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Review - Engineering, Technology and Techniques

Artificial Neural Networks and Neuro-Fuzzy Models: Applications in Pharmaceutical Product Development

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HIGHLIGHTS

- Introduction regarding artificial neural networks and neuro-fuzzy logics.
- Application of neuro-fuzzy logic in pharmaceutics product development.

Abstract: Pharmaceutical product development is a challenging, time-consuming, and cost-intensive process. Computational methods could be used for assistance and speed up the industrial process. Artificial neural networks (ANN) and neuro-fuzzy models are tools of artificial intelligence that can be used to develop pharmaceutical products to enhance productivity, quality, and consistency. In the present review, the working principle of ANN and neuro-fuzzy models has been discussed, elaborating on their different types, advantages, and disadvantages. Furthermore, the application of these computational techniques in developing pharmaceutical products like suspension, emulsion, microemulsion, nanocarriers, tablets, transdermal preparations, etc., has been discussed in detail.

Keywords: Artificial neural networks; Neuro-fuzzy logic; Artificial intelligence; Pharmaceutical products; Computers; Computational.

INTRODUCTION

Pharmaceutical product development requires active and inactive ingredients and several procedures and process-related factors, all of which are difficult to regulate and optimize. For decades, this process has been accomplished by trial and error with the help of the formulator's understanding. Pharmaceutical product development is a time-consuming, expensive, and complicated procedure. Computational approaches could be used for assistance and speed up the industrial process. Artificial neural networks (ANN) and neuro-fuzzy models are artificial intelligence techniques that may improve efficiency, quality, and consistency in the production of pharmaceutical products. Artificial intelligence is a branch of computer science that creates and implements algorithms for data analysis and interpretation. Computation is a broad term that encompasses statistics, machine learning, pattern recognition, clustering, similarly based methods, logics, probability theory, and biological techniques like neural networks and fuzzy modeling.

Neural networks have gotten a lot of attention in the last decade, scientists and engineers are paying close attention to them, and they are one of the most powerful computing tools ever constructed. Artificial neural networks (ANNs) technology simulates the brain's neural networks' pattern recognition skills. Like a single neuron in the brain, an artificial neuron unit takes inputs from various external sources, analyses them, and makes a decision. ANNs are vital for modeling diverse non-linear systems since they do not require rigorously organized experimental designs and may map functions using historical or partial data. Medical chemistry, psychology, engineering, and pharmaceutical research are just a few of the domains where ANNs may be used, Because of their ability to make predictions, see patterns, and model. ANN includes analytical data analysis, pre-formulation, optimization of pharmaceutical formulations, in-vitro and in-vivo correlation, quantitative structure-activity relationship and quantitative structure-property relationship, proteomics, prediction permeability of the skin and blood-brain barrier, pharmacokinetic and pharmacodynamic modeling. A neuro-fuzzy method depends on a fuzzy system that is educated using a neural network learning method. The (heuristical) learning technique works with local input and only modifies the underlying fuzzy system locally. A three-layer feed-forward neural network can be used to describe a neuro-fuzzy system. Input variables are represented by the first layer, fuzzy rules are represented by the middle (hidden) layer, and output variables are defined by the third layer. The adopted neuro-fuzzy model is an adaptive neuro-fuzzy inference system (ANFIS) (17), which integrates artificial neural networks (ANNs) with fuzzy logic (FL) to simulate complicated nonlinear issues like pharmaceutical formulation optimization. Fuzzy logic is a powerful signal processing method that has been utilized effectively in various domains such as system modeling and control, detection, pattern recognition, and denoising. Artificial intelligence is a field that deals with the design and applications of algorithms for analysis and interpreting data. It's a broad set of categories of statistical, machine learning, pattern recognition, clustering, similarly based method, logics, and probability theory, and involved in biological approaches such as neural networks and fuzzy modelling collectively called computational intelligence [1]. This information enables a specialist to characterize the data that carry on the way toward and altered a primary method to reach perceptive sight settle it by an alternate arrangement of standardized data. The procedure incorporates associations between crude material and procedure conditions [2].

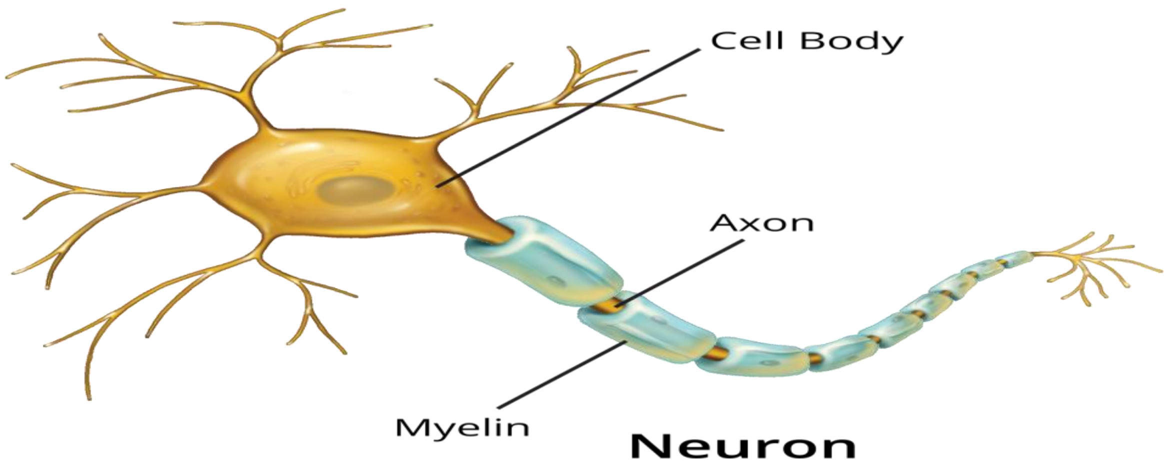

Figure 1. Structure of biological neuron.

