



## Artificial Neural Networks in Pharma: Revolutionizing Drug Development, Optimization and Smart Manufacturing: (A Comprehensive Review)

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### ABSTRACT

Artificial Neural Networks (ANNs) are transforming pharmaceutical research by enhancing drug development, formulation optimization, and pharmacokinetic modeling. ANNs excel at predicting *in vitro*–*in vivo* correlations (IVIVC), drug metabolism, and permeability, surpassing traditional linear models. They enable data-driven decision-making, reduce animal testing, and support personalized dosing. In manufacturing, ANNs improve product quality prediction and identify variability sources. Supported by specialized software like MATLAB, STATISTICA, and SNNs, ANNs integrate seamlessly across Pharma 4.0 workflows, offering robust tools for complex data modeling and process optimization throughout the drug lifecycle. This study highlights the application of Artificial Neural Networks (ANNs) in pharmaceutical development. ANNs effectively predict drug release, optimize formulations, and model complex, nonlinear relationships without predefined equations. Their integration enhances process understanding, reduces experimental workload, and accelerates development. In the case of cerasomes-silica-coated bilayered nanohybrids-ANNs assist in optimizing key parameters for cancer-targeted delivery. Overall, ANNs support data-driven decision-making and robust pharmaceutical design, offering superior accuracy and efficiency compared to traditional modeling approaches.

**Keywords:** Artificial neural networks, Formulation development, Softwares.

### INTRODUCTION

Artificial Intelligence (AI) aims to replicate human intellectual tasks, with machine learning (ML) as a key subfield that enables machines to learn from data and improve over time. Deep learning (DL), a subset of ML, uses artificial neural networks

(ANNs) to process vast datasets through multilayer nonlinear units. ANNs mimic the brain's neural structure, enabling data recognition, classification, and learning. Introduced in 1958 by Frank Rosenblatt with the perceptron model, ANNs evolved with key contributions like Hopfield's nonlinearity (1982) and Rumelhart's backpropagation (BP) algorithm,



enabling effective training of multilayer perceptrons (MLPs). ANNs adapt their architecture during learning, reducing system errors and improving prediction accuracy. Unlike traditional models, they require no fixed equations or detailed input knowledge. While biologically inspired, ANNs are rooted in diverse disciplines like statistics and computing, functioning as powerful tools for knowledge extraction and predictive modeling in complex systems.<sup>1</sup>

This investigation demonstrates the use of Artificial Neural Networks (ANNs) in conjunction with a Quality-by-Design (QbD) framework in an attempt to create a tablet formulation of a poorly soluble BCS Class IV drug. The drug is a weak acid with an approximate pKa of 9 and a low logP, and it was developed in the form of a crystalline free base. It was shown that controlling the drug particle size distribution (PSD) is a critical material attribute that needs to be controlled. An ANN with five hidden nodes and hyperbolic tangent transfer functions

was trained and validated on a dataset where 33% of the data was held back. The model achieved  $R^2 > 0.94$  for all responses and was used to define the design space for PSD and process parameters. The model's predictions guided contour plots and process optimization. Three Good manufacturing Practice (GMP) exhibit batches of 180,000 tablets were successfully produced, with *in vitro* dissolution predictions showing a 5% bias. The formulation met Food & Drug Administration (FDA) bioequivalence criteria in clinical trials under both fed and fasting conditions. This work highlights ANNs as powerful, self-learning tools capable of modeling complex, nonlinear datasets without prior assumptions. Their integration into QbD supports data-driven decision-making, accelerates development, and strengthens formulation-process-performance linkages for robust, efficient pharmaceutical development.<sup>2</sup>

### Role of ANN

The potential roles of Artificial Neural Networks depicted in Figure 1.

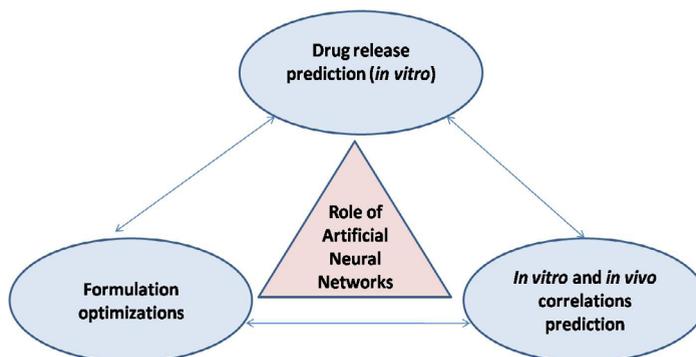


Fig. 1. Role and application of Artificial Neural Networks

### Drug release prediction (*in vitro*)

Artificial Neural Networks (ANNs) offer a reliable, efficient approach to predicting drug release behavior, addressing the limitations of traditional diffusion-based models. Conventional methods often fail to capture complex interactions among formulation variables, such as drug-excipient interactions and processing effects. ANNs overcome this by modeling nonlinear relationships using formulation inputs-like drug content, pH, and excipient composition-to predict *in vitro* dissolution profiles. Studies show ANNs outperform traditional models like PLS regression, offering higher accuracy (e.g., lower RMSE, higher  $f_2$  values). For instance, ANNs successfully predicted the dissolution of sustained-release formulations like caffeine tablets

