YAZID GMAL BENTAHER

ARTIFICIAL NEURAL NETWORK MODEL FOR PREDICTION OF QUADRO COMIL MILLS

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A THESIS SUBMITTED TO THE GRADUATE SCHOOL OF HEALTH SCIENCES OF NEAR EAST UNIVERSITY

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YAZID GAMAL BENTAHER

In Partial Fulfillment of the Requirements for The Degree of Master of Science in Pharmaceutical Technology

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Approval of Director of Graduate School of

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I hereby declare that all information in this document has been obtained and presented in accordance with academic rules and ethical conduct. I also declare that, as required by these rules and conduct, I have fully cited and referenced all material and results that are not original to this work.

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Date:

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"Where there is a will, there is a way ". This has been one of the quotes I always took into hand when completing a target. This degree has been one my biggest targets in my life.

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It has been a great feeling when my dearest brothers and sisters have been there for me when I needed them. Moreover, I would like to thank all my friends who have participated and helped me with the entire process of my degree.

ABSTRACT

Artificial intelligence (AI) is an area of computer science that emphasizes the creation of intelligent machines that work and react like humans. One of the AI techniques is the Artificial Neural Network (ANN) which can be defined as a computational model based on the structure and functions of biological neural networks. Information that flows through the network affects the structure of the ANN because a neural network changes - or learns, in a sense - based on that input and output. The utilization of ANNs in the design and development of pharmaceutical products has been increased during the last few decades. In this work, an ANN was employed to predict the expected mean particle size of sodium chloride from a Quadro-Comil milling equipment. The ANN input parameters were from the process parameters of model, impeller type, screen size and impeller speed. Data were taken from previous experimental results of the conical mill. The correlation between the actual and the prediction results confirmed that the ANNs could be used in the milling process successfully.

ÖZET

Yapay zekâ, bir bilgisayarın veya bilgisayar kontrolündeki bir robotun çeşitli faaliyetleri zeki canlılara benzer şekilde yerine getirme kabiliyeti. Yapay zekâ çalışmaları genellikle insanın düşünme yöntemlerini analiz ederek bunların benzeri yapay yönergeleri geliştirmeye yöneliktir. Yapay zeka kullanım tekniklerinden bir tanesi olan yapay sinir ağları (YSA), insan beyninin çalışma mekanizmasını taklit ederek beynin öğrenme, hatırlama genelleme yapma yolu ile yeni bilgiler türetebilme gibi temel işlevlerini gerçekleştirmek üzere geliştirilen mantıksal yazılımlardır. Son yıllarda yapay zekanın ilaç araştırma, geliştirme ve imalat alanında kullanımı önemli derecede artmıştır. Bu çalışmada, sodium chloride kullanarak, yapay sinir aglarının katı dozaj formların prosesinde kullanılan milling operasyonunda, milling sonrası elde edilen partiküllerin ortalama sodium chloride partikül büyüklerinin tahmininde kullanılması araştırılmıştır. Proses parametreleri olarak Quadro-Comil markalı aletin modeli, elek açıklığı, impeller tipi ve impeller hızı alınmıştır. Yapay zeka tahmini ve gerçek veriler arasındaki korelasyon başarılı bulunmuştur.

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LIST OF ABBREVIATIONS:

ADME: Absorption, Distribution, Metabolism, and Excretion.

ANNs: Artificial Neural Networks.

API: Active Pharmaceutical Ingredient.

BBB: Blood Brain Barrier.

CPG: Counter-Propagation.

FFNN: Feed Forward Neural Network.

GRNN: Generalized Regression Neural Network.

HTS: High- Thought Screening.

IVIVC: In Vitro In Vivo Correlation.

MLR: Multilayer Perceptron.

MSE: Mean Square Error

MLR: Multiple Linear Regression.

PDI: Polydispersity Index.

PSs: Photo-Sensitizers.

QSPR/QSAR: Quantitative Structure Activity (Property) Relationship.

RDF: Radial Distribution Function.

RNN: Recurrent Neural Network.

SRR: Structure Retention Relationship.

SVM: Support Vector Machine.

VS: Virtual Screening.

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CHAPTER ONE

INTRODUCTION

1.1 Milling

Milling is the pharmaceutical method to decrease the particle size, which is related to the downstream pharmaceutical processes. Milling is the utilized to decrease the mass of crude particles, specifically for the active substances of the pharmaceutical particles, to delump powders or to decrease the dimension of granules which are produced from the wet granulation or dry granulation (Nakach et, al, 2004). Conical screen mills, for instance comils, may be utilized for delumping of powders, or for coarse to fine control of wet or dry granule size. Cone shaped screen mills comprise of a cone screen with an impeller embedded into the middle. The impeller revolves and material is ground between the impeller and the screen until it is sufficiently little to go through the openings in the screen and leave the mill. The key structure parameters for a conical mill incorporate the screen mesh size, the dimension of the cone, the impeller shape and the impeller to screen distance, which can be balanced utilizing spacers. Vital working parameters incorporate powder sustain rate and agitator speed (Sharma et. Al, 2012). The properties of granules entering the procedure likewise assume to have a huge role in the level of size decrease that can be accomplished (Verhezeen et al., 2004). Granule size can likewise be decreased utilizing oscillating granulators, which are basically screens coordinated with the roller compaction process. The compact ribbon is constrained through a screen utilizing an oscillating rotor, purported in the way that rotor velocity can shift in time. Screen size and rotor speed and rotation angle direct particle dimension (Vendola and Hancock, 2008). Comils are regularly utilized for granule size reduction yet other milling advances might be utilized if a littler particle dimension is sought. These incorporate air jet mills. Different kind of setup can be used for every kind of mills. Air jet mill for the most part comprise of a granulating chamber, where particles are broken, and an arrangement chamber, where particles are isolated by size. Adequately little particles are passed to the following unit operation while fines can be gathered in a clean channel. For these sorts of mills the fundamental outline parameters of intrigue incorporate the geometry, number and setup of the air nozzle. Important working parameters incorporate the solid feed rate and the grinding pressure (Nakach et al., 2004). Impact mills incorporate include conical mills and hammer mills.

In both sorts of mills, material is passed through the focal point of the mill and ways out at the external edge of the chamber. A selector net can be utilized to permit just adequately little particles to leave the processing chamber. Conical mill granulates the item between two circles to accomplish size decrease while hammer mills. depend on high effect particle divider, particle sharp edge and particle impacts. For conical mills, the mill size is the principle size is main variable. For hammer mills the hardware measure, cutting edge setup and selector grid size are all significant outline factors. Variable working parameters for conical and hammer mills incorporate solids feed rate and the rotor speed (Reynolds, 2010). Despite the hardware utilized, the target of processing is to accomplish the estimate particle size. The effectiveness of a processing procedure can accordingly be surveyed as far as its capacity to accomplish mean size or size distribution (Akkisetty et al., 2010). Specific surface area, which is concerned with particle size, can be utilized to decide milling efficacy. Yield as well linked in milling operations, as the creation of an huge amount of fines that are regained in the dust filter could bring about critical losses of possibly costly crude material (e.g., API) (Verhezeen et al., 2004). Comils have been concentrated more widely for granule size decrease than have effect or air jet mills. Trial have demonstrated that screen size, impeller speed and impeller shape can be fluctuated to influence granule size distribution (Reynolds, 2010 and Samanta, 2012). It has additionally been illustrated that decrease screen Size combined with enhanced impeller speed brings about smaller granule size (Motzi and Anderson, 1984). Some connection be tween's granule properties and milling efficacy has likewise been illustrated. Inghelbrecht and Remon, 1998) have found that low friability related to decreased clean development during processing. Verheezen et al. (2004) have examined impact mill for granule size decrease and found that granule quality significantly affects the final particle size accomplished. As well, fines formation was observed to be related with the aggregate level of size decrease.

1.2 Artificial Neural Networks

An Artificial Neural Network (ANN) is a computational model motivated by system of natural neurons, wherein the neurons process output from sources of information. All signs can be allotted parallel values as either 1 or -1 (Puri, 2016). The neuron figures a weighted total of information sources and looks at it to a limit of 0. If aggregate is higher than the threshold, the yield is set to 1 or to-1. The power of the neuron comes about because of its aggregate conduct in a system where all neurons are interconnected. The meshwork begins developing: neurons consistently assess their

yield by taking an observation at their information sources, figuring the weighted aggregate, and after that contrasting with a threshold to choose in the event that they ought to fire. One study is that the advancement of an ANN causes it to achieve a state where all neurons keep working, however no further changes in their state happen. A network may have more than one stable state, and it is controlled by the decision of synaptic weights and threshold for the neurons (Puri, 2016) ANN is a computational model that depends on a machine learning method. It works like a human brain neuron framework. This machine learning system takes after a similar example of discovering that is gaining from its past experience and mistakes like mammalian neurons to accomplish the objective value. A calculation outlined on the fact that a neural system framework to implement a parallel computational power of neurons. ANN memorize from its past experience and mistakes in a nonlinear parallel way utilizing a mainstream calculation named "feed forward and backpropagation." The expression "feed forward" depicts how the neural system acts and reviews arrangement. In a feed forward neural system, neurons are just associated forward. Every layer of the neural system contains associations with the following layer, however there are no associations back. The expression "back propagation" portrays how this kind of neural system is prepared. Back propagation is a type of managed preparation. When utilizing a managed preparing technique, the system must be furnished with both specimen inputs and predicted output. The predicted output is matched against the genuine output for given information. Utilizing the predicted output, the back propagation preparing calculations takes an ascertained error and alters the weights of the different layers in reverse from the output layer to the input layer to decrease the estimation of error (Puri, 2016). The data is conveyed to output in the case that it accomplishes the objective; else, it is back propagated. Thus, the name of the calculation is feed forward back propagation. The objective value might be accomplished if the total weighted amount will meet the base limit and thus encourage feed forward or back propagate for further preparing. ANN could be a brilliant decision to process huge natural information for a more precise forecast. The prognostic tools can be planned in view of ANN's capable learning and processing qualities, which can work splendidly even in an exceedingly probabilistic and strident environment. The power of the neuron is because of its aggregate activity in a system where all neurons are interconnected. The system is being developing; neurons consistently assess their yield by taking a comparing with their sources of information, computing the weighted total, and afterward contrasting with a threshold to conclude to have activity or no (Puri, 2016).

1.3 Contributions of the Research

The preparing factors related with the comminution of pharmaceutical granulations were examined. The four factors picked were quadro model, mill speed, screen size and impeller shape. Analyses were performed on a sodium chloride particles utilizing appropriate systems of experimental scheme. Investigation demonstrated that the four factory factors can't be considered freely yet rather at the level of mixes. An entire description of the mill output as indicated by particle size distribution is then conceivable based upon these mixes of plant factors.

In the above description, the artificial neural network (ANN) is the parameter for the prediction of the mean particle size.

This project is utilized to make another approach. Artificial neural network, for the prediction of the mean particle size and the evaluation of the parameters for the contribution on powder milling of sodium chloride. The information was collected by experimental and theoretical model.

The investigations presented in this thesis prove that the ANN can predict the mean particle size.