The central unit of the nerve is called a neuron or nerve cell. This possesses a cell body called a nucleus. The cell body has a nucleus, which stores information about genetic characteristics, and a plasma that includes molecular equipment for generating the neuron's material. A nerve fibre is having a tree-like structure called dendrites. These dendrites are mainly termed as a receptor that receives signals from other neurons. There is additionally an inclusive bit of long fibre from a cell body called the axon (as shown in Figure 1). Which is mainly divided into various strands, sub-strands, connecting to many other neurons at synaptic junctions or synapses. The Axon of a neuron carried thousands of neurotransmitters related to different neurons. The transfer of signal from one cell to another cell is mainly carried out at the synapse is a very intricate chemical methodology in which explicit transmitter substances are discharged from the dying downside of the intersection [3].

Artificial neural networks (ANNs)

ANNs, also known as neural networks (NNs), are computer systems modelled after the biological neural networks that make up animal brains. Artificial neurons are a set of linked units or nodes in an ANN that loosely resemble the neurons in a biological brain. Each link, like the synapses in a human brain, can convey a signal. An artificial neuron receives a signal, analyses it, and then sends signals to neurons linked to. Each neuron's output is generated by some non-linear function of the sum of its inputs, and the "signal" at a connection is a real number on their inputs, various layers may apply different transformations. Signals pass from the first layer (input layer) to the last layer (output layer), perhaps several times [4].

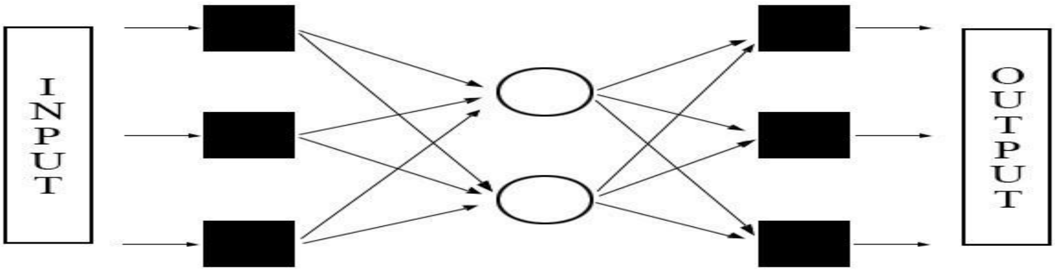

Figure 2. A three-layered artificial neural network model with a single hidden layer.

The feedback model is another kind of capacity where one layer's yield moves back to the past layer or a similar layer. Two sorts of the structure are clarified by the presence and absence of the feedback connection model. The structure of the feed-forward model doesn’t have the function of backward flow, so it doesn’t have the record of previous outputs. Neurons have the option type of information sources loads that will peak an extra opportunity. Such systems are predominantly designed like that the following condition of activity relied on the information loads and the previous condition of the system [5-7]. Three layered ANN model with a single hidden layer is depicted in Figure 2.

Neuro-Fuzzy logic

A data-driven learning approach developed from neural network theory trains a neuro-fuzzy system based on an underlying fuzzy system. Only local information is used in this heuristic to induce local modifications in the basic fuzzy system. As demonstrated in Figure 3, a neuro-fuzzy system is represented as a unique three-layer feed-forward neural network; The input variables are represented by the first layer, The fuzzy rules are represented by the second layer, The output variables are represented by the third layer, The (fuzzy) connection weights are created from the fuzzy sets.

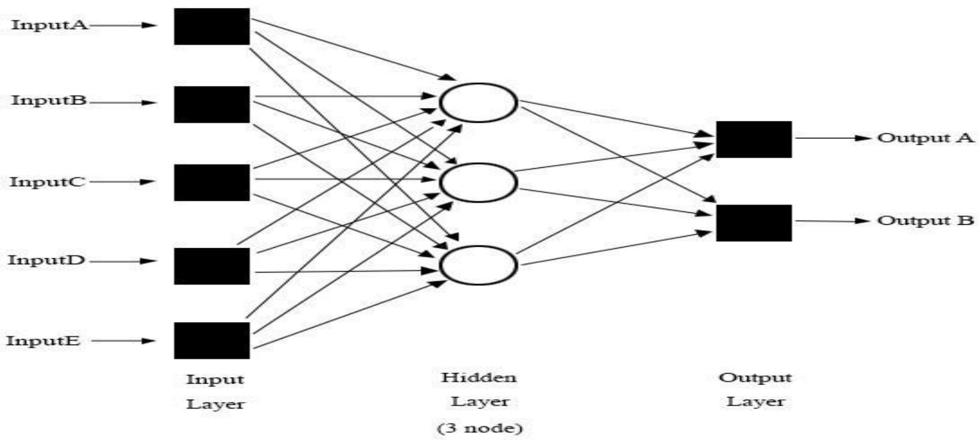

Figure 3. Multilayer perceptron model with one hidden layer.

Some methods employ five layers, with the fuzzy sets stored in the second and fourth layer units. These models, on the other hand, maybe turned into a three-layer architecture [8]. Neuro-fuzzy framework portrayed as a lot of various fuzzy tenets, this framework absolutely reliance upon the characters of input and output with prior knowledge of fuzzy principles. By intertwining the fuzzy framework with neural systems, the resultant item requires learning through examples and the simple elucidation of its usefulness [9]. There are several different ways to develop a hybrid neuro-fuzzy system. The benefit is to allow a comparison between other models and interpret their structural differences. There are several neuro-fuzzy architectures like: -Fuzzy adaptive learning control network (FALCON), Adaptive-network-based fuzzy inference system (ANFIS), Generalized approximate reasoning-based intelligence control (GARIC), Neuronal fuzzy controller (NEFCON), Fuzzy inference and neural network in fuzzy inference software (FINEST), Fuzzy net (FUN), Self-constructing neural fuzzy inference network (SOFIN), Fuzzy neural network (NFN), Dynamic/evolving fuzzy neural network. ANFIS is the implementation process of a fuzzy inference system for the adaptive network to develop the function of fuzzy rules with a suitable function of fuzzy rules with righteous functions of inputs and outputs. Single node and crisp characters are showcasing as the output model depicted in the 5th layer. Adaptive learning type is generally chosen as learning of a hybrid system. Designing of the fuzzy logic controller with ANFIS, the following arrangements are implemented: SUGENO type must necessarily to be established for the controller, There must be input-output pairs to implement the system better for a better optimal solution, ANFIS modification and architecture employed by the MATLAB membership functions, Each rule must be worked on a single output membership function in the systemic function [10].