and various matrix tablets, with optimization via genetic algorithms. Additionally, ANNs have been applied to predict ultrasonic-triggered release in liposomes and disintegration time in oral tablets. By reducing experimental workload and providing rapid, accurate predictions, ANNs prove valuable not only in formulation development but also as a quality control tool in pharmaceutical manufacturing.<sup>3-8</sup>

The study applied artificial neural networks (ANNs) to predict the release profile of nimodipine from tablet formulations, using four formulation variables: Polyethylene Glycol (PEG), Polyvinylpyrrolidone (PVP), Hydroxypropyl Methylcellulose (HPMC)-K100, and HPMC E50LV. Three dissolution responses  $t_{90}$  (time to 90%

release), Y2 (release at 2 h), and Y8 (release at 8 h) were modeled. ANN performance was compared with multiple linear regression (MLR) using an external validation set. The ANN, configured with eight hidden layers and logistic sigmoid activation functions, outperformed MLR in predicting all responses, demonstrating superior accuracy and fit. This highlights the effectiveness of ANNs in optimizing drug release modeling.<sup>9</sup>

### Formulation optimizations

Formulation development involves numerous variable factors, making traditional trial-and-error and Design of Experiment (DoE) approaches time-consuming. Artificial Neural Networks (ANNs) offer a powerful alternative, effectively capturing nonlinear relationships between critical material attributes (CMAs), processing parameters, and formulation outcomes. For instance, Amasya *et al.* optimized 5-Fluorouracil lipid nanoparticles using ANN, achieving ideal characteristics for dermal delivery. Compared to response surface methodology (RSM), ANNs demonstrate superior predictive and optimization capabilities. Studies by Koletti, Li, and Reza Zaki validated that ANNs outperform multilinear regression and RSM in predicting encapsulation efficiency, particle size, and  $\zeta$ -potential. Moreover, Sansare *et al.*, used Multiple Input, Multiple Output (MIMO) and Multiple Input, Single Output (MISO) ANN models to optimize liposome preparation, with MISO showing lower mean errors. Rodríguez-Dorado applied an Multilayer Perceptron–Genetic Algorithm (MLP-GA) model to fine-tune alginate core-shell microparticle formation, minimizing experiments while maximizing formulation quality. Overall, ANNs enable efficient, accurate, and cost-effective optimization of pharmaceutical formulations, outperforming conventional methods in both prediction and process understanding.

Cerasomes-silica-coated, bilayered nanohybrids-merge the structural benefits of liposomes with enhanced stability and functionality, finding broad applications in drug delivery and cancer diagnostics. Their vesicular structure allows for precise targeting of cancer cells via the enhanced permeability and retention (EPR) effect, leveraging tumor-specific vascular permeability. Techniques like thin-film hydration and ultrasonic dispersion enable

the formation of spherical cerosomes with aqueous cores, where factors such as sonication time, intensity, and phospholipid composition influence particle size. Advanced design using artificial neural networks (ANN) can optimize these parameters for ideal size and performance. Additionally, surface modifications like PEGylation or ligand conjugation can further improve targeting specificity and therapeutic efficacy. Thus, cerasomes represent a promising platform, combining nanostructural precision with machine learning-driven formulation for effective cancer treatment.<sup>10-14</sup>

In developing curcumin nanophytosomes surface-functionalized with chondroitin sulfate-A (CSA), a Quality by Design (QbD) approach using Box-Behnken Design combined with an Artificial Neural Network (ANN) based on the Levenberg-Marquardt (LMT) algorithm was employed. This strategy enabled the creation of a robust CSA-PEG-CR formulation within an acceptable design space. The ANN model featured 10 hidden layers with 15 neurons each, using tansig as the hidden layer transfer function and purelin for the output layer. The model achieved high reproducibility, with a training mean squared error (MSE) of 0.0969, highlighting its effectiveness in optimizing formulation parameters.<sup>15</sup>