The specific objective of this assignment is to create Artificial Neural Network (ANN) models to foresee mean particle size in powder milling of sodium chloride.

1.4 Outline of thesis

In this chapter, the introduction of milling, artificial neural network is presented. Overview of artificial neural network including the definitions and the basic concepts of artificial neural networks, and the advantages of ANNs over conventional statistics is provided in Chapter 2. In Chapter 3, the applications of neural network in the fields of drug delivery, target validation, target discovery, ADME and toxicity were reviewed. The limitation of neural network in drug discovery was also discussed in this chapter. The applications of neural network in pharmaceutical formulations, preformulations, in-vivo in-vitro correlations were presented in Chapter 4 while the ANN applications in pharmaceutical product and process development were reviewed in Chapter 5. Finally, the materials and methods, results and discussion and conclusion were presented in Chapters 6, 7 and 8, respectively

CHAPTER TWO

LITERATURE REVIEW

2.1 Introduction

Artificial neural networks (ANN) simulation tool that would have outlined on mimic exactly works of the human brain utilizing diverse Taking in algorithms, which could figure out from experience. ANN need those amazing data transforming features about human mind for example, nonlinearity, high parallel- ism, robustness, shortcoming Also disappointment tolerance, learning, capacity with handle loose and fluffy data and their proficiency will be generalized. (Basheer and Hajmeer, 2000).

Thus, ANN could be used to take care of confounded genuine issues for example, design classification, clustering, function approximation, and streamlining (Suna et al., 2003).

There are several ANN models that have been produced to various requisitions. Dependent upon those taking in (training) algorithm, preparation of the ANN model might be a chance to be under observation of experts or unendorsed. To be under observation of experts training, the ANN model may be exhibited with input / output information sets; for unendorsed training, those ANN model will be introduced for input information alone, and the model evaluates the design of the information. Considering those topology, the association for ANN might be feedforward and feedback. Over A feedforward ANN model, those associations the middle of the nodes don't structure cycles. In a feedback or repetitive ANN model, there need cycles in the connections. To some feedback ANN models, every occasion when an information is presented, the ANN model must repeat to a possibly while in front of it produces a response. Feedback ANN models are usually more difficult to train than feedforward ANN models (Sarle, 1994).

2.2 Brain Networks

Seeing neuronal networks of the brain need opened prospect of the artificial neuronal network software and adaptive framework. These frameworks differ starting with single-alternately double-layered units to multiple-layered units for different inputs. To build up the programming that decide task, "weights" have been presented with change in the output by changing the limitations and the connectivity of the neurons. In this way, through the variable limitations of connectivity,

ANNs can be self-governing and self-directed yet constructible system through external information or indigenous input to the type of verbalized Standards.

The computational capacity of ANNs might be related with the quantity of Neurons and their network and the configuration and number of weights. In spite of the way that multilayer perceptron is thought to be a universal approximator, no known firm information is accessible with respect to the quantity of neurons Involved and the rational or irrational weights (Arslan, 2016). Following research work showed that a particular linear and cycled neuronal design of a set number of neurons with estimated(rational) valued weights can keep up total qualities of an all universal turning machine (Siegelmann, 1999). Different experts have demonstrated that changing the weights in the correspondent recurring estimations of the neural systems from rational and real to irrational weights delivers a machine with super-turing calculation that takes care of the halting issue of Turing machines (Siegelmann, 1999). ANNs contain the capacity to store data. The quantity and intricacy can decide the model of function (Arslan, 2016). Although not a fully dependable guide to applications, convergence in ANNs May be achieved if several factors coexist, namely local minima, optimization, and the amount of data or parameters presented. The test of overtraining emerges when an over quantified framework is made in an application and the limit of the system outperforms the wanted parameters. This could be cured by the cross-validation. Cross-validation permits the appraisal of the level of precision of the execution of a predictive model. Keeping in mind the goal to accomplish this expectation, a model is presented to a known dataset used to prepare the model and a new dataset against which the model is checked (Rochester, et al., 1956). Cross-validation gives a comprehension with respect to the way that a model simplifies a new dataset from a genuine dataset, shields type III data error from happening where oversampling ended up being unsafe, exorbitant and thus limits some of the associated challenges, such as over fitting (Rosenblat, 1958). To guarantee insignificant fluctuation, various arrangement of cross-validation must be performed. Regularization, then again, is a characteristic idea that indicates a procedure proposed to balance overfitting and resolve new tasks, for example, experimental and structural hazards, by selecting probabilities over less difficult models to profoundly complex models with various parameters in respect to the number of investigations. A mean squared error cost function can be used to survey variance through the figuring of confidence intervals of the system Output, which depends on the recurrence with which investigated intervals contain genuine parameters (Berndt et al., 1974).

2.3 Basic Concepts

The fundamental theme of ANNs, as illustrated by Hopfield (1982) is that computational properties can develop as aggregate properties of frameworks having countless proportional parts (i.e., neurons). This idea is equivalent to the rise of a vortex design in fluid flow. The synthetic neuron (likewise called handling component, PE) is the building segment of the ANN. It is intended to mimic the qualities of the biological neuron (Figure 2.1). The arriving impulse, called inputs (xi), intensified by the association weights (wi), which similarly to natural neurons can be "excitatory" (+) or "inhibitory" (-), are initially summed. An "activation" function is then applied to create the output(y). The decision of the activation function is optional. It is normally nonlinear, monotonic, and produces a yield inside a limited range ({0, 1} or {-1, 1}). For some learning calculations (e.g., backpropagation of error) the capacity must have a limited subordinate. Generally utilized activation functions are the sigmoidal capacity, hyperbolic tangent function, linear functions, Gaussian function, and threshold functions. ANN for the most part include a progression of interconnected layers of PEs, every PEs accepting input(xi) from each of the PEs constituting the former layer, and sending its output to every PEs of the accompanying layer. The organization of the PEs in ANN can be marginally more convoluted than depicted above and will be explained more in following detail (Hopfield, 1982).

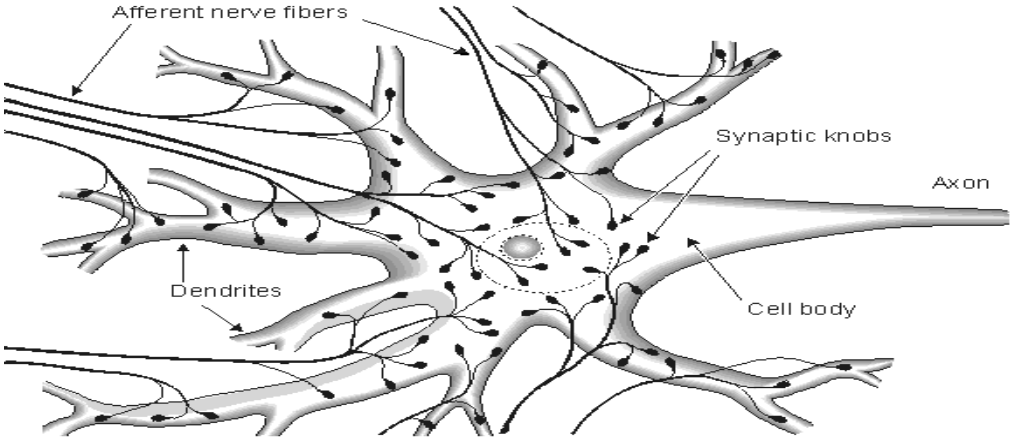

Figure 2.1: Neuron cell

2.4 Types of ANNs

In view of the design and association form of the framework, ANNs are categorized either feedforward or repetitive systems. There are five essential form of neural framework:

1. Multilayered perceptron/backpropagation framework: The most well-known neural system model is the multilayer perceptron. These are controlled frameworks that work on the backpropagation calculation.

The error got per repetition is back propagated in the framework with the end goal that the mistake is minimized extensively.

2. Kohenen neural Framework: These are unsupervised frameworks and the property to be observed is not utilized during the preparation procedure. The Kohenen framework ventures the points from a multidimensional space into a 2D plane.

The data is passed on from every layer to layer simply like the data is passed starting with one neuron then onto the next (Figure 2.2). The cell body is accountable of handling the data; comparatively, the processing components of the hidden layer are accountable of investigating the information. All information provided is allotted a particular weight. The information is weighted, collected, and the output created in correlation with that of the reference set utilized during the training of the ANN. The mistake is minimized with each cycle.

3. Counter propagation framework: Supervised framework utilizing Kohenen's preparation calculation are called counter propagation (CPG) systems. In CPG systems, just the input layer is considered for space figuring though in the adjustment steps; the weights of both the input and the output layers are adjusted.

4. Bayesian neural framework: Neural frame work that work with the Bayesian perspective and give a reliable structure to statistical design acknowledgment and information evaluation.

5. Recurrent neural network (RNN): In a RNN, the associations between the PEs shape a coordinated cycle. This represents the dynamic time-based performance of the system. RNNs can utilize their internal memory to process inputs. Elman neural systems are a kind of recurrent neural network where the information is spread in a standard feedforward form before the learning

principle is practiced. During the learning, the background units continuously keep up a duplicate of the past quantities show in the hidden units (Vineetha, 2016).

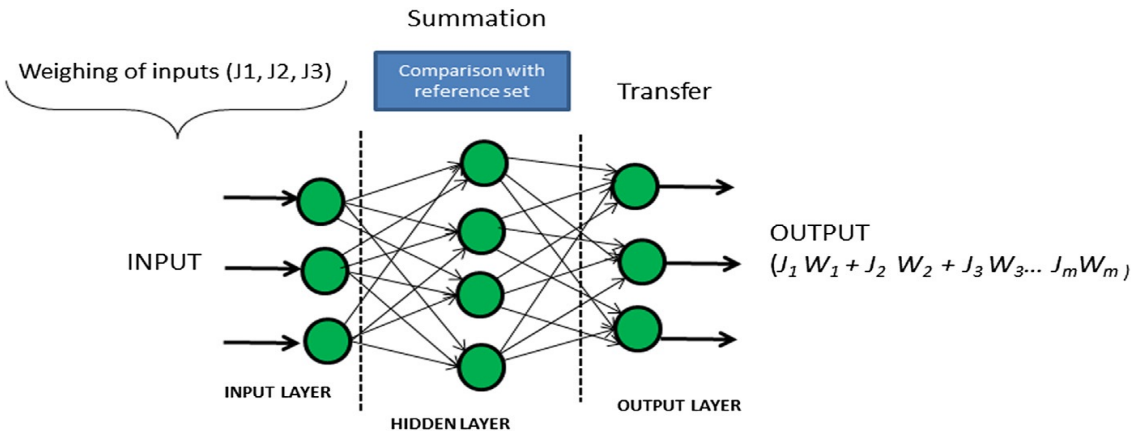

Figure 2.2: Functioning of an ANN.