Applications of ANN and Fuzzy Logics

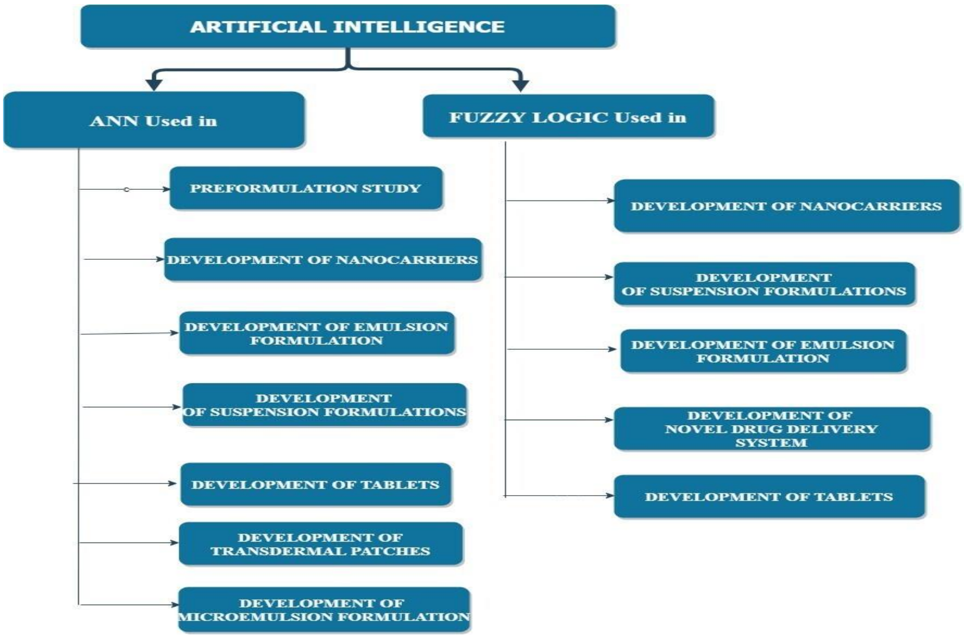

Figure 4. Applications of ANNs and Fuzzy logics in the pharmaceutical field.

- **Application of ANN in pre-formulation study**

ANN model show has been utilized in communicating the plan and study of pre-formulation to determine the physicochemical properties of amorphous polymers. Ebube and coauthors [11] proposed in a study that the water uptake characteristics, rheological properties and glass transition temperatures of the different polymers also indicated how the ANN model specifically depicted the water uptake characteristics, water vapor sorption of viscoelastic properties of various amorphous hydrophilic polymers and their physical blends with low prediction errors {0-8%}. It showcased the use of ANN as a tool for pre-formulation study. The model helps predict polymer blending property with their hydration capacity and polymers solutions viscosity, the relationship of the hydration, and their glass transition temperatures. Onuki and coauthors [12] discussed the tablet properties creating the tablet database for designing tablet formulations. In the design, it is vital to think about the impact of active pharmaceutical ingredients (API) on the tablet itself and where a different form of API is available. Using ANNs study considers the 14 sorts blends as the model of experiment of APIs portrayed without anyone else's input dealing with maps to highlight on the speedy release database and the effect of APIs on the tablet properties. Chin and coauthors [13] affirmed in the study that using ANNs estimation of rheological wall slip velocity. The study showed an advanced multilayer perceptron model with input variables of shear stress, particle size, concentration, temperature with the resulting output of wall slip velocity. It concluded in the study that its proficient method for analyzing rheological wall slip velocity by use of artificial intelligence. Furthermore, ANNs have been effectively used in the development of stable formulations for a variety of active ingredients, including rifampicin and isoniazid microemulsions. ANNs are unquestionably valuable in preformulation design, and they could help lower the cost and duration of the investigation (as shown in Figure 4).

