crestani CE, Bernardo A, Costa CB, Giulietti M. An artificial neural network model applied to convert sucrose chord length distributions into particle size distributions. Powder Technology. 2021 May 1;384:186-94.

25. Szilagyi B, Nagy ZK. Aspect ratio distribution and chord length distribution driven modeling of crystallization of two-dimensional crystals for real-time model-based applications. Crystal Growth & Design. 2018 Jul 23;18(9):5311-21.

26. Öner M, Montes FC, Ståhlberg T, Stocks SM, Bajtner JE, Sin G. Comprehensive evaluation of a data driven control strategy: Experimental application to a pharmaceutical crystallization process. Chemical Engineering Research and Design. 2020 Nov 1;163:248-61.

27. Dou Y, Sun Y, Ren Y, Ren Y. Artificial neural network for simultaneous determination of two components of compound paracetamol and diphenhydramine hydrochloride powder on NIR spectroscopy. Analytica Chimica Acta. 2005 Jan 3;528(1):55-61.

28. Wang B, Liu G, Liu S, Fei Q, Ren Y. Orthogonal projection to latent structures combined with artificial neural network for quantitative analysis of phenoxymethylpenicillin potassium powder. Vibrational Spectroscopy. 2009 Nov 10;51(2):199-204.

29. Tewari J, Strong R, Boulas P. At-line determination of pharmaceuticals small molecule's blending end point using chemometric modeling combined with Fourier transform near infrared spectroscopy. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy. 2017 Feb 15;173:886-91.

30. Davies T. The history of near infrared spectroscopic analysis: Past, present and future" From sleeping technique to the morning star of spectroscopy". Analusis. 1998 May 1;26(4):17-9.

31. Beke ÁK, Gyürkés M, Nagy ZK, Marosi G, Farkas A. Digital twin of low dosage continuous powder blending–Artificial neural networks and residence time distribution models. European journal of pharmaceutics and biopharmaceutics. 2021 Dec 1;169:64-77.

32. Petrović J, Chansanroj K, Meier B, Ibrić S, Betz G. Analysis of fluidized bed granulation process using conventional and novel modeling techniques. European journal of pharmaceutical sciences. 2011 Oct 9;44(3):227-34.

33. Behzadi SS, Klocker J, Hüttlin H, Wolschann P, Viernstein H. Validation of fluid bed granulation utilizing artificial neural network. International journal of pharmaceutics. 2005 Mar 3;291(1-2):139-48.

34. Murtoniemi E, Yliruusi J, Kinnunen P, Merkku P, Leiviskä K. The advantages by the use of neural networks in modelling the fluidized bed granulation process. International journal of pharmaceutics. 1994 Aug 1;108(2):155-64.

35. Behzadi SS, Prakasvudhisarn C, Klocker J, Wolschann P, Viernstein H. Comparison between two types of artificial neural networks used for validation of pharmaceutical processes. Powder Technology. 2009 Oct 25;195(2):150-7.

36. Sampat C, Ramachandran R. Identification of granule growth regimes in high shear wet granulation processes using a physics-constrained neural network. Processes. 2021 Apr 22;9(5):737.

37. Inghelbrecht S, Remon JP, De Aguiar PF, Walczak B, Massart D, Van De Velde F, De Baets P, Vermeersch H, De Backer P. Instrumentation of a roll compactor and the evaluation of the parameter settings by neural networks. International journal of pharmaceutics. 1997 Mar 14;148(1):103-15.

38. Turkoglu M, Aydin I, Murray M, Sakr A. Modeling of a roller-compaction process using neural networks and genetic algorithms. European journal of pharmaceutics and biopharmaceutics. 1999 Nov 1;48(3):239-45.

39. Meng W, Román-Ospino AD, Panikar SS, O'Callaghan C, Gilliam SJ, Ramachandran R, Muzzio FJ. Advanced process design and understanding of continuous twin-screw granulation via implementation of in-line process analytical technologies. Advanced Powder Technology. 2019 Apr 1;30(4):879-94.

40. Acevedo D, Muliadi A, Giridhar A, Litster JD, Romañach RJ. Evaluation of three approaches for real-time monitoring of roller compaction with near-infrared spectroscopy. Aaps Pharmscitech. 2012 Sep;13:1005-12.

41. Watano S, Sato Y, Miyanami K. Application of a neural network to granulation scale-up. Powder technology. 1997 Feb 1;90(2):153-9.

42. Millen N, Kovačević A, Khera L, Djuriš J, Ibric S. Machine learning modelling of wet granulation scale-up using compressibility, compactibility and manufacturability parameters. HEMIJSKA INDUSTRIJA (Chemical Industry). 2019 Jul 12;73(3):155-68.