2.5 Back propagation

The back-propagation system frequently alters the weights of associations in the system in order to minimize the distinction between the real output vector of the system and the anticipated output vector. The preparation of a MLP starts by first allocating irregular quantities to the associations' weights (wi) between every PE. A first example (x) (or scope of tests, i.e., batch method) of the training input information set is sustained through the MLP creating a first arrangement of system output, utilizing these fundamental steps: (1) input summation C xi wi and (2) actuation function (C xi, wi). The first arrangement of output are contrasted with the objective estimations of the training information set. New associations' weights are then registered in light of the contrasts between system output and target values. This represents one iteration (or epoch. The procedure is cycled until the contrasts between system output and target values achieve an acceptably low level.

2.6 Advantages of ANNs Over Conventional Statistics

ANNs have the followingl advantages as compare to the other conventional statistical methods:

- An ANN gives an acceptable outcome when the reaction variable is highly nonlinear.
- Historic or literature information can be utilized for preparing. Neural systems are more helpful to meager and uproarious information than statistical modeling packages.

- ANNs can make utilization of inadequate information.
- No earlier information of the basic statistical nature is required.
- A neural system has a one of a kind capacity of detecting configuration in data. Thusly, it can be utilized to rank detailing factors that are most basic in impacting the parameters of intrigue.
- Once trained, neural systems are intrinsically quick and can prompt to saving in time and the cost of product development.
- Unlike statistical models, an ANN display works upon the investigational information without data transformation.
- An ANN requires no hypothesis to be made about the nature or importance of interconnections between composing parts or the relationship between the elements and the properties of the formulation (Das et al., 2016).

2.7 Software Used for ANN Applications

Various ANN-based integrated computer programs are commercially available. These programs are widely used by researchers and are gaining more acceptances in the area of pharmaceutical formulation development (Das et al., 2016).

Table 2.1: Used software for Artificial intelligence.

Commercial Software	Freeware Software Net-II
1-Statistica Neural Network	-Spider Nets Neural Network Library1
2-TNs2Server	2-NeuDC
3-DataEngine	3-Binary Hopfield Net with free Java Source
4-Know Man Basic Suite	4-Neuralshell
5-Pertek	5-PlaNet
6-Saxon	6-Valentino Computational
7-eCANSE (Environment for Computer-	7-Neuroscience
8-Aided	8-Work Bench
9-Neural Software Engineering(	9-Neural Simulation Language Version-
10-Neuroshell	10-NSL
11-Neurogen	11-Brain Neural Network Simulator
12-Matlab: Neural Network Toolbar	

CHAPTER THREE

APPLICATIONS OF ANN MODELING IN DRUG DELIVERY AND PHARMACEUTICAL RESEARCH

3.1 Introduction

The potential applications of ANN methodology in the Pharmaceutical sciences are broad as ANNs capabilities can be summarized by modeling, pattern recognition and prediction. Thus, applications of ANNs include drug modeling, dosage design, protein structure and function prediction, pharmacokinetics and pharmacodynamics modeling, as well as, interpretation of analytical data, and in vitro/in vivo correlations (Sutariyaa et al., 2013). ANNs Applications Analytical Data Analysis and Structure Retention Relationship (SRR) Methodology in Pharmacological Research as ANNs can recognize patterns from complex sets of analytical data, they become very useful in data analysis of pharmacological research due to their ability to recognize even non-linear relationships from noisy data. For instance, ANNs can be applied in analysis of spectral data of multicomponent samples such as mixtures for quantification of the concentrations in the mixture using the whole spectrum in the identification process (Ni et al., 2009). Hasani et al. (2007) used ANNs for detection and calibration of amino acids with similar structures and spectrums such as tryptophan, tyrosine, and histidine. Moreover, ANNs can assist in determining of concentrations of a chiral sample and enantiomeric excess in a single spectrophotometric measurement due to their ability to identify non-linear relationships (Zhu, 2006). For instance, ranitidine hydrochloride, one of the most commonly prescribed antihistamines, exists in two forms, Form 1 and 2. Application of ANNs in development of method of quantification of ranitidine-HCL using diffuse reflectance IR spectral data and X-ray diffraction allows for sensitive and quick identification of Form 1 concentration in a multicomponent tablet without extraction of active ingredient and Form 1 (Agatonovic-Kustrin et al., 1999 and 2000). Usefulness of ANNs in analysis of peptide MS/MS spectral data has been also demonstrated. The constructed ANN was used to analyze the data generated by Sequest, a widely used protein identification program. ANN was demonstrated to classify automatically as either "good" or "bad" the peptide MS/MS spectra otherwise classified manually. An appropriately trained ANN proves to be a high throughput tool facilitating examination of Sequest's results and authors recommended

a routine use of this approach in handling large MS/MS data sets (Ba et al., 2004). ANNs can also be used as the basis of computer-assisted optimization method for selection of optimal gradient conditions for anion separations in chromatograph (Maddena et. Al, 2001).

3.2 Applications of ANNs in Drug Discovery

ANN can capacity find complicated, nonlinear relationship. ANNs are in this way additionally alluded to as "digitalized models of the brain." Neural framework. Discover their application in numerous differing fields, for example, engineering, pharmaceutical Sciences, and medicine. ANNs are frequently being used for regression and discriminant data analysis one of the numerous uses of ANN lies in the field of medication plan and disclosure. ANNs are being increasingly applied for the screening of large inhibitor libraries, also referred to as virtual screening (VS) or high-throughput screening (HTS), assessment of the properties of the ligand in terms of their pharmacophoric features, docking, quantitative structure activity relationship(QSAR) studies, and prediction of the ADME-Tox properties. "Target" is illustrated as atoms and sites that contribute in the start and advancement of disease. Their restraint or down-regulation lessens the capacity of illnesses and aides in reestablishing the ordinary condition of cells/tissues/organ (Chauhan et al., 2016).

3.3 Target Validation

It includes the recognizable proof of a feasible viable target, its role in the pathological pathway, and the assessment of chemically inhibiting it with drug (Chauhan et al., 2016).

3.4 Target Discovery

The initial two phases of target endorsement include, in progression, the revelation of biomolecules of intrigue and the assessment of such biomolecules for their potential as medication targets a procedure we might overall allude to as target discovery (Chen and Du, 2007). Given the huge number of type of particles that can be targets (e.g., receptors, proteins, genes, enzymes, etc.), a correspondingly huge number of strategies (e.g., in vitro examination, information mining of existing information, phenotype screening, and so on.) are utilized as a part of target disclosure, in numerous cases, however, ANNs can increment both the speed and viability of these approaches. ANNs have likewise demonstrated utility in finding physical areas of focused particles. In an

examination of the areas of photosensitizers (PSs) for photodynamic malignancy treatment of strong tumors. Utilized ANNs to anticipate the nearness or nonappearance of PSs on cell organelles, accordingly making a device to recognize contender for such treatment (Tejedor-Estrada et al., 2012).

3.5 Target Screening

When potential drug targets are recognized, a bioassay must be intended to quantify the activity from chemical interactions with such focuses on, a high throughput Screening (HTS) handle must be produced to test thousands (if not millions) candidates, the screening performed, and any investigated interaction confirmed (Chen and Du 2007). Given the interconnections between these Steps, we might allude to the whole procedure as target screening. ANNs can be utilized to both recognize whether targets are available in known sites and distinguish already unknown target sites and to anticipate different properties of the agents being researched once the information are obtained (Murphy, 2011 and Xu et, al, 2008).

ANNs might be utilized for an assortment of tasks occurrence to, or related to, target screening; these incorporate, however are not constrained to, the accompanying: (1) the expectation of which targets are probably going to transform and in this way cause drug resistance (Hao et al., 2012); 2) the prediction of drug potency at particular sites, for instance, Borisek et al. (2012) utilized a counter-spread ANN QSAR model of benzamide-containing amino nitriles with great predictive capacity. The nature of all models created was assessed inside by leave-one-out cross-validation on the training set and externally by a self-governing authentication; and (3) virtual screening against numerous objectives (Speck-Planche et al., 2012)**.**

3.6 ADME

Computational modeling and advancement of of absorption, distribution, metabolism, and elimination (ADME) has turned into an essential piece of drug design, with comparing achievement in excreting unsuccessful substances in the medication development procedure; while in the 1990s roughly 40%of clinical trials unsuccessful for ADME-related reasons, by 2010 this rate had been lessened to 10-14% (Hecht, 2011). ANNs, while by no ways only held accountable for the above reduction, shape or form exclusively cause of the above lessening, have discovered use in every parameter of the four parts of ADME. Talevi et al. (2011) created linear and nonlinear predictive QSPR models to anticipate the human intestinal ingestion rate. They utilized only four

atomic descriptors as a part of the model to get structure property relationship. Yan et al. (2013). built up a few quantitative models for the expectation of penetration through the blood brain barrier(BBB) by a multilinear regression, a SVM, and an ANN investigation. In their work, every atom was spoken to by worldwide and shape descriptors, 2D autocorrelation descriptors, and RDF descriptors figured by ADRIANA Code. The models indicate great prediction performance on the test set compounds in another case, the ANN-group contribution (ANN-GC) technique has been connected to anticipate the solubility of unadulterated substance mixes in water over the (293-298) K temperature range at atmospheric pressure. The outcome demonstrates a squared correlation coefficient (R2) value of 0.96 and a root mean square error of 0.4 for the calculated/predicted properties with respect to existing experimental values, demonstrating the reliability of the proposed model (Gharagheizi et al., 2011). There are guidelines and recommendation distributed by Larregieu and Benet (2013) for enhancing the exactness in anticipating human intestinal penetrability utilizing Caco-2 permeability measurements and in vitro predictive models**.**

3.7 Toxicity

As is toxicity overwhelmingly the most widely recognized reason that medications are expelled from the market (Zhang et al., 2012) it is vital that toxicities be identified at first notice could reasonably be expected in the medication advancement process. Here, once more, ANNs can play a role. ANNs are utilized as a part of a wide range of parts of toxicity recognition and expectation, ranging from foreseeing toxicities of ant streptococcal medications in rats (Speck-Planche et al., 2013) to generate mandated toxicological data for drugs marketed in the European Union (Dearden and Rowe, 2015). More prosaically, they are used in detecting numerous human toxicities such as Ames genotoxicity (Xu et al., 2012), cardio toxicity (Huang 2013), hepatotoxicity (Liew et al., 2011).

3.8 Limitations of ANNs in Drug Discovery

A portion of the restrictions and issues that neural systems experience are as Follows:

1. Assorted of the training information set: The dataset utilized for training the ANN should be variable enough. Absence of assorted of the sample Dataset is the most widely recognized issue that ANNs confront. Training the ANN with the right dataset is essential for the correct prediction of the test dataset.

2. Mistakes in standard dataset: The standard dataset ought to be free of mistakes as this may prompt to mistakes in the expectations made for the test set.

3. Overfitting: This alludes to the extent of the ANN and the quantity of PEs included. ANN ought to be of a suitable size with the end goal that there is no undertraining.

4. Overtraining: Overtraining of the ANN ought to be avoided, generally ANN tries to acquaint itself with the output.

5. The analyst ought to be very much aware of the issue he or she is attempting to unravel utilizing ANN. ANNs could be especially valuable for medication disclosure attributable to their capacity to interpret nonlinear relationships and complex patterns and examples in the datasets and models.