- **ANN in the development of nanocarriers**

While working in anticancer medication looking for its targeted action but can't ignore the side effects shown by the drugs, Qaderi and coauthors [14] worked on a study of the artemisinin drug for breast cancer proposed form of nanocarrier for medication to reduce the harmful effects towards healthy cells. The study mainly used the ANN design to express the high possibility of nonlinear modulation; it was used mainly for predicting the toxicity that the working nano liposomal formulation showed less toxic than the PEGylated formulation. For early diagnosis, imaging treatment of diseases nanoparticles of various sizes and shapes needs to be developed. So, for this, Boso and coauthors [15] studied optimizing the particle size and shape for the effective action with reducing sophisticated numbers of the experiment. They developed two networks ANN231 and ANN2321, to predict the accurate number of nanoparticles with the complexity associated with terms like shear rate and particle diameter. This demonstrated the optical particle diameter in the parallel plate flow chamber apparatus. By this application of ANNs in this study is a heuristic approach to minimize the number of the experiment for prediction of action of nanoparticles at disease site without compromising the study's accuracy. They studied the comparison of response surface and ANN modelling by a genetic algorithm approach in the preparation of agar microsphere. The multivariate nature of drug-loaded nanosphere manufacturing is the monotonous task expensive because of Nanosphere's various multiplicity factors. Koletti and coauthors [16] show that the present study tests the preparation by design and artificial neural networks of systemically administered NSAID gelatine nanocarriers to benefit quality (ANNs). Compared to MLR, the implementation of ANN shows substantially improved prediction ability, while the verification test demonstrated strong agreement between the expected ANN and the findings obtained experimentally. In the study showcased by Shahbanzadeh and coauthors [17], ANNs were used to exhibit its function to evaluate silver nanoparticles size in the bio composites substrate. A multilayer feed-forward ANN is mainly used to express the output of silver nanoparticles size with correlating different inputs. Hashad and coauthors [18] study demonstrated the use of ANNs to optimize formulation parameters to get a better yield of chitosan-tripolyphosphate nanoparticles. This study mainly states the ability of ANN to predict not only the particle size but also the percentage yield of nanoparticles; this may step in a great work to customize the target form of delivery action. Shalaby and coauthors [19] studied ANNs to determine the particle size and the entrapment capacity in noscapine in PLG/PEG nanoparticles by varying different factors how the effect may characterize the efficiency of entrapment and particle size that maintain the use of polymer factor PEG/PLG. It found molecular weight greater effect on particle size and the polymer-drug ratio influenced the drug entrapment efficiency. Esmaeilzadeh - Ghardeghi and coauthors [20] used the ANNs parameters to determine the effects of processing parameters on the particle size of ultrasound prepare chitosan nanoparticles. It mainly found out the pharmacokinetic action depended upon the particle size of the nanoparticles. The data were structured by using the ANNs results showing that four input factors affect the size of the prepared chitosan nanoparticles. Baharifar and coauthors [21] used the comprehensive ANNs model by input the three-input variable polymer concentration, stirring time, PH, and a second study said the toxicity factor influenced by the particle size of chitosan/streptokinase nanoparticles. The study mainly expressed out how the size of nanoparticles played a vital role in cytotoxicity and showcased that smaller particles showed more toxicity, regardless of the input parameters. Imanparast and coauthors [22] study the characterization, optimization, preparation of simvastatin nanoparticles by electrospraying but by the preparation of nanoparticles main focusing upon the size factors which studied by using ANNs using three input variables polymer concentration, salt, solvent flow rate, and the dimension of the nanoparticles were considered as the output variable. Tejedor-Estrada and coauthors [23] study the factor of subcellular localization of photosensitizers of photodynamic therapy of solid tumours. ANNs classification method used to distinguish the photosensitizers located in the two site mitochondria and lysosomes. Using ANNs, the virtual screening of drugs for PDT, using the ANNs is mainly helpful for predicting outright target action for solid tumours by removing out the false assignation. Sarajlic and coauthors [24] depicted the surface area of the surface of microspores and the prediction of the size of the nanoparticles by using ANNs. By varying the three inputs in a two-layer feed-forward network with a sigmoid transfer function of ANNs showcased the output determining the factor for accuracy data of the size of nanoparticles and microspore surface area. The preparation of a nanostructured lipid carrier is the most sophisticated approach. Rouco and coauthors [25] worked to determine the design space by applying artificial intelligence tools on the nanostructured lipid carrier materials. Artificial intelligence makes it evaluate the mainstream parameters that vary each formulation property and established a pioneering approach towards nanoparticles as a lipid carrier. Baghaei and coauthors [26] worked by using artificial intelligence to maintain the particle size and release factor of PLG biodegradable nanoparticles. By studied the variables, PLG molecular weight played an important role by varying the study of its characteristics of PLGA size and initial burst proposed by genetic algorithm. Bozuyuk and coauthors [27], using the ANNs, study the key parameters of the PEGylation of bio adhesive chitosan nanoparticles. ANNs were mainly a modelling tool to structure to optimize the inherent properties of nanomedicine. ANNs tools are mainly helpful in predicting the different characteristics such as as- size and zeta potential, and adhesion properties on cell surface PEGylation chitosan nanoparticles. El Menshawe and coauthors [28] developed terbutaline sulphate-loaded liposomes and formulated transdermal gel employing ANN modelling. These findings suggested the prospective use of bio losomes loaded gel for the treatment of asthma. Rizkalla and coauthors [29] depicted the study using the ANNs model to determine nanoparticles' nanoparticle size and micropore surface area developed by the double emulsion method. In this study, there use of two commercial ANNs software, neuro cell predictor and neuro solutions. This resulted in the optimization of various characteristics by varying the different properties and resulted that the users of these models for estimation of characteristics greater response than that of a statistical model. It concluded that these ANNs tools are efficient that used to analysis of different physical properties and analysis of the different processes.

- **ANNs in the development of emulsion formulations**

Kundu and coauthors [30], by using the ANNs with a genetic algorithm, showed action for the development of petroleum emulsion formation and a heuristic approach towards the stability factor. It manly found out as preparation of emulsion concerned for stability by using ANNs-GA with response surface methodology will optimize the various parameters needed for stability factor for petroleum emulsion formation. Gupta and coauthors [31] proposed a study of the extraction of NSAIDs(diclofenac) through emulsion liquid membrane by the input of ANNs work. ANNs optimized the various factors surfactant concentration, homogenizer speed, stirring speed, and stripping phase concentration. Its result depicted that ANNs in this section were a prolific model for simulation of the process. Monazzami and coauthors [32] determined the rheological behaviour of β-cyclodextrin loaded Pickering-type oil in water emulsion by implying ANNs using three input variables and an output variable as shear stress. Also, the feed-forward backpropagation algorithm with input three different methods like quasi-newton, conjugate gradient, and gradient descent for network training. The resulting data mainly showed that quasi-newton was the most prolific method for determining shear stress than the other two methods. Messikh and coauthors [33] proposed a study for extraction efficiency of turnout cooper and breakage percentage using emulsion liquid membrane process. Neural networks radial basis function optimized the various factors for efficient extraction of copper like emulsification time, ultrasonic power, mixing speed, sulphuric corrosive fixation, extractant and surfactant concentration, internal phase/organic stage volume proportion, emulsion/outer stage volume proportion, and copper focus. Fang and coauthors [34] mainly proposed a study of the extraction of l-phenylalanine using the process by emulsion liquid membrane from the sodium chloride solutions. A backpropagation neural network was also improved by a genetic algorithm study to simulate the l-phenylalanine in the external phase and extraction efficiency under various operational conditions. Elkatatny and coauthors [35] predicted the drilling fluid rheological properties during the drilling operations carried to expressed various crucial factors like yield point, apparent viscosity, plastic viscosity, and remove out the problems related to change of properties. ANNs back box design converted the white box to create a mathematical model that implicated the determination of properties drilling fluid rheological using Marsh funnel viscosity, solid content, density. They showed the study of a rheological factor of inverse emulsion-based mud during drilling. They used the same method mathematical model of ANNs in white box manners as written in upper for rheological properties. Mahdi and coauthors [36] studied the operational parameters of microdroplet size prediction in microfluidic systems by using ANNs modeling in water in oil emulsion formulation. The study showed the mainly relative importance inputs of the size of microdroplets by using the Garson algorithm. Amasya and coauthors [37] worked on a QbD approach to study fluorouracil-loaded lipid nanoparticles W/O/W double emulsion. Using the ANNs model to evaluate the data obtained data to optimize various parameters that need to be stabilized in preparation. Experimental review of maintaining the design space of both input and output. Vu and coauthors [38] proposed a research study to refine the rosuvastatin-containing self-nano-emulsifying drug delivery system (SNEDDS) formula and determine its physicochemical characteristics. The solubility and compatibility of rosuvastatin have been tested in surfactants, cosurfactants, and oil excipients. To study the effects of excipients on physicochemical properties, the D-optimal experimental design produced by JMP 15 software was used, SNEDDS to refine the SNEDDS formula of rosuvastatin. Droplet size, polydispersity index, and trapping efficiency were characterized by the produced nanoemulsions from Ros SNEDDS. Izadi and coauthors [39] proposed a study of o/w emulsion scattering phytosterol particles by ANNs and multivariate model. As the investigation for the most part in the emulsion, the principle factor is to keep up the thickness and rheological property, so ANNs consider fundamentally assesses consistency, molecule size, phytosterol paraffinization in o/w emulsion. The result mainly showed that the ANNs model was the most accurate work other than the multivariate regression. Wei and coauthors [40] used various emulsifiers set up by centrifugation to inspect dependability by utilizing ANN. Different mixtures like span 80 and tween 80 are being used, which gives W/O/W emulsion with delicate sensitivity. BY utilizing polymer surfactants like Arlacel P135 for the long-term stability of emulsion particles. ANNs in the development of suspensions