43. Landin M. Artificial intelligence tools for scaling up of high shear wet granulation process. Journal of Pharmaceutical Sciences. 2017 Jan 1;106(1):273-7.

44. Korteby Y, Kristó K, Sovány T, Regdon Jr G. Use of machine learning tool to elucidate and characterize the growth mechanism of an in-situ fluid bed melt granulation. Powder Technology. 2018 May 15;331:286-95.

45. Kazemi P, Khalid MH, Pérez Gago A, Kleinebudde P, Jachowicz R, Szlęk J, Mendyk A. Effect of roll compaction on granule size distribution of microcrystalline cellulose–mannitol mixtures: computational intelligence modeling and parametric analysis. Drug Design, Development and Therapy. 2017 Jan 18:241-51.

46. Sajjia M, Shirazian S, Kelly CB, Albadarin AB, Walker G. ANN analysis of a roller compaction process in the pharmaceutical industry. Chemical Engineering & Technology. 2017 Mar;40(3):487-92.

47. Shirazian S, Kuhs M, Darwish S, Croker D, Walker GM. Artificial neural network modelling of continuous wet granulation using a twin-screw extruder. International journal of pharmaceutics. 2017 Apr 15;521(1-2):102-9.

48. Roggo Y, Jelsch M, Heger P, Ensslin S, Krumme M. Deep learning for continuous manufacturing of pharmaceutical solid dosage form. European journal of Pharmaceutics and biopharmaceutics. 2020 Aug 1;153:95-105.

49. Ismail HY, Singh M, Darwish S, Kuhs M, Shirazian S, Croker DM, Khraisheh M, Albadarin AB, Walker GM. Developing ANN-Kriging hybrid model based on process parameters for prediction of mean residence time distribution in twin-screw wet granulation. Powder Technology. 2019 Feb 1;343:568-77.

50. Ismail HY, Singh M, Shirazian S, Albadarin AB, Walker GM. Development of high-performance hybrid ann-finite volume scheme (ann-fvs) for simulation of pharmaceutical continuous granulation. Chemical Engineering Research and Design. 2020 Nov 1;163:320-6.

51. Reddy JP, Jones JW, Wray PS, Dennis AB, Brown J, Timmins P. Monitoring of multiple solvent induced form changes during high shear wet granulation and drying processes using online Raman spectroscopy. International Journal of Pharmaceutics. 2018 Apr 25;541(1-2):253-60.

52. Huang J, Kaul G, Utz J, Hernandez P, Wong V, Bradley D, Nagi A, O'Grady D. A PAT approach to improve process understanding of high shear wet granulation through in-line particle measurement using FBRM C35. Journal of pharmaceutical sciences. 2010 Jul;99(7):3205-12.Kachrimanis K, Karamyan V, Malamataris S. Artificial neural networks (ANNs) and modeling of powder flow. International journal of pharmaceutics. 2003 Jan 2;250(1):13-23.

53. Wahl PR, Fruhmann G, Sacher S, Straka G, Sowinski S, Khinast JG. PAT for tableting: Inline monitoring of API and excipients via NIR spectroscopy. European journal of pharmaceutics and biopharmaceutics. 2014 Jul 1;87(2):271-8.

54. Khalid GM, Usman AG. Application of data-intelligence algorithms for modeling the compaction performance of new pharmaceutical excipients. Future Journal of Pharmaceutical Sciences. 2021 Dec;7:1-1.

55. Lou H, Chung JI, Kiang YH, Xiao LY, Hageman MJ. The application of machine learning algorithms in understanding the effect of core/shell technique on improving powder compactability. International Journal of Pharmaceutics. 2019 Jan 30;555:368-79.

56. Belič A, Škrjanc I, Božič DZ, Karba R, Vrečer F. Minimisation of the capping tendency by tableting process optimisation with the application of artificial neural networks and fuzzy models. European Journal of Pharmaceutics and Biopharmaceutics. 2009 Sep 1;73(1):172-8.

57. Zawbaa HM, Schiano S, Perez-Gandarillas L, Grosan C, Michrafy A, Wu CY. Computational intelligence modelling of pharmaceutical tabletting processes using bio-inspired optimization algorithms. Advanced Powder Technology. 2018 Dec 1;29(12):2966-77.

58. Goicoechea HC, Collado MS, Satuf ML, Olivieri AC. Complementary use of partial least-squares and artificial neural networks for the non-linear spectrophotometric analysis of pharmaceutical samples. Analytical and bioanalytical chemistry. 2002 Oct;374:460-5.