### *In vitro* and *in vivo* correlations prediction

The rise in drug candidates and clinical trials has elevated development costs, prompting a need for validated *in vitro*–*in vivo* correlations (*IVIVC*) to enhance efficiency and reduce ethical burdens like animal testing. *IVIVC* links *in vitro* drug dissolution to *in vivo* pharmacokinetics, aiding drug development, formulation changes, and regulatory processes. While traditional *IVIVC* often relies on linear models, Artificial Neural Networks (ANNs) offer superior capabilities by capturing complex nonlinear relationships. Fatouros *et al.* established an ANN-based neuro-fuzzy *IVIVC* model for a probucol self-emulsifying drug delivery system (SEDDS), yielding plasma concentration predictions closely aligned with *in vivo* data. The neuro-fuzzy model demonstrated excellent predictive performance across various data sets, achieving a correlation above 0.91 and prediction errors near zero, all without requiring complex configurations. These promising preliminary results indicated that integrating the dynamic lipolysis model with ANN-*IVIVC* offers a valuable approach for accurately forecasting the *in vivo* behavior of lipid-based formulations, enhancing

formulation design and performance prediction<sup>16</sup>. ANNs also show promise in pharmacokinetic studies, such as predicting human drug clearance from animal data, as demonstrated by Iwata *et al.* Using structural and clearance inputs, they achieved accurate ANN-based predictions. Unlike Partial Least Squares (PLS) regression, ANN-based *IVIVC* models provide improved accuracy and adaptability,

indicating their strong potential in optimizing drug development and pharmacokinetics.<sup>17-20</sup>

### Other Applications

The other miscellaneous applications in formulation development<sup>21-25</sup> were presented in Table 1 and probable inputs and outputs were depicted in Figure 2.

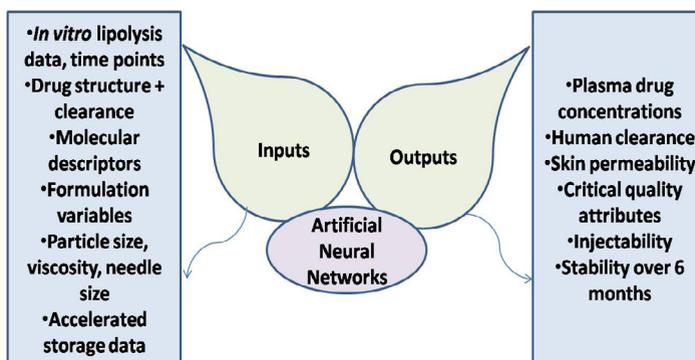


Fig. 2. Depiction of Inputs and Outputs for Artificial Neural Networks

Table 1: Miscellaneous applications of Artificial Neural Networks in formulation development

Application Area	ANN Structure	Inputs	Outputs/Prediction goals
<i>IVIVC</i> establishment	Neuro-fuzzy ANN (Adaptive Fuzzy Modeling (AFM)- <i>In vitro In vivo</i> Correlation ( <i>IVIVC</i> ))	<i>In vitro</i> lipolysis data, time points	Plasma drug concentrations
Human PK prediction	ANN with tensor model	Drug structure+clearance	Human clearance
Drug concentration prediction	Multilayer Perceptron (MLP)	Fluorescent signal data	Etanercept concentration
Transdermal permeability	Not specified	Molecular descriptors	Skin permeability
CQA identification	ANN	Formulation variables	Critical quality attributes
Intrinsic solubility prediction	ANN	Molecular and structural features	Solubility
Fluidized bed granulation control	Not specified	Process variables	Granulation endpoint
Dosage form stability	4-layer MLP, others	pH, storage time	Drug content and impurity levels
Drug dissolution behavior	ANN (75-1-3-1)	API size, formulation needle size	Q30 (30-min drug release %)
Solubility enhancement via hydrotropy	ANN (10-2-2-1)	Hydrotrope concentration	Indomethacin solubility
Microparticle injectability	ANN (2-10-1)	Particle size, viscosity, needle size	Injectability
SDS gel diffusion	Not specified	Formulation, intrinsic/extrinsic parameters	Diffusion coefficient
Tablet porosity prediction	ANN	Compression force, granule properties	Tablet porosity
Controlled release DDSs	ANN	DDS parameters (composition, method)	Release kinetics, CQA
High-content imaging analysis	Deep learning ANN	Time-series image data	Release behavior
3D printing optimization	ANN	Process parameters	Print quality, drug content uniformity
Granule size prediction	ANN with 2 hidden layers	Process conditions	D10, D50, D90
PLGA microparticle sizing	Multiple ANN models	Device type+formulation variables	Particle size
Nanoparticle adhesion prediction	ANN	Particle size, shear rate	Number adhered to vessel walls
Nanoparticle size prediction	ANN with Tanh	PVA conc., MW, hydrophobicity	Nanoparticle size (70–400 nm)
Protein formulation stability	Bayesian Regularized Backpropagation (BR-BP) ANN (11 models)	Accelerated storage data	Stability over 6 months