Heidari and coauthors [41] proposed a study to design a suspension of PID controller by the backpropagation neural network to simplify the one-dimensional springer damper problems. BPN method is mainly used as the most appropriate for this method. For best results obtained by using the algorithm of levenberg-Marquardt training with 10 neurons and one hidden layer. By utilizing various inputs, it was mainly found that the usability of BPN in this area was helpful for the gain of a PID controller. Bash and coauthors [42] studied the dynamic response of arm-based suspension using artificial neural networks techniques. By using the three inputs and three outputs, it detects out the Max and the dynamic displacement. Finally, regression analysis is performed between finite element results and the values summed up by the neural network model. It mainly found out that the radial basis function neural network was the prominent one to use that diminishes the time required and the effort to evaluate the dynamic response of displacement in the suspension arm technique. Moran and coauthors [43] depicted in the study that using the performance of neural networks used for the analysis of optimal control and identification of nonlinear vehicle suspension. For the most part, it's discovered that the neuro vehicle models were effectively demonstrated to distinguish the dynamic qualities of the actual suspension vehicle. It showed that proper investigation of front suspension with the goal that the dynamic activities of front suspension accommodate advance the qualities of back suspension.

- **ANNs in the development of tablets**

Shao and coauthors [44] studied experimental comparison data on immediate-release tablets using the ANNs and neuro-fuzzy, which showed the prominent models for tablet tensile strength and dissolution profiles. It mainly resulted that ANNs specified the superior capability to predict unseen data where neuro-fuzzy models generated the rules for cause-effect relationships depicted in experimental data. Chen and coauthors [45] proposed a controlled release structure to recreate the pharmacokinetic property by utilizing the ANNs. ANN model improved different cooperation, various interaction additionally reproduces pharmacokinetic property and the disintegration, bioavailability profiles. This mainly resulted that assisted in the evolvement of complex dosage forms. Sun and coauthors [46] studied the modelling of controlled release drug delivery systems using the ANNs. Mainly in the controlled release delivery system, various problems arise in the previously used surface methodology technique. Still, for limitations, they more specified upon the ANNs, which optimized the data and set a heuristic approach to developing controlled-release delivery systems. Barmapalexis and coauthors [47] expressed a study in developing nimodipine floating tablets of solid dispersion optimized by ANNs and genetic programming. These are shown a better class of floating and controlled release characteristics. ANNs and GP resulted in an effective tool for optimizing the characteristics. GP equations maintained an optimum global formulation. Stanojevic and coauthors [48] proposed research with a purpose to explore the feasibility of adapting drug release rates from immediate to extended-release through varying tablet thickness and drug processing, as well as designing predictive atomoxetine (ATH) release rate artificial neural network (ANN) models from DLP 3D-Printed tablets. The successful manufacture of a series of tablets with doses ranging from 2.06mg to 37.48mg, displaying immediate and adjusted release profiles, demonstrates the promise of this technology in the development of dosage forms on-demand, with the prospect of modifying the dose and release actions by changing medication loading and tablet measurements. Xie and coauthors [49] studied artificial neural network optimization and evaluation of sustained and immediate-release tablets. The use of the ANN model is mainly helpful for optimized various released properties and complex combination forms. ANN also determines the efficiency factor on dependent and independent variables, which prolifically expressed the release profile. Turkoglu and coauthors [50] studied roller compaction modelling to vary the binder agent, type, and concentration by applying ANN and genetic algorithms. The study mainly stated that both ANNs and genetic algorithms optimized a variety of approaches to make it the best fit for data analysis for determining the approaches of the binder. It resulted out in a study that the genetic algorithm predicted tablet characteristics better than the ANNs models. Colbourn and coauthors [51] studied the gene expression programming to formulate the different formulations with a comparative study of ANNs. Gene expression programming is a development new way of a computing system of modelling data and automated equations that plotted the cause-effect relationship and compared neural models; these techniques are now widely used. The output resulted that GEP being considered an effective and efficient way of structuring the data. Chen and coauthors [52] studied the data of the in-vitro dissolution profile of controlled-release tablets by using the four ANN models and show a comparative study. The commercially used four software are Neuroshell v3.0, Brainmaker v3.7, CAD/Chem v5.0, neural works professional 2/plus. These ANNs programming enhanced diverse variety and kept up a design that demonstrates the heuristic methodologies required for disintegration controlled-discharge tablets. Those resulted in data given out the prediction that the Neuralshell2 showed the best prediction in vitro dissolution data of controlled-release tablets amid the other software used in the study. Ilic and coauthors [53] developed a relevant IVIVC model in osmotic release Nifedipine tablet-based a mechanistic simulation of gastrointestinal and ANNs analysis and their applicability usefulness in the consideration biopharmaceutical characterization of a drug. The study mainly resulted that both the GIS and ANN model was sensitive towards the application of in-vitro profile kinetics also employed in vitro-in silico-in Vivo development by the input of different in silico approaches. Matas and coauthors [54] studied over the in vitro in vivo correlations for delivery in nebulizer by using the ANNs. In the studied data predicted model that would help for the lung bioavailability of salbutamol formulation from the nebulizers lit concluded in study ANNs has the most prolific one for pharmacokinetic performance related to lung disposition. Chansanroj and coauthors [55] were studied the characteristics of drug release from the directly compressed matrix tablets of sucrose ester. The model mainly used in the study is the multilayer perceptron neural model and self-organizing map neural network for the accurate prediction of drug release from the sucrose ester matrix tablets. Colbourn and coauthors [56] proposed a study with defined approaches to neural networks and evolutionary computing towards the pharmaceutical formulation. These models picked up a separated base to decide the instance of optimizing parameters with representation instruments. It was deduced in the investigation that both the models were far-reaching of utilization in pharmaceutical formulations rather than the old traditional statistical methods. Aksu and coauthors [57] worked on the orally disintegrating tablets of ondansetron optimized different characteristics by using the ANN model in this study mainly used the two model’s neuro-fuzzy logic and gene expression programming. This study mainly stated that the ANNs programs were a useful tool for detecting out the various development characteristics for R and D, which was beneficial for various terms like raw materials cost and time for ondansetron orally release tablets. Hussain and coauthors [58] studied the property of mucoadhesive tablets working in buccal containing flurbiprofen and lidocaine (HCL) to relieve dental pain. The uses of ANN to carry the different form of characteristics of the tablet-optimized formulations, making it a heuristic approach towards giving stable formulations. Takayama and coauthors [59] worked on simulated different optimizations techniques to determine the different forms of controlled release tablets of theophylline based on ANNs. Working on various approaches by using ANNs strongly optimized the good agreement between the resulted values of release parameters and predicted results. Plumb and coauthors [60] investigated the experimental design strategy to model film coating formulations by using the ANNs. These ANNs used six input and two output nodes with a single hidden layer of five nodes worked with Box Behnken, central composite, pseudo-random designs to train multilayer perceptron. It concluded that extensive internal mapping required the prolific use of the ANN model to determine the basic form of designing tablet coating. Ghennam and coauthors [61] used intelligent model (ANN-GA), an artificial neural network paired with a genetic algorithm is used to predict the in vitro release of Ibuprofen kinetic profiles from two types of formulations: microcapsules and multiple unit pellet system (MUPS) tablets based on soy protein and its two derivatives and the ANN-AG model has shown very good success in predicting the kinetic release of Ibuprofen from all formulations and the impact of pH and the mechanism of vegetal protein alteration on the action of drug release in the simulated gastric and intestinal medium. Simon and coauthors [62] worked on the drug delivery rate optimized the characteristics of formulations by using ANNs with a relatable algorithm. It depicted the approached study of estradiol release of ethylene-vinyl acetate membranes. It concluded in a study that the customized design of different formulations that suitable for its releasing rate desired property. Sovany and coauthors [63] studied the parameters of raw materials that specified the effectiveness of formulations' characteristics and the compression forces on breaking the parameters of tablets. ANNs were mainly used to optimize the different approaches of data analyzing and the modelled in a desired way of properties. ANNs statically outfitted its information uncovered that the subdivision of scored tablets impacted by the diverse parameters and the organizations of powder blends.