59. Naguib IA, Darwish HW. Support vector regression and artificial neural network models for stability indicating analysis of mebeverine hydrochloride and sulpiride mixtures in pharmaceutical preparation: A comparative study. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy. 2012 Feb 1;86:515-26.

60. Hasanjani HR, Sohrabi MR. Artificial neural networks (ANN) for the simultaneous spectrophotometric determination of fluoxetine and sertraline in pharmaceutical formulations and biological fluid. Iranian journal of pharmaceutical research: IJPR. 2017;16(2):478.

61. Mazurek S, Szostak R. Quantitative determination of diclofenac sodium in solid dosage forms by FT-Raman spectroscopy. Journal of pharmaceutical and biomedical analysis. 2008 Nov 4;48(3):814-21.

62. Zhao LZ, Guo Y, Dou Y, Wang B, Mi H, Ren YL. Application of artificial neural networks to the nondestructive determination of ciprofloxacin hydrochloride in powder by short-wavelength NIR spectroscopy. Journal of Analytical Chemistry. 2007 Dec;62:1156-62.

63. Dou Y, Qu N, Wang B, Chi YZ, Ren YL. Simultaneous determination of two active components in compound aspirin tablets using principal component artificial neural networks (PC-ANNs) on NIR spectroscopy. European journal of pharmaceutical sciences. 2007 Nov 1;32(3):193-9.

64. Felipe MA, Baldovino R. Real Time Release Approach: At-Line Prediction of Ascorbic Acid Concentration in Nutraceutical Syrup via Artificial Neural Network. InInnovations in Smart Cities Applications Volume 4: The Proceedings of the 5th International Conference on Smart City Applications 2021 (pp. 770-781). Springer International Publishing.

65. Wu J, Luo W, Wang X, Sun C, Li H. A new application of WT-ANN method to control the preparation process of metformin hydrochloride tablets by near infrared spectroscopy compared to PLS. Journal of Pharmaceutical and Biomedical Analysis. 2013 Jun 1;80:186-91.

66. Luo W, Liu Y, Peng F, Li S, Li H. Enhanced characterization of naproxen formulation by near infrared spectroscopy. Analytical Letters. 2014 Sep 22;47(14):2384-93.

67. Chen Y, Thosar SS, Forbess RA, Kemper MS, Rubinovitz RL, Shukla AJ. Prediction of drug content and hardness of intact tablets using artificial neural network and near-infrared spectroscopy. Drug development and industrial pharmacy. 2001 Jan 1;27(7):623-31.

68. Bourquin J, Schmidli H, van Hoogevest P, Leuenberger H. Comparison of artificial neural networks (ANN) with classical modelling techniques using different experimental designs and data from a galenical study on a solid dosage form. European journal of pharmaceutical sciences. 1998 Oct 1;6(4):287-300.

69. Takagaki K, Arai H, Takayama K. Creation of a tablet database containing several active ingredients and prediction of their pharmaceutical characteristics based on ensemble artificial neural networks. Journal of pharmaceutical sciences. 2010 Oct 1;99(10):4201-14.

70. Aksu B, Matas MD, Cevher E, Özsoy Y, Güneri T, York P. Quality by design approach for tablet formulations containing spray coated ramipril by using artificial intelligence techniques. International Journal of Drug Delivery. 2012 Jan 1;4(1):59.

71. Akseli I, Xie J, Schultz L, Ladyzhynsky N, Bramante T, He X, Deanne R, Horspool KR, Schwabe R. A practical framework toward prediction of breaking force and disintegration of tablet formulations using machine learning tools. Journal of Pharmaceutical Sciences. 2017 Jan 1;106(1):234-47.

72. Djuris J, Cirin-Varadjan S, Aleksic I, Djuris M, Cvijic S, Ibric S. Application of machine-learning algorithms for better understanding of tableting properties of lactose co-processed with lipid excipients. Pharmaceutics. 2021 May 5;13(5):663.

73. Goh WY, Lim CP, Peh KK, Subari K. Application of a recurrent neural network to prediction of drug dissolution profiles. Neural Computing & Applications. 2002 Apr;10:311-7.

74. Sun Y, Peng Y, Chen Y, Shukla AJ. Application of artificial neural networks in the design of controlled release drug delivery systems. Advanced drug delivery reviews. 2003 Sep 12;55(9):1201-15.

75. Leane MM, Cumming I, Corrigan OI. The use of artificial neural networks for the selection of the most appropriate formulation and processing variables in order to predict the in vitro dissolution of sustained release minitablets. Aaps Pharmscitech. 2003 Jun;4:129-40.