ANNs have the capacity to determine nonlinear relationships and consequently are invaluable over other statistical strategies during pattern investigation. They can be connected to model complex connections between various physicochemical properties, mapping the relationship between few factors with the compound structures. ANNs are thusly progressively being utilized as a part of the drug discovery process. The regular drug discovery turns out to be long and costly. It is valuable to apply diverse neural systems for a faster, effective, practical, and more secure drug delivery (Mandlik et al., 2016).

CHAPTER FOUR

4.1. ANNs in Pharmaceutical Formulation Development

Pharmaceutical design requires the enhancement of preparation and process factors. These associations are hard to model utilizing traditional strategies. One of the challenges in the quantitative way to deal with design configuration is the understanding of connections between causal variables and individual pharmaceutical outcomes. Moreover, a required formulation for one property is not generally required for alternate property. The utilization of ANNs is by all accounts most appropriate for managing complex multivariate nonlinear connections. ANNs can recognize and learn correlative scheme amongst input and output information sets. These components make them appropriate for taking care of issues in the zone of advancement of definitions in pharmaceutical item improvement (Das et al., 2016).

The worth of neural systems for formulation optimization has been accounted for by different analysts, and diverse methodologies are being utilized persistently for formulation optimization. Several authors have investigated the utilization of formulation variables, for example, the level of excipients utilized as a part of a formulation as input or causal factors and the rate of drug release at various phases of a disintegration test as reaction elements for ANNs.

Some examples of ANN systems used in formulation and in pharmaceutical processing with their reference (Das et al., 2016).

Liposomes: ANN as an alternative to multiple regression analysis in optimizing formulation Parameters for cytarabine liposomes (Subramanian et al., 2003).

Hydrogels:

1. Multiobjective simultaneous optimization based on ANN in a ketoprofen Hydrogel formula containing o-ethyl menthol as a percutaneous absorption enhancer (Takahara et al., 1997).
2. Simultaneous optimization based on ANNs in ketoprofen hydrogel formula containing o-ethyl-3-butylcyclohexanol as percutaneous absorption enhancer (Wu et al., 2001).

Tablets:

1. The effect of experimental design on the modeling of a tablet coating Formulation using an ANN (Plumb et al., 2002).

2. Utilization of ANNs for the determination of the most suitable formulation and processing variables to anticipate the in vitro disintegration of sustain release minitablets (Leane et al., 2003).

3. ANN and pharmacokinetic simulations in the design of controlled release Dosage forms (Chen et al., 1999).

4. The application of generalized regression neural network in the Modeling and optimization of aspirin extended-release tablets with Eudragit® RS PO as matrix substance (Ibric et al., 2002).

5. Formulation and optimization of theophylline controlled-release tablet Based on ANNs (Takayama et al., 2000).

6. ANN in the modeling and optimization of aspirin extended-release Tablets with Eudragit L 100 as matrix substance (Ibric et al., 2003).

7. Comparison of ANN with classical modeling technique using different Experimental designs and data from a galenic study on dosage form (Borquin et al., 1998).

8. Pitfalls of ANN modeling technique for datasets containing outlier Measurements using a study on mixture properties of directly compressed dosage forms (Borquin et al., 1998).

9. Optimization of diclofenac sodium dissolution from sustained release Formulation using an ANN (Bozic and Kozjek, 1997).

Powders:

1. Modeling properties of powders using ANN and regression: the case of Limited data (Zolotariov and Anwar, 1998).

2. ANN and modeling of powder flow (Ibric et al., 2002).

Pellets:

Use of ANNs to predict drug dissolution profiles and evaluation of Network performance using similarity factor (Peh et al., 2000).

Gelispheres:

Textural profiling and statistical optimization of cross-linked calcium Alginate pectinate-cellulose acetopthalate gelisphere matrices (Pillay and Danckwerts, 2002).

Transdermal:

1. Prediction of skin penetration using ANN modeling (Degim, et al. , 2003).

2. Optimization of a vehicle mixture for the transdermal delivery of Melatonin using ANNs and response surface method (Kandimalla, et al. , 2000). Granules The advantages by the use of neural networks in modeling the fluidized Bed granulation process (Murtoniemi et al., 1994).

Emulsion: Lipophilic semisolid emulsion system viscoelastic behavior and Prediction of physical stability by neural network modeling (Gasperlin et al., 1998).

4.2 ANN Applications in Preformulation Studies and Optimization of Pharmaceuticals

ANNs can be a valuable device for preformulation concentrates on, as they can be utilized to give way the chemical properties of various substances. Ebube et al. (2000) utilized ANNs to predict physiochemical properties of amorphous polymers. The model could precisely anticipate (mistake of 0.8%) the connections between chemical formulation of the polymer and the water take-up profiles, consistency, and glass transition temperatures. (Ebube et al., 2000). These results show the potential that the ANN model has as a preformulation tool. The nonlinear pattern recognition abilities of ANN models can also be incredibly useful in the optimization of pharmaceutical formulations and dosage methods. ANNs have been shown to be capable predictors of formulations in vivo dissolution time profiles and bioavailability profiles, making it possible to identify formulations with such desired characteristics (Chen et al., 1999). Subramanian et al. compared the optimization ability of ANNs to that of MLR analyses (Subramanian et al., 2003). An ANN model and 33 factorial design model were used to optimize the formulation parameters of cytarabine liposomes. A set of input variables was used with 11 hidden layers and one output variable (percentage drug entrapment). Optimal drug entrapment was found to occur in a 1:13 drug to-lipid ratio. The optimization was then verified by preparing additional formulations, revealing that the ANN model provides more accurate predictions (Subramanian et al., 2003). Kumar et al. (2011) used ANNs to optimize fatty alcohol concentration in oil/Water emulsions. An R2 value of 0.84 shows that the ANN model was successful in predicting the optimal concentration. In order to optimize the polydispersity index of acetaminophen nanosuspensions, Aghajani et al. used an ANN model with independent variables: surfactant concentration, Solvent temperature, and flow rate of solvent and antisolvent (Aghajani et al., 2012). Using the Model, it was determined that low polydispersity index (PDI) can be obtained with high antisolvent flow rates and solvent temperatures and low solvent flow rates. ANNs have also shown potential as optimization tools for time dependent pharmaceutical formulations (Xie, 2008).

4.3 In Vivo in Vitro Correlations

The most favorable utilization of the ANN model is, maybe, its capacity to predict In vivo connections from in vitro outcomes. Here once more, it is the nonlinear capacity of the ANN show isolation from other regression methods. Dowell et al. contemplated the capacity of various ANN models as in vitro in vivo correlation (IVIVC) apparatuses. For less difficult arrangements of information, the feed forward neural network (FFNN) and the generalized regression neural network (GRNN) were the best due to their wide prescient capacity, while for more mind-boggling datasets, it might be important to utilize different sorts of neural systems, for example, bounce association neural systems or intermittent neural systems (Dowell, 1999). Parojcic (2007) compared the ability of the GRNN model to that of deconvolution and convolution approaches in predicting IVIVC for the drug release of paracetamol matrix tablet. Findings showed that the GRNN model was superior to both approaches, resulting in a better IVIVC in a model that is easier to use for further research. IVIVC for orally inhaled drugs is difficult to obtain, as there are more variables affecting the drug's efficacy, such as lung deposition and total systemic bioavailability, making ANNs great candidates as possible solutions (De Matas et al., 2010). A similar study developed an IVIVC for mild/moderate asthmatics receiving monodisperse salbutamol sulfate aerosols, with seven input variables and one hidden layer (De Matas et al., 2010). Here again, the ANN model showed its ability to be an effective predictive tool with results revealing the significance that aerodynamic particle size has on patient bronchodilator responses (De Matas et al., 2010). ANN models have also shown the ability to develop IVIVC for self-emulsifying delivery systems, dissolution kinetics in the GI tract, and metabolic clearance for new drugs (Fatouros et al., 2008).

CHAPTER FIVE
ANN IN PHARMACEUTICAL PRODUCT AND PROCESS DEVELOPMENT

5.1 ANNs in Tablet Manufacturing

Tablets are the common dosage form available on the market because of their desirable advantages, which include the following: patient suitability; noninvasive; convenience; it is difficult to damage with tablets; they are easy to swallow, especially if coated; they are relatively easy to manufacture and package; they deliver precise dosing; they provide increased stability of the drug when compared with liquid dosage forms; product identification is easy, especially with use of imprints; and they can be enteric coated or designed for delayed release. Disadvantages of tablets include formulation complications if the drug resists compression; some drugs have poor wetting, poor water solubility, or poor dissolution, which might affect the drug's bioavailability; and a bitter taste of the drug might require coating.

There are three main methods to produce tablets:

- Direct compression: The drug itself is compressible and/or it can be mixed with a filler that is compressible (e.g., lactose).
- Wet granulation: The powder mixture of the drug and excipients is Granulated by wet methods before compression.
- Dry granulation: The powder mixture of the drug and excipients is Granulated by dry methods before compression (Arora, 2013).

Aksu et al. (2012) applied ANNs in the manufacturing of tablets by a direct compression technique. From the study, they concluded that ANNs provide a huge time benefit; in addition, these programs are not used for the pharmaceutical industry as much as other industries. The commercial software program FormRules was trained to describe the relationships between raw material properties and output properties. Using the key inputs, another commercial software package, INForm, was used. The objective of their study was to optimize Ramipril tablet formulation and to create knowledge and design spaces, which were the new approach for the pharmaceutical product development with the aid of an ANN program and genetic programming. After the optimization, it was confirmed that the explored formulation was within the design space. In addition, given that the knowledge

and the design areas were too close to each other, they realized that it was possible to acquire more information regarding the knowledge area through trials using hydroxypropyl methylcellulose and lubricants in proportions other than those used in the present study.

In addition to the effect of the formulation on the tablet properties, the determination of the values that may create a model is of importance for design area studies. Using different computer programs for this study provided a significant benefit in terms of evaluating the accuracy of the findings. This was especially true for the programs that generated an equation at the end (Aksu et al., 2012 and Chen, 1999).

5.2 ANNs in Minimization of the Capping Tendency by Tableting Process Optimization

Capping is the term used to describe the partial or complete separation of the top or bottom crowns of a tablet from the main body of the tablet during ejection from the tablet press or during subsequent handling. Causes of tablet capping include the following:

1. A huge quantity of particles in the granulation
2. Too dry or very low water content (leading to loss of proper binding action)
3. Not carefully dehydrated granules
4. Inadequate quantity of binder or unsuitable binder
5. Inadequate or unsuitable lubricant
6. Granular mass too cold (Rana and Kumar, 2013).

ANN were used for modeling of the effect of the particle size and the tableting machine settings on the capping coefficient. The suitability of routinely measured quantities for prediction of the tablet quality was tested. The results showed that model-based expert systems based on the contemporary routinely measured quantities can significantly improve the trial and error procedures; however, they cannot completely replace them. The modeling results also suggest that in cases in which it is not possible to obtain enough measurements to uniquely identify the model, it is beneficial to use several modeling techniques to identify the quality of model prediction (Ales et al., 2009 and Takka et al., 2011).