- **ANNs in the development of transdermal formulations**

Few researchers worked in the ketoprofen hydrogel containing O-ethyl menthol transdermal formulations by simultaneously incorporated optimized the action of ANNs. The tools of ANNs used for the betterment of action to determine the lag time, rate of penetration, and irritation score removed the tedious task. It concluded that nonlinear relationship between casual factors and response variables and represented that response predicted by ANNs. Onuki and coauthors [64] worked on adhesive dermatological patches of photo crosslinked polyacrylic acid with modified 2-hydroxyethyl methacrylate hydrogel. By using various optimization tools like quadratic regression model, Artificial Neural networks, and multivariate spline interpolation. It concluded they worked on multiple variables to optimize predictions right characteristics of developed dermatological patches of the hydrogel. El menshawe and coauthors [28] present study was to devise, optimize and evaluate the gel transdermal terbutaline sulphate (TBN)-loaded bilosomes (BLS) compared to traditional oral TBN and free TBN-loaded transdermal gel to prevent hepatic first-pass metabolism. The pharmacokinetic analysis found that the enhanced formulation of TBN-CTS-BLS successively strengthened TBN bioavailability by approximately 2.33-fold solution and increased $t^{1/2}$ to approximately 6.21 ± 0.24 h relative to the oral solution. These results support the prospective use of BLS in the treatment of asthma as an active and healthy transdermal carrier of TBN. Tergic and coauthors [65] studied various data approaches to determine the suitability for the transdermal application of passive absorption. ANN was worked on optimizations of various physicochemical, pharmacokinetic, and biological characteristics that endeavoured the prolific one for the transdermal applications. It concluded in the study that ANNs the best method to move out the stochastic approaches of problems in heuristic manners.

- **ANNs in the development of microemulsion formulations**

Fatemi and coauthors [66], using the ANNs, mainly modelled and predicted microemulsion electrokinetic chromatography. After worked with ANNs, it's enhanced the different parameters at that point went for similar examinations with the test esteems just as got regression models which demonstrated that ANNs model effectiveness of optimization. It came about that the ANNs prevalence over the regression models. Glass and coauthors [67] considered details of formulation of fixed-partition portion blends of rifampicin, isoniazid, and pyrazinamide in microemulsions. ANNs demonstrate that the dependability and affectability investigation was connected to advance the determination of details. It is chiefly deduced in the investigation that the client of the model to improve the selection of solvents, solubilizing specialists and surfactants preceding definitions of the microemulsion. The model mainly works in advanced the diverse qualities that will be useful for restricting the analyses, decreasing the costs utilized in the pre-formulations examinations. Richardson and coauthors [68] affirmed in the study that the idea of phase behaviour in microemulsions systems was envisioned using an artificial neural networks model.