Moreover, ANNs have become popular tools in the research involving the pharmacokinetics and pharmacodynamics (PK/PD) of the drugs, capable of predicting key parameters such as clearance rates, protein binding, and volume of distribution. They also model drug permeability across biological barriers like the blood-brain barrier and stratum corneum. ANNs aid in assessing drug metabolism, which is crucial for minimizing toxicity and improving bioavailability. Deep learning models, trained on large datasets like Lowe's, have enhanced metabolite prediction accuracy, outperforming traditional rule-based methods. Tools like Synthetic Generation of Metabolites (SyGMa), GLORYx, and BioTransformer exemplify this progress. Compared to conventional nonlinear mixed-effects models (NONMEM), ANN models such as backpropagation-ANN (BP-ANN) show lower prediction errors in population PK studies. They also integrate animal PK data with physicochemical parameters to predict human PK outcomes. By simulating dosing based on physiological and pathological inputs, ANN reduces reliance on animal testing, accelerates drug development, and supports personalized dosing strategies in clinical settings.<sup>26-29</sup>

As Pharma 4.0 evolves, the pharmaceutical sector is shifting toward reliance on predictive methodologies to maintain a specific level of product quality through industrial and in-process data. While Artificial Neural Networks (ANNs) are ideal for data abundant situations, their "black-box" characteristic hampers their adoption in pharmaceutical manufacturing. This work illustrates applying ANNs to improve understanding of processes with retrospective analysis of development data. The *in vitro* dissolution and hardness of extended-release tablets were predicted using material attributes and operational parameters, achieving better results than models that only relied on Near Infra Red (NIR) or Raman spectra. Sensitivity analysis of ANN models revealed root causes of batch variability such as differences in particle size and hydroxypropyl methylcellulose grade. Variability from uncontrolled conditions within tableting operations were lessened when applying an ANN-based control strategy. This methodology can be applied universally to all levels of manufacturing processes starting from the synthesis of the active ingredient to the formulation,

enabling improved quality forecasting and deeper understanding of processes throughout the product lifecycle.<sup>30</sup>

### Softwares used

Various software tools support Artificial Neural Network (ANN) development and simulation, each offering unique features. MATLAB provides an Artificial Neural Toolkit for designing and visualizing networks, particularly useful in pattern recognition and nonlinear analysis. Computer-Aided Design for Chemistry (CAD/Chem v5.0) enables users to customize neural network parameters like hidden layers and training iterations. STATISTICA 10 includes a wide range of statistical and machine learning tools with PMML and C code generation support. The Stuttgart Neural Network Simulator (SNNS) supports various architectures such as feedforward, backpropagation, and reverse transmission networks. Pythia, a neural network designer, emphasizes learning and regeneration phases for performance optimization. NeuroSolutions offers a modular interface with advanced features like Levenberg–Marquardt training, C++ code generation, and DLL support. BrainMaker v3.7 targets healthcare and financial applications, supporting tasks like diagnosis and sales forecasting. Neural Works Professional II/PLUS stands out in industrial environments, offering comprehensive tools for ANN development across UNIX, Linux, and Windows platforms, with strong documentation and user support.<sup>31</sup>

### CONCLUSION

Artificial Neural Networks (ANNs) have emerged as transformative tools in pharmaceutical sciences, offering significant advantages in formulation design, drug release prediction, pharmacokinetic/pharmacodynamic (PK/PD) modeling, and *in vitro*–*in vivo* correlation (IVIVC). Their ability to model complex, nonlinear relationships without prior assumptions makes them superior to traditional statistical methods in many applications. ANNs enhance the Quality-by-Design (QbD) approach, streamline manufacturing, reduce development time, and minimize reliance on animal testing. Their integration into pharmaceutical manufacturing, especially under the Pharma 4.0 paradigm,

supports predictive analytics and real-time process control, ensuring product consistency and regulatory compliance. The future of ANNs in pharmaceutical development is promising. With advancements in deep learning, neuro-fuzzy systems, and hybrid models (e.g., ANN-genetic algorithms), their predictive power and interpretability will continue to improve. Coupling ANNs with big data from real-time sensors, clinical studies, and electronic health records will further drive personalized medicine and adaptive manufacturing. The continued evolution of user-

friendly ANN software platforms will foster broader adoption, enabling interdisciplinary collaboration and innovation in drug development and regulatory sciences.

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#### Conflict of interest

The authors declare no conflict of interest.

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