5.3 ANNs in Determination of Factors Controlling the Particle Size of Nanoparticles

Nanoparticles are roughly defined as particles with a product measurement of less than 100 nm, particularly in the field of pharmaceuticals. They contain particles that are as large as 500 nm. For comparison, a human hair is nearly 80,000 nm wide. Most characteristics of nanoparticles are related to size. Despite, the novel characteristics of nanoparticles do not prevail until the size has been reduced to the nanometer scale. The particle size and size distribution of nanoparticle as critical properties can be determined by transmission electron microscopy, photon correlation spectroscopy, surface area analysis (Brunauer-Emmett-Teller), X-ray diffraction peak broadening analysis, etc. Researchers have also shown that opsonization and subsequent recognition and phagocytosis by macrophages are strongly correlated with the size of particle, and there is a significant correlation between particle size and protein absorption to the particle. Different formulation factors affect the particle size of nanoparticles obtained, such as type of polymer used, molecular weight of polymers, medium used for nanoparticle preparation, pH of the medium, temperature, presence of ions in the medium, stirring speed, stirring time, etc. (Akbari B, et al. , 2011). Asadi et al. (2011) prepared biodegradable nanoparticles of triblock poly (lactide)-Poly (ethylene glycol)-poly (lactide) - (PLA-PEG-PLA) copolymer and studied the factors controlling the particle size of the prepared nanoparticles using an ANN. The purpose of their study was to prepare nanoparticles made of triblock PLA-PEG-PLA with controlled size as the drug carrier. ANNs were used to identify factors that influence particle size. In this way, PLA-PEG-PLA was synthesized and was made into nanoparticles by nanoprecipitation under different conditions. The copolymer and the resulting nanoparticles were characterized by various techniques such as proton nuclear magnetic resonance spectroscopy, Fourier-transform infrared spectroscopy, gel permeation chromatography, photon correlation spectroscopy, and scanning electron microscopy. The developed model was evaluated and found to be of high quality. The model was then utilized to study the effects of processing factors including polymer concentration, amount of drug, solvent ratio, and mixing rate on particle size of Polymeric nanoparticles. They observed that polymer concentration is the most affecting parameter on nanoparticle size distribution. Their salts demonstrate the potential of ANNs in modeling and identification of critical parameters effective on final particle size (Asadi et al., 2011).

5.4 Prediction /optimization of controlled release drug delivery systems

Several investigators have used different types of ANN models and learning algorithms to predict and or optimize different types of controlled release formulations. (Suna et al, 2003).

5.5 Controlled release tablets

Chen et al. (1999) utilized an artificial neural network (ANN) and pharmacokinetic reenactments in the outline of controlled-release formulations. Seven formulation factors and three other tablet factors (water content, molecule size and hardness) for 22 tablet details of a model sympathomimetic medication were utilized as the ANN model inputs. In vitro aggregate rate of medication discharged at 10 distinctive examining time focuses were utilized as output. The ANN model was created and prepared from the input and the output information sets utilizing CAD/ Chem software (Process Simulation Software is one of best tools to increase productivity and improve engineering decisions in chemical industry) (version 4.6). The prepared ANN model was utilized to anticipate ideal plan structures considering two wanted in vitro dissolution–time profiles and two craved in vivo release profiles. The creators expected that the disintegration is the rate-restricting stride in the in vivo ingestion of the medication and that the division of medication retained in vivo is straightly identified with the in vitro disintegration of the medication. Three out of the four anticipated plans indicated great understanding between the ANN anticipated and the saw in vitro release profiles in view of contrast element, factor, f1 and similarity factor, f2 (Suna et al., 2003).

Bozic et al. (1997) built up an ANN model to enhance diclofenac sodium sustained release matrix tablets. Formulation variables including concentrations of cetyl alcohol, polyvinylpyrrolidone K 30 and magnesium stearate, and sampling time were selected as inputs. Twelve hidden nodes were included in the hidden layer. The rate of medication release at every examining time point was utilized as the output. A trained ANN model was employed to predict release profile and optimize formulation composition based on the percentage of drug re-leased (Suna et al., 2003).

Takayama et al. (2000) built up a concurrent streamlining procedure in which an ANN model was utilized to upgrade controlled release theophylline tablets prepared with Controse®, the blend of hydroxypropylmethyl cellulose with lactose and cornstarch. The release profiles of theophylline

were described as the whole of the quick and moderate release fractions. To construct the ANN show, the measures of Controse®, cornstarch and compression pressure were chosen as causal elements; the underlying weight of theophylline, the rate consistent in the fast release fraction and the release rate constant in the moderate release portion were picked as response factors. The outcomes anticipated by the prepared ANN show concurred well with the observed values. Accepting that the release rate of theophylline in the GI tract is equivalent to the absorption rate, the rate constant in the fast release fraction and the release rate constant in the slow release fraction were used as absorption rate constants. The plasma concentration profiles were simulated based on the pharmacokinetic parameters of theophylline. Optimal release parameters were chosen based on the simulated plasma concentration profiles. The optimization of the controlled release theophylline tablets was performed by generalized distance function method using the optimal release parameters (Suna et al, 2003).

A generalized regression neural network (GRNN) was utilized as a part of the outline of extended-release aspirin tablets by Ibric et al. Ten aspirin matrix tablet model formulations were set up with Eudragit® RS PO. The measure of Eudragit® RS PO and compression pressure were chosen as causal variables. In vitro dissolution–time profiles at four different sampling time points, as well as coefficients n (Release order) and log k (release constant) from the Peppas equation (NA., 1985) were assessed as release parameters. An arrangement of discharge parameters and causal variables were utilized for preparing. The upgraded GRNN model was utilized to predict the composition and process components for the optimized formulations, which could give the coveted in vitro drug release profiles. The two optimized formulations were then prepared and tested in vitro. The comparison between the GRNN predicted and observed in vitro profiles, and estimated coefficients showed that there is no distinction between the predicted and experimentally observed drug release profiles for the two tried formulations based on the difference factor, f1 and similarity factor, f2 (Suna et al., 2003).

A formulation optimization program based on the ANN model was developed to optimize salbutamol sulfate osmotic pump tablets by Wu et al. (2001). The amounts of hydroxyl propyl methyl cellulose (HPMC), polyethylene glycol 1500 (PEG 1500) in the coating solution, and the coat weight were selected as the causal factors. Both the average drug release rate v for the initial

8 h, and the correlation coefficient r of the combined measure of medication discharged versus time were utilized as response variables. Twenty sets of data were employed as training set. Ten sets of data were used as test data. Ten arrangements of information were utilized as test information. An ideal release rate and zero-order release characteristics were used as optimal response to optimize formulation factors. The improved detailing was arranged and tried in vitro. The optimal formulation factors were obtained using trained ANN model. The optimized formulation was prepared and tested in vitro. The release rate and correlation coefficient for the optimized formulation coincided well with the predicted results (Suna et al., 2003).

5.6 Controlled release particulates (pellets, beads and microspheres)

Several ANN models were developed to predict dissolution profiles of matrix-controlled release theophylline pellets prepared with microcrystalline cellulose (MCC) and glyceryl monostearate (GMS) by Peh et al. (2000). The multilayered perceptron (MLP) neural network with four inputs and one output was built using the NEURAL program. The conjugate gradient and simulated annealing algorithms were used as learning method for the ANN model. The portions of MCC, and GMS in the formulations, the time of sampling and the difference between the release rates of the preceding two time points were used as inputs, while the percentage of drug released at each sampling point was used as the output. The approach of leave-one-out cross-validation was used to train the ANN models. A complete release profile was obtained based on the prediction of each time point. The similarity between the ANN predicted and the actual dissolution profile was determined using the similarity factor, f2. The ANN predicted dissolution profiles were similar to the dissolution profiles obtained from the physical experiments indicated by high f2 values (above 60). (Suna et al., 2003). Vaithiyalingam et al. (2002) used the ANN to model the effect of process and formulation variables, viz., coating weight gain, duration of curing, and plasticizer concentration on in vitro release profile of verapamil HCl from multiparticulate beads formulated with a novel aqueous based pseudolatex dispersion. Inert beads (Nonpareil) were loaded with verapamil HCl and subsequently coated with a custom designed aqueous-based pseudolatex dispersion of cellulose acetate butyrate. Various bead formulations were prepared based on centered central composite experimental design. Aforementioned formulation and process factors were employed as inputs, and the cumulative percentage of drug re-leased at five different time points were employed as outputs to build ANN model using CAD/ Chem software (version 5.1).

A trained ANN model was used to pick formulation and process factors for optimized formulations. The optimized formulations were prepared and tested in vitro. The observed drug release data of the optimized formulations was close to the predicted release pattern, based on the ANN model (Suna et al., 2003). An ANN model was built using NeuroShell Easy Predictor, Version 1.01 (Ward systems Group, Frederic, MD, USA) by Yuksel et al. The ANN model was used to understand the effect of selected preparative variables during the solvent evaporation procedure for the preparation of acrylic micro-spheres. To develop the ANN model, three preparative variables, namely, the concentration of the dispersing agent (sucrose stearate), the stirring rate of emulsion system, and the ratio of polymers (Eudragit RS-L) were chosen as input variables; the particle size of the microspheres and T63.2%, the time at which 63.2% of drug is released were selected as response (output) variables. Thirteen model formulations were used to train the ANN model. Four additional formulations were prepared and evaluated to check the prediction and generalization ability of the trained ANN model. The results showed that an ANN method could provide a flexible and accurate method to study process and formulation factors (Suna et al., 2003).

5.7 Limitations of ANN in controlled release drug delivery system

ANN models cannot be used to elucidate the mechanistic nature of the correlation established between the variables. To obtain a reliable and trained ANN model, a formulator may need a lot of training data and computer time to do the training. The front end of work such as experimental design and data collection may be more time consuming than the traditional approach used by experienced formulation scientists. In addition, it is important for a formulator to recognize that there is no single software or modeling algorithm that can solve all problems (Suna et al., 2003).

CHAPTER SIX
Materials and Methods

6.1 Materials and Method

The data used in this study were obtained from a milling experiment carried out by Çelik (1995). In that experiment, Sodium Chloride was milled using two different models of a conical Quadro Comil equipment. The 193 and 197 models of Comil were attached with different screens and impellers and were run at different operating speed. The experimental variables were:

1- 2 Models of Quadro Comil (Model 197 and Model 193)
2- 3 types of Screen sizes (45, 75, and 94)
3- 3 different speeds (1700, 3250, and 4150 rpms)
4- 2 impellers (compressive and shear)

These represent variables or parameter (input) that affect mean particle size (output). Our aim in this study is to use these variables to predict the mean particle size (output) by using neural network and to analyze which parameters affect particle size.

6.2 Software

A MATLAB software. MATLAB 7.8 (R2009a) was installed on a windows system with processor of 2.1 GHz speed and 2 GHz of random access memory speed. A MATLAB script was written which loaded the data file, trained and validated the networks and saved the models architecture and performance in a file ready for use in Microsoft Excel. The input and output data were normalised and de-normalised before and after the actual application in the network.

6.3 Computational Method and Data processing

Inputs were: (1) Machine models (2) impellers (3) screen size, Outputs were in Mean particle size (in speeds of 1700; 3250; and 4150 /min).