ANNs model used to consider the use of backpropagation and feed-forward to predict the phase behaviour. It concluded in the study that it's a valuable tool for the development of microemulsion drug delivery systems. Kustrin and coauthors [4] worked in the combination form of rifampicin and isoniazid oral delivery formulation using the ANN methodology. ANN model showed the potential of working by varied the different ingredients that specified the stability of formulations. They went for the study of observed phase behavior using a radial basis function network. Then it resulted from that which experimental study predicted the most successful model as a percentage of success. Gasperlin and coauthors [69] purpose of the study was to predict the internal structure of microemulsions by using ANNs with the combined form of genetic algorithm. ANNs model used to be the specified source with the combined algorithm that maintained composition stability factors. It resulted in findings that the ANN models with genetic algorithm reducing research and development costs for characterizing microemulsion properties and stated that its another source of delivery is colloidal drug delivery system. Klampfl and coauthors [70] worked in the preparation of suntan lotion focused on separating UV filters by applying microemulsion electrokinetic chromatography. The set of ANN model mainly affirmed that the user of the model to optimize the best possible composition of microemulsions with the structured analytes concerning separation factors. Djekic and coauthors [71] studied the factors of phase boundaries of microemulsion by utilizing ANNs. This model is primarily highlighted with different methodologies that will be the productive instruments for advancing the qualities of microemulsion stage limits and the most superlative components searching for it, decreasing the test cost. Ferrer and coauthors [72] has made an effort to evaluate the percolation temperature of different AOT microemulsions in the presence of various additives (crown ethers, glycemes, and polyethylene glycols) developed in the laboratory; three predictive models are presented based on Artificial Neural Network, it can be inferred that the models demonstrated intense percolation temperature predictive ability. Nevertheless, the modification obtained for the model of crown ethers suggests that learning new inputs variables, increasing the number of instances, and using other training algorithms and methods will be convenient.

Advantages of ANN in pharmaceutical product development:

1. ANNs provided a useful tool for the development of microemulsion-based drug-delivery systems in which experimental effort was minimised. ANNs were used to predict the phase behaviour of quaternary microemulsion-forming systems consisting of oil, water and two surfactants.
2. ANNs can identify and learn correlative patterns between input and output data pairs. Once trained, they may be used to predict outputs from new sets of data. One of the most useful properties of artificial neural networks is their ability to generalise. These features make them suitable for solving problems in the area of optimization of formulations in pharmaceutical product development.
3. ANN models showed better fitting and predicting abilities in the development of solid dosage forms in investigations of the effects of several factors (such as formulation, compression parameters) on tablet properties (such as dissolution).
4. ANN models were used to determine the structure activity relationship of compounds.
5. ANN were used to detect the microbiological activity in a group of heterogeneous compounds.
6. Neural networks produced useful models of the aqueous solubility within series of structurally related drugs with simple structural parameters. Topological descriptors were used to link the structures of compounds with their aqueous solubility.
7. A three-layer, feed-forward neural network has been developed for the prediction of human intestinal absorption (HIA%) of drug compounds from their molecular structure.
8. A four layer genetic neural network (GNN) model was used to predict the degree of drug transfer into breast milk.
9. ANNs could accurately predict PD profiles without requiring any information regarding the active metabolite. Since structural details are not required.
10. ANNs are widely used for medical applications in various disciplines of medicine especially in cardiology. ANNs have been extensively applied in diagnosis, electronic signal analysis, medical image analysis and radiology

- **Fuzzy logic in the development of tablets**

Rebouh and coauthors [73] Used ANFIS to study ibuprofen activity by using different alternatives of cellulose derivatives like CMC, HPC, HPMC, MC and checked the release rate by using a fuzzy logic system. Results mainly showed that it has effective prediction capability in designing and testing a new formulation. Mesut and coauthors [74] designed alfuzosin HCL in the tablet using neuro-fuzzy system software. Which showed polymer type and its concentration, compression force, and lubricant concentration used in tablet formation. Results showed good compatibility between input and output, which was obtained from the system. Tan and coauthors [75] used clopidogrel bisulphate for controlled release tablet formulation by decrease its bioavailability. The release effect of the drug was examined by a computer program (INFORM.v.3.7. and FORMRULES). Results showed that the controlled release tablet was more efficient for an extended period of use. Wafa and coauthors [76] have proposed a new method that combines a particle swarm optimization algorithm with a fuzzy logic scheme to introduce a new paradigm that systematically decides the right-first-time output of granules and tablets, through this control technique, the optimum operating conditions to manufacture the necessary granules and tablets can be established, and the waste and recycling ratios can be reduced via actual laboratory-scale test that involve measurements tolerances, both systems have been successfully validated. Hyseni and coauthors [77] used PLGA in their experiment for the preparation of microsphere monodisperse. The controlled release rate depends upon drug porosity which may cause zero-order release kinetics of encapsulated molecules. Results showed high efficacy when it converted from three-phasic to continuous released of a drug in the body.

- **Fuzzy logic in the development of Nanocarriers**

Heidari and coauthors [78] used nanoparticles like ZIKV nanocarriers to help radiations used as a blood-brain barrier for human cancer treatment. He used fuzzy logic for Nano-fullerenes molecules under synchrotron radiations for controlled production and conditions that may be applied to the process like surfactant condition and reaction temperature without rudimentary bonding changes. Kazemipoor and coauthors [79] studied the anti-obesity of Carumcarvi by using an adaptive neuro-fuzzy interference system, and the results obtained from experimentation were compared with support vector relapse with the assistance of root-mean-square mistake (RMSE) and (R (2)). Results demonstrated that ANFIS helped in the forecast and precision improvement. Kumar and coauthors [80] have developed the study over the nanoparticles due to their biocompatible, degradable, and stable nature, and their biopolymeric (polysaccharide/proteins) revolutionized the drug delivery environment. It also explains existing difficulties in delivering insulin. These polysaccharide-based insulin nanocarriers, along with potential possibilities, can be used for selective delivery of insulin with more bioavailability, non-toxicity, and efficacy by using fuzzy logic and insulin pump technology.