76. Mendyk A, Güres S, Jachowicz R, Szlęk J, Polak S, Wiśniowska B, Kleinebudde P. From heuristic to mathematical modeling of drugs dissolution profiles: application of artificial neural networks and genetic programming. Computational and Mathematical Methods in Medicine. 2015;2015(1):863874.

77. Petrović J, Ibrić S, Betz G, Parojčić J, Đurić Z. Application of dynamic neural networks in the modeling of drug release from polyethylene oxide matrix tablets. European journal of pharmaceutical sciences. 2009 Sep 10;38(2):172-80.

78. Ivic B, Ibric S, Betz G, Zorica D. Optimization of drug release from compressed multi unit particle system (MUPS) using generalized regression neural network (GRNN). Archives of pharmacal research. 2010 Jan;33:103-13.

79. Zannikos PN, Li WI, Drennen JK, Lodder RA. Spectrophotometric prediction of the dissolution rate of carbamazepine tablets. Pharmaceutical research. 1991 Aug;8:974-8.

80. Porfire A, Filip C, Tomuta I. High-throughput NIR-chemometric methods for chemical and pharmaceutical characterization of sustained release tablets. Journal of Pharmaceutical and Biomedical Analysis. 2017 May 10;138:1-3.

81. Hernandez E, Pawar P, Keyvan G, Wang Y, Velez N, Callegari G, Cuitino A, Michniak-Kohn B, Muzzio FJ, Romañach RJ. Prediction of dissolution profiles by non-destructive near infrared spectroscopy in tablets subjected to different levels of strain. Journal of pharmaceutical and biomedical analysis. 2016 Jan 5;117:568-76.

82. Tabasi SH, Moolchandani V, Fahmy R, Hoag SW. Sustained release dosage forms dissolution behavior prediction: a study of matrix tablets using NIR spectroscopy. International journal of pharmaceutics. 2009 Dec 1;382(1-2):1-6.

83. Galata DL, Zsiros B, Mészáros LA, Nagy B, Szabó E, Farkas A, Nagy ZK. Raman mapping-based non-destructive dissolution prediction of sustained-release tablets. Journal of pharmaceutical and biomedical analysis. 2022 Apr 1;212:114661.

84. Nagy B, Petra D, Galata DL, Démuth B, Borbás E, Marosi G, Nagy ZK, Farkas A. Application of artificial neural networks for Process Analytical Technology-based dissolution testing. International journal of pharmaceutics. 2019 Aug 15;567:118464.

85. Galata DL, Farkas A, Könyves Z, Mészáros LA, Szabó E, Csontos I, Pálos A, Marosi G, Nagy ZK, Nagy B. Fast, spectroscopy-based prediction of in vitro dissolution profile of extended release tablets using artificial neural networks. Pharmaceutics. 2019 Aug 9;11(8):400.

86. Galata DL, Könyves Z, Nagy B, Novák M, Mészáros LA, Szabó E, Farkas A, Marosi G, Nagy ZK. Real-time release testing of dissolution based on surrogate models developed by machine learning algorithms using NIR spectra, compression force and particle size distribution as input data. International journal of pharmaceutics. 2021 Mar 15;597:120338.

87. Hasani M, Moloudi M. Application of principal component-artificial neural network models for simultaneous determination of phenolic compounds by a kinetic spectrophotometric method. Journal of hazardous materials. 2008 Aug 30;157(1):161-9.

88. Paengjuntuek W, Thanasinthana L, Arpornwichanop A. Neural network-based optimal control of a batch crystallizer. Neurocomputing. 2012 Apr 15;83:158-64.

89. Gupta A, Austin J, Davis S, Harris M, Reklaitis G. A novel microwave sensor for real-time online monitoring of roll compacts of pharmaceutical powders online—A comparative case study with NIR. Journal of Pharmaceutical Sciences. 2015 May 1;104(5):1787-94.

90. Hole G, Hole AS, McFalone-Shaw I. Digitalization in pharmaceutical industry: What to focus on under the digital implementation process?. International Journal of Pharmaceutics: X. 2021 Dec 1;3:100095.

91. Finelli LA, Narasimhan V. Leading a digital transformation in the pharmaceutical industry: reimagining the way we work in global drug development. Clinical pharmacology & therapeutics. 2020 Oct;108(4):756-61.

92. Novikov SV, Sazonov AA. Application of the open operating system ‘MindSphere’in digital transformation of high-tech enterprises. Economics Journal. 2019 Dec 15;1(1):20-6.

93. Zupancic K, Pavlek T. Digital Transformation of the Laboratory.

94. Picker TS. Digitalization in laboratories of the pharmaceutical industry. Solid State Development and Processing of Pharmaceutical Molecules: Salts, Cocrystals, and Polymorphism. 2021 Nov 1;79:397-420.