Data were classified into three groups, that is, a training data set, a validation data set, and a test data set. The validation samples were 15% of the training samples and were selected randomly by the software. The network was trained using a batch training procedure where all samples in the training data set were packed together and passed through the network as a single signal. All outputs in the network were trained simultaneously.

During the training process, the network performance was validated by a cross-validation method using samples from the validation data set at every five training iteration. This validation was assigned to test the adaptive system on the data that had not been used for training to benchmark the system performance. After the training process, prediction ability of the developed network was examined by external validation with the unseen samples of the test data set.

In this work, multilayer perceptron with back propagation learning algorithm are used for the prediction purpose of the network. General structure of the used networks (shown in Figure 6.1) and their components are presented and discussed in more details during this work.

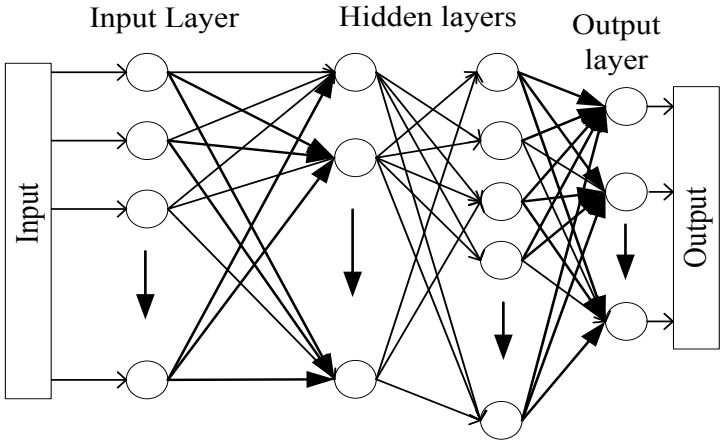

Figure 6.1: Structure of Artificial neural networks

The input of the neural network is fed from the data sets toward the input layer of the neural network. This input is passed without processing to the second stage of the network where hidden layers exist. The first hidden layer receives the input data and process it. Each single variable is passed to all the weights in the layer. The results are then summed in each neuron of the layer and passed again to the next layer. The next layer can be either another hidden layer or an output layer. The same process is repeated in all the layers of the network.

The output of the last layer of the network is been compared with a known desired signal that is used as an exam variable. The error obtained from the comparison is employed as a feedback used to correct the weights in all previous layers of the networks. It is back propagated to throughout all the layers. The process is then repeated iteratively until the error is small enough. At this stage, the network is said to be trained and new datasets that were not presented previously are passed through the network. The network will generate outputs of these datasets based on the previous training. If the results are accepted, then the neural network can be generalized and well trained. Otherwise, the training is restarted from the beginning with different parameters.

CHAPTER SEVEN

RESULTS AND DISCUSSIONS

7.1 Results

In this study, the artificial neural network structure based on the back-propagation learning process was used in the training of the system to predict the results of the industrial processes. The prediction of the results is very important to determine the best methods to achieve the intended results from milling. The artificial neural networks have been widely implemented in the prediction of oil prices or the weather forecasting. It has presented a high efficiency and low cost prediction methods that can non-linearly predict unknown values. In order to apply the predictive work of the artificial neural network, some data is needed to be used for the training and validation of the neural network weights. This data was collected and presented to the ANN in a suitable form and the training of the network was carried out.

As mentioned earlier, the data were collected using two different models of the machine. Two different types of experiments were applied on each one of the machines. These are the shear and compressive experiments. The data was also collected at different speeds of the machine and with different screen sizes. The collected data for each machine type are presented in the Table 7.1 below. The data shown in the table shows that 3 screen sizes were used in the data collection experiments. These sizes are 45, 75, and 94 screen size. The rotation speed also was varied during the experiments to examine the effect of the speed on the mean particle size obtained from each one of the machines. Three different speeds were used in the experiments; these are 1700 rpm, 3250 rpm, and 4150 rpm.

7.2 Discussions

Figure 7.1 and Figure 7 2 show the impact of screen sizes and the speed as well as the type of the impeller and the model of Comil on particle size distributions.

From the data presented in Table 7.1 and the Figures 7.1 and 7, 2, it can be deduced that all of the parameters listed above have significant impact on the particle size distribution as well as the mean particle sizes of the milled sodium chloride at different levels. The data suggest that the machine type have the minimum impact on the particle size distribution and the mean particle size. This is important in terms of scale up process as the formulation scientist desire the same results as they increase the size of the equipment. Impeller type have greater impact than that of the model on

the particle size distribution and the mean particle size of the milled material. This shows the importance of the correct impeller type according to the material. The compressive impeller is suggested to reduce the particle size of the dry products while the shear type impeller is recommended for reducing the particle size of wet granules (although it is used for some dry materials as well)

The most significant impact on the particle size distribution and the mean particle size was, as expected, due to the screen size and the rpm of the operation speed. As expected the mean particle size was getting smaller as the opening of the screen is getting smaller. It was also known that as the speed of milling is increased, the mean particle size is reduced (See Table 7.1).

The prediction of the mean particle size of the milled products is always critical and important. The aim of this work was to use the neural network to predict the size of the obtained particle from each machine and, as detailed below in this section, it was shown that artificial neural network can successfully employed for this purpose.

Table 7.1: Data collected using the machine model (197) AND (193)

Machine model			**197**	**193**
Impeller	Screen	Speed	Mean PS	Mean PS
Compressive	45	1700	312,03	272,91
		3250	238,45	269,08
		4150	213,26	255,4
	75	1700	389,86	356,12
		3250	428,25	394,28
		4150	344,92	416,38
	94	1700	519,71	590,1
		3250	544,35	617,75
		4150	483	581,26
Shear	45	1700	266,34	306,13
		3250	238,45	313,6
		4150	222,7	283,8
	75	1700	468,97	587,73
		3250	423,09	505,22
		4150	337,19	463,88
	94	1700	542,1	578,6
		3250	527,32	554,35
		4150	373,53	515,75

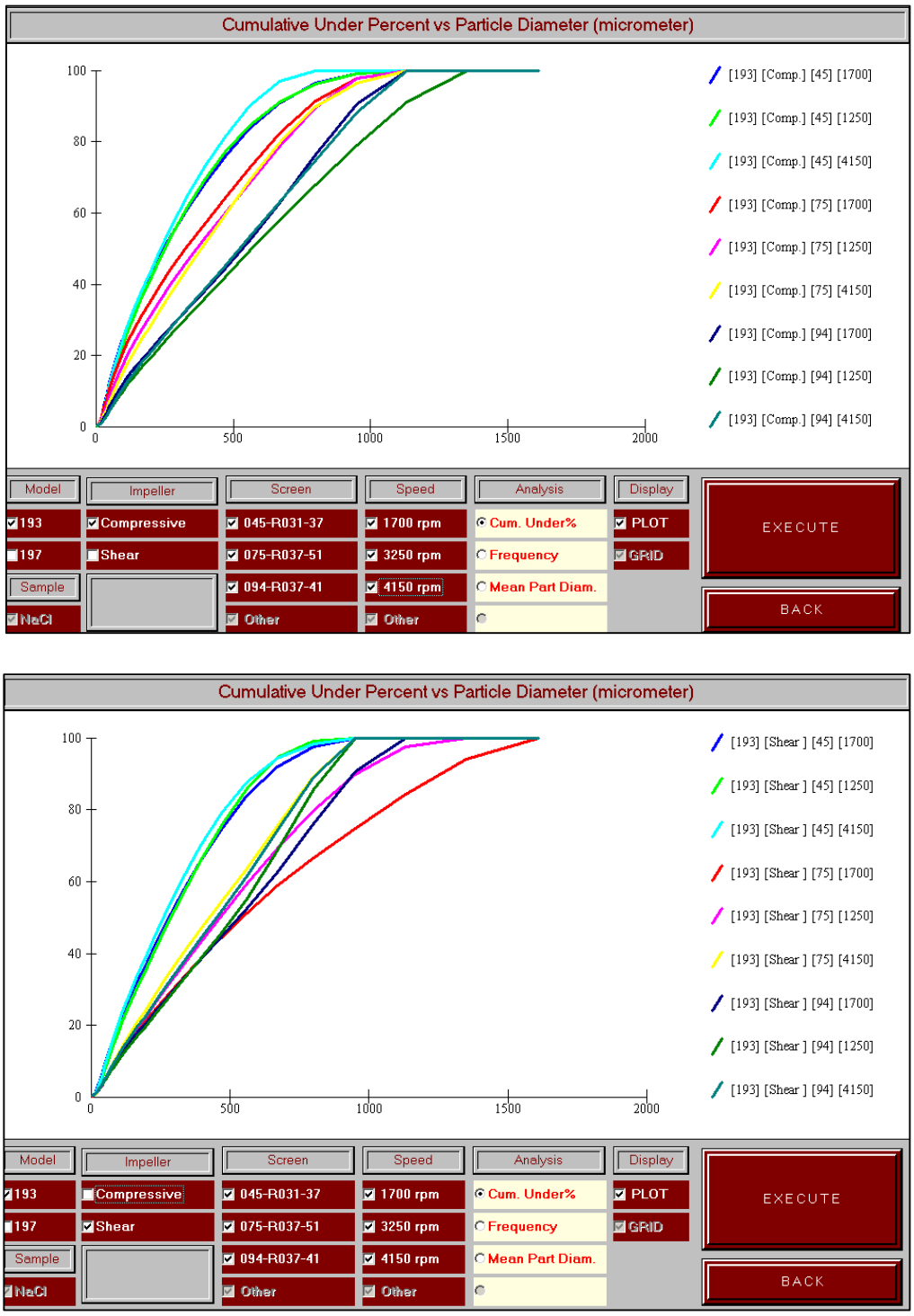

Figure 7.1: The effect of screen opening and milling speed on particle size distribution for model 193 Comil attached with compressive (top figure) and shear type impeller (bottom figure)

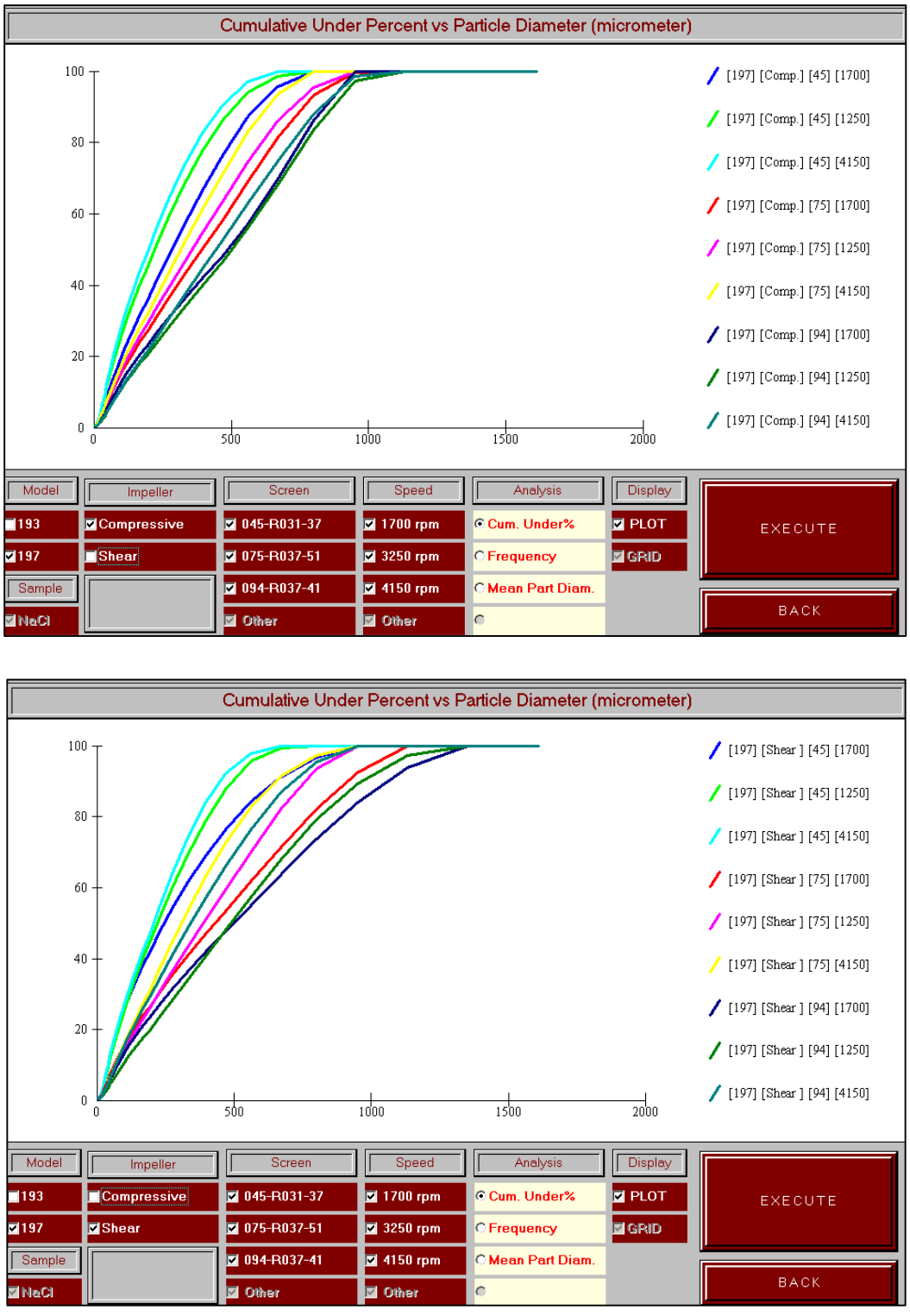

Figure 7.2: The effect of screen opening and milling speed on particle size distribution for model 197 Comil attached with compressive (top figure) and shear type impeller (bottom figure)

The collected data was used in the training of the artificial neural network system. The neural network was built using MATLAB software. MATLAB 7.8 (R2009a) was installed on a windows system with processor of 2.1 GHz speed and 2 GHz of random access memory speed. The process of using artificial neural networks implied the processing of the obtained data in such a way that it can be fed to the network structure. The data was divided into two parts namely input and output data. The particle size was used as output of the network while the other parameters were presented to the ANN as inputs. Each group of input output is presented to the network structure once at every epoch. The function of the neural network is then to build a nonlinear relationship between all inputs and outputs. The process of training continuous iteratively until the obtained outputs becomes identical to those of the experiments. At this stage, the neural network is said to learn the pattern of the data. The trained network is then used to predict the results of other arbitrary inputs. In our work, the arbitrary data is taken from the experiments results to verify the ability of the network to learn the pattern in the obtained results.

7.3. Neural Network Characteristics

The neural network tool of MATLAB 2009a was used to apply the training and test of the neural network. The script was written as an m-file containing all the coding of the program. The program started by loading all the data from the directory to the workspace of the MATLAB. The loaded data was then divided to training data, validation data, and test data. The structure of the network was then constructed with arbitrary initial values of all the weights. Figure 7.3 presents the general structure of the used network.

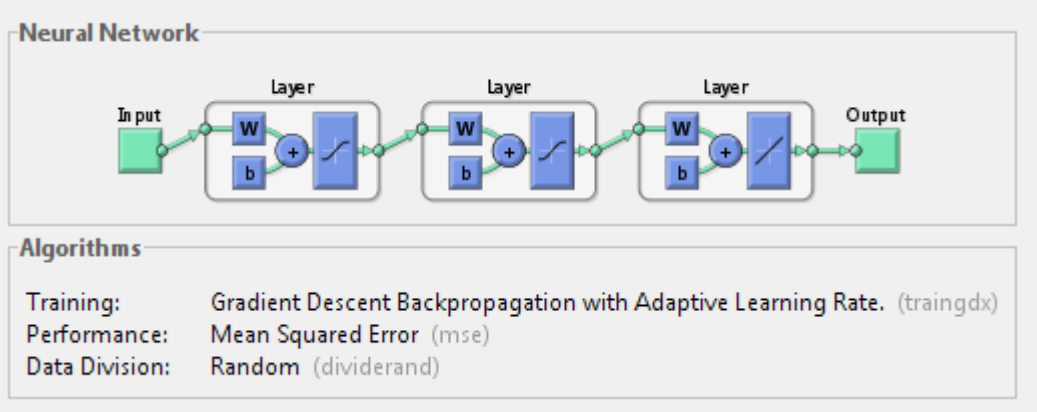

Figure 7.3: Structure of the used ANN

From the structure of the network shown above, the used network is constructed of one input layer, two hidden layers, and one output layer. The input layer in the neural network is a non-processing layer whose function is to transfer the inputs to the hidden layers. The parameters of the network shown above are given in the next table.

Table 7.2: Parameters of the used ANN structure

Hidden layer 1	400 neurons	Transfer function 1	Tangent sigmoid
Hidden layer 2	400 neurons	Transfer function 2	Tangent sigmoid
Output layer	1 neuron	Output transfer function	Linear line
Input layer	4 neurons	Destination MSE	0
Maximum iterations	50000	Training Time	234 seconds

During the training of the system, MATLAB neural network toolbox applies validation checks at constant intervals of time. The validation is done using randomly selected samples of the dataset. The training is stopped automatically when the validation error is not decreasing. The validation set is a measure of the generalization of the neural network for the prediction purpose. Figure 7.4 presents the MATLAB artificial neural networks tool during the training of the system.

Figure 7.5 illustrates the mean square error curves of the training, validation, and test sets. It's clear that the MSE curves are decreasing during the training and hence the network is learning perfectly. The training MSE reached a value of $1.7*10^{-7}$ which is small enough to stop the training of the network. After stopping the network, all results were obtained and printed as shown in the next table. It is to notice that, during the training 30 samples out of the 36 available samples were presented to the neural network. The rest of samples were used for the test of the performance of the neural network. From Tables 7.2 and 7.3, it is clear that the network was able to learn the pattern in the training set and predict the results of the test set with minor differences

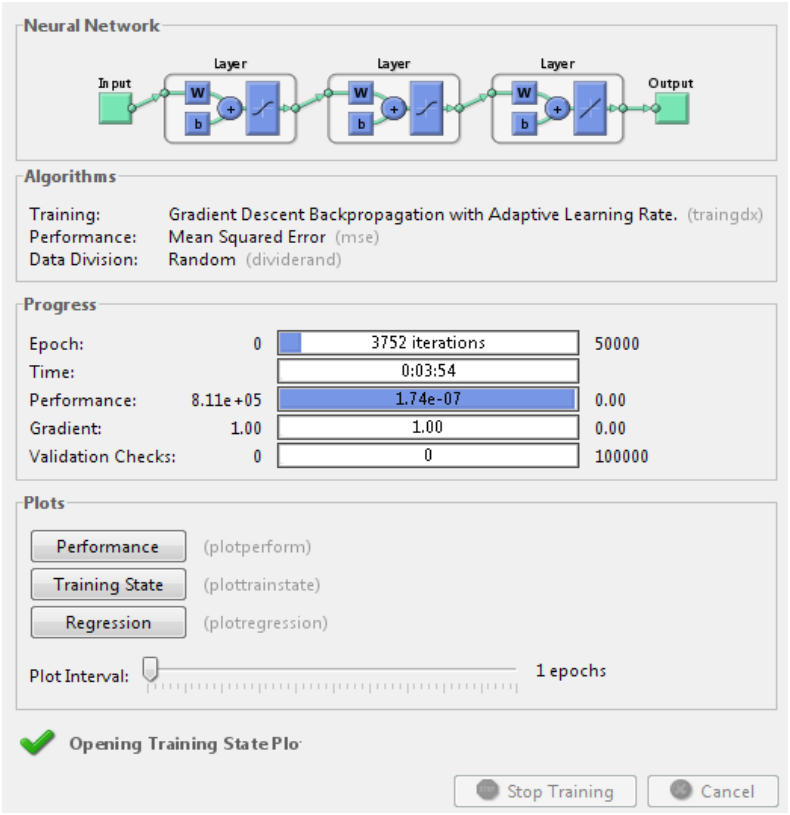

Figure 7.4: ANN tool of MATLAB during the training

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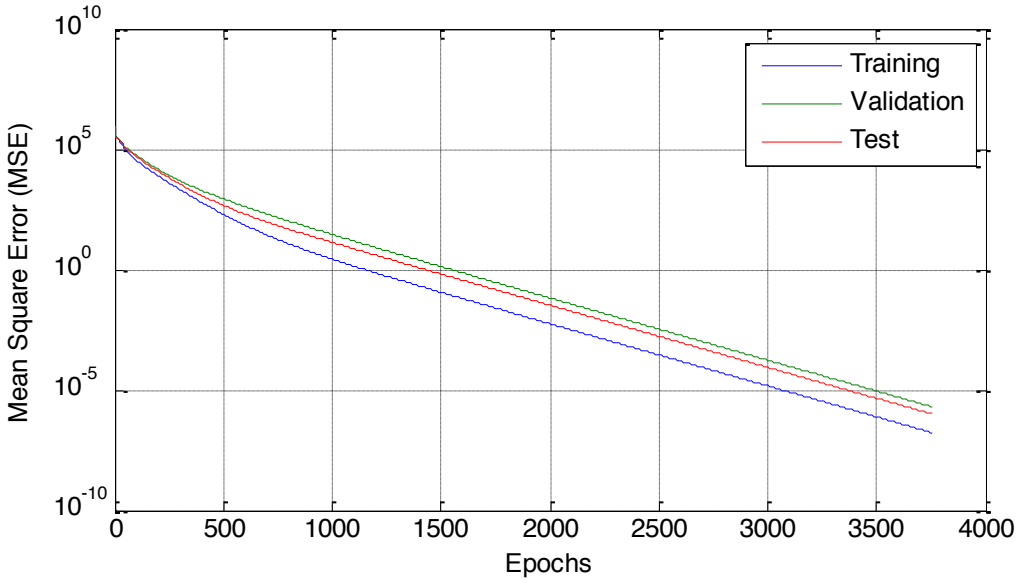

Figure 7.5: The MSE of the training, validation and test sets during the training

Table 7.3: Training results of the system

ANN	EXP	ANN	EXP	ANN	EXP
312.03	312.03	238.45	238.45	255.40	255.4
238.45	238.45	222.70	222.7	356.12	356.12
213.26	213.26	468.97	468.97	394.28	394.28
389.86	389.86	423.09	423.09	416.38	416.38
428.25	428.25	337.19	337.19	590.10	590.1
344.92	344.92	542.10	542.1	617.75	617.75
519.71	519.71	527.32	527.32	581.26	581.26
544.35	544.35	373.53	373.53	306.13	306.13
483.00	483	272.91	272.91	313.60	313.6
266.34	266.34	269.08	269.08	283.80	283.8

Table 7.4: Testing results of the system

ANN	EXP
580.02	587.73
508.29	505.22
458.01	463.88
588.11	578.6
550.72	554.35
590.34	515.75

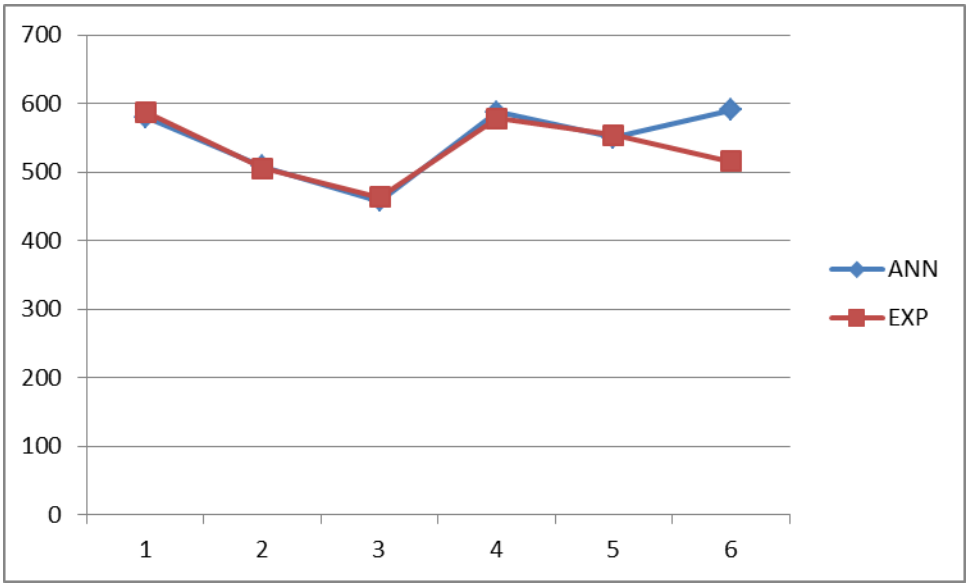

Figure7.6: Testing results of the system

In the next experiment, the training and test data will be normalized before starting the training of the system. The normalization is very useful in limiting the inputs and outputs of the neural network to defined values. It offers more options for the choice of transfer function. All output data was normalized by dividing the values to 1000. As all output data is less than 1000, the resultant target data is within [0 1]. The parameters of the training network in this case are given in Table 7.5 below. The training results with normalization are presented in Table 7.6 while test results are shown in Table 7.7. Figure 7.7 and 7.8 shows the curve of the MSE during the training and test results with normailzation.

Table 7.5: Parameters of the used ANN structure

Hidden layer 1	**300 neurons**	**Transfer function 1**	**Pure line**
Hidden layer 2	100 neurons	Transfer function 2	logarithmic sigmoid
Output layer	1 neuron	Output transfer function	Linear line
Input layer	4 neurons	Destination MSE	0
Maximum iterations	50000	Training Time	86 seconds

Table 7.6: Training results with normalization

ANN	**EXP**	**ANN**	**EXP**	**ANN**	**EXP**
316	312	214	238	257	255
219	238	217	223	420	356
236	213	399	469	408	394
385	390	405	423	381	416
364	428	358	337	546	590
396	345	583	542	568	618
546	520	507	527	619	581
537	544	410	374	327	306
469	483	278	273	329	314
320	266	280	269	305	284

Table 7.7: Test results with normalization

ANN	**EXP**
569	588
410	405
415	434
589	599
572	554
523	516

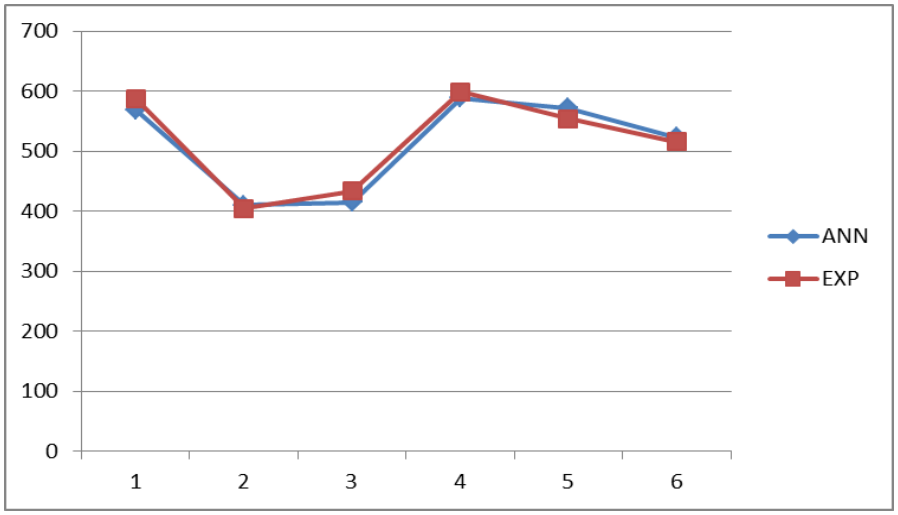

Figure 7.7: Test results with normalization

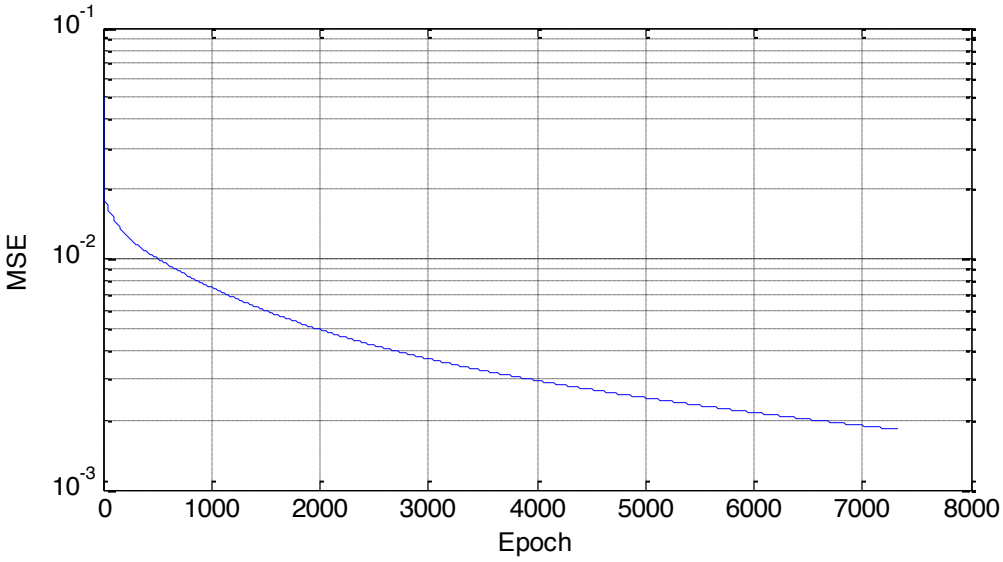

Figure 7.8: MSE of the training with normalization of data

From the data presented in Table 7.5, we can notice that all data obtained using neural network was similar to those obtained experimentally. It shows that the neural network could approximate the relationship between the inputs and the output of the experiments. The results of Table 7.7 and Figure 7.7 show that the neural network can predict values that were not presented to it. The first column represents the results obtained using neural networks. While the second column represents the data obtained experimentally. There exists a small tolerance in the data that can be considered

acceptable as shown in Table 7.6 and 7.7. It is important to mention here that the more training is done the better the results are achieved.

In order to experiment the performance of the system under different training and test combinations, the number of training and test samples was changed during the training of the network. 25 values will be used in the training and 11 in the test of the new network. The parameters of the network are the same as in Table 7.4. It is clear that the mean square error is decreasing during the training of the network. This means that the output of the neural network is perfectly converging toward the desired values. Training results and test results are presented in Tables 7.8 and 7.9. The table 7.8 shows that the training has given perfect results and that the results given by the network are similar to those obtained experimentally. This signifies that the network has learned the pattern of the training dataset. All outputs were calculated with small tolerances and training accuracy of 100%. The overall training mean square error is equal to 411 and the normalized MSE is 0.0011 (Figure 7.9). From the test table 7.9 and Figure 7.10 it is noticed that one value was not predicted correctly out of the 11 test samples. This gives an accuracy of 90.9% in the test results.

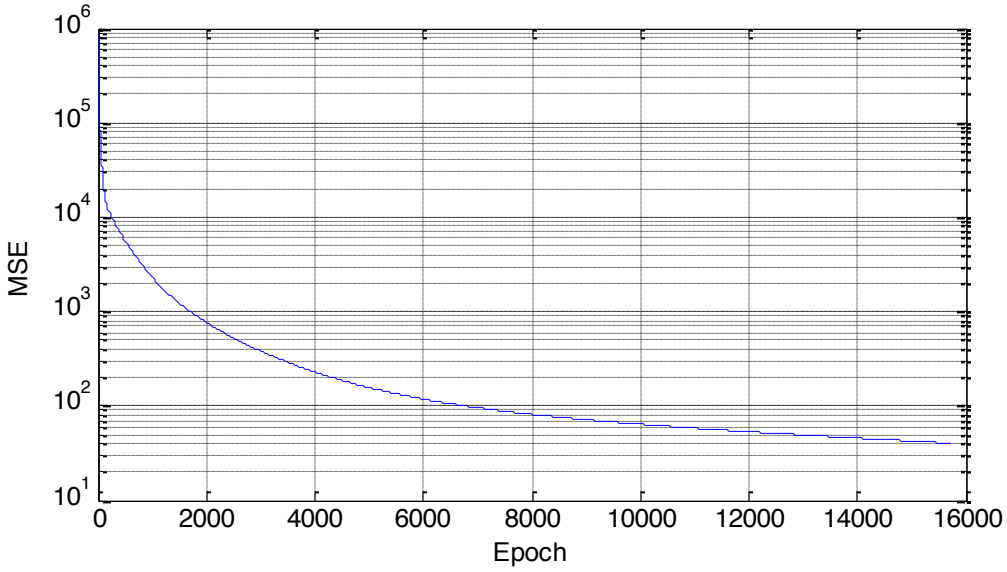

Figure 7.9: MSE in function of training epoch

Table 7.8: Training results of 25 training samples

ANN	EXP	ANN	EXP	