- **Fuzzy logic in the development of suspensions**

Jara and coauthors [81] found uniformed polymeric nanoparticles with Nano-precipitation and were used for filtration and another separation application. By using fuzzy logic technology for uniformed and, mono-modal yield can be produced by using polymethacrylates derivatives. Through these results uniform, NpERS can be achieved and was used as an optimal method for production and biological potential for drug delivery systems. Kisi and coauthors [82] investigated the accuracy of ANF computing technology by collecting monthly data of suspension sedimentation from assorted places and was compared by using the fuzzy model for ANN and sedimentation order curve with root mean square error, mean square error, a coefficient of correlation. Results showed that fuzzy models can be with successive estimation for monthly suspended sedimentation. Azadeh and coauthors [83] execute adaptive neuro-fuzzy as partial least square for controlled drying process by reducing or predicting particle size of granules and produced the non-linear model. Results can have been used to predict drying processes by using ANN, ANFIS and PLS formulations and they were easy to apply on processes. Arab and coauthors [84] used a computational approach based on the fuzzy inference method (FIS) for peptic ulcer treatment; the efficiency of FIS was assessed with a ROC curve that prepares the 90% FCM accuracy and 85% ANFIS accuracy to compare the two methods. The blurry specialist system will theoretically improve the accuracy and efficacy of diagnostic procedures for peptic ulcer diseases to move towards more precision medicine and care.

- **Fuzzy Logics in development of emulsions**

Fingas and coauthors [85] Formulate w/o based emulsion by using adaptive neuro-fuzzy approaches. Some factors like viscosity, density, resin content may show effects on the water-in-crude-oil emulsion. Most regressive models cannot capture non-linear relations. Results demonstrated that ANFIS can be utilized to anticipate the stability of w/o emulsion and SARA (soaks, aromatics, saps, and asphaltenes). It used a neural system and neural-fluffy model on ketoprofen strong scattering (SD)and physical blend (PM). Neuro-fluffy connected as a contribution to Qualitative and subjective examination on SD and PM. Results showed a transformation in neural modal to achieved performance in the sensitivity analysis. Lu and coauthors [86] have employed the Alexnet to automatically identify, quantify and classify three different mechanisms of emulsions. Knowledge entropy determines the degree of disturbance in function images of each mechanism, and the highest activations show that the proposed networks learn the suitable characteristics. These observations thus lead from the viewpoint of deep learning to a greater understanding of emulsion physics. Hussain and coauthors [58] used ultrasonic power to a great extent in preparation for stable O/W emulsion. ANFIS modelling was applied, and specialized emulsion properties were found from the results. Results showed that droplet size range reduced with accrued in sonication time, and various gums like pectin, xanthan were used to intensify stability of the emulsion.

- **Fuzzy logic in developing novel drug delivery systems**

Fatouros and coauthors [87] used a dynamical lipolysis model and neuro-fuzzy network to saw the in-vitro in-vivo correlation. Oil solution, two self-micro, Nano blended drug delivery was tested with a liposomal model, and results were compared. It shows a less extended-release rate than SMEEDS and SNEEDS. So, outcomes were beneficial to anticipate IVIVC with dynamic lipolysis model and AFM-IVIVC. Azar and coauthors [88] Used an adaptive neuro-fuzzy system to predict post-dialysis urea rebound by using 30-60 samples. Accuracy was compared to predict equilibrated urea (Ceq). Results showed that they are highly promised for comparison of urea kinetic models. Amuthameena and coauthors [89] used a proportional, interconnected derivatives (PID - FLC) controller to estimate errors between setpoint and variables can be measured. The fuzzy controlled system was used to give inputs like 0 and 1. These systems are used for linear quadratic regulation unspecialized results. He observed that PID - FLC is more robust than insulin, which is delivered daily. Alvarez and coauthors [90] Used fuzzy logic in the production of isomerized hop pellets. Isomerized pellets created warming properties which make pellets stable at 50 C. By utilizing fuzzy controller vigorous delivered a high level of products. Arauzo Bravo and coauthors [91] used adaptive neuro-fuzzy systems to produce atomized penicillin by using the soft sensor for internal model controllers (IMC) with different modules. Results showed that accuracy and high production of penicillin were allowed to perform. Wan and coauthors [92] studied supramolecular nanocapsules with a high specific molecular reorganization. These capsules were derived from hyperbranched poly-ethylenimine (HPEI) for selective hosts. The fuzzy mechanism was used to promote specific molecular interactions. Results showed for defined, readily macromolecules and recognizing the potential of the highly particular host with the fuzzy mechanism. Karar and coauthors [93] introduced a new closed-loop fuzzy logic controller for regulating intravenous delivery of anti-cancer drugs. The controller was based on intuitionistic fuzzy sets and invasive weed optimization algorithms. Shahidi and coauthors [94] performed an extraction of polyphenols for flixweed seeds employing fuzzy based logic method. Extraction yield, time, and total phenolic content were the selected fuzzy logic inputs.

Advantages of fuzzy logic.

1. It is a robust system where no precise inputs are required
2. These systems are able to accommodate several types of inputs including vague, distorted or imprecise data
3. In case the feedback sensor stops working, you can reprogram it according to the situation
4. The Fuzzy Logic algorithms can be coded using less data, so they do not occupy a huge memory space
5. As it resembles human reasoning, these systems are able to solve complex problems where ambiguous inputs are available and take decisions accordingly
6. These systems are flexible and the rules can be modified
7. The systems have a simple structure and can be constructed easily
8. You can save system costs as inexpensive sensors can be accommodated by these systems
9. In medicine it is used to Control arterial pressure when providing anaesthesia to patients, Used in diagnostic radiology and diagnostic support systems, Diagnosis of prostate cancer and diabetes
10. NF models also proved a useful alternative IVIVR tool for drugs with complicated PKs where relations between input and output variables are complex and nonlinear, and our mathematical understanding of the system is incomplete

CONCLUSION

It has been shown that ANN and neuro fuzzy-based computational techniques are powerful tools in pharmaceutical product development. Essential basic knowledge of these techniques is required before their implementation in pharmaceutical processes. In pre-formulation studies, prediction analysis could be performed with these techniques. In pharmaceutical product development activities like optimization of various processes and parameters, the relationship between dependent and independent variables, production of responses, compatibility studies could be performed using ANN and neuro fuzzy-based models. The generation of understandable and reusable knowledge demonstrates the delivery of information extracted employing ANN and neuro fuzzy-based computational techniques.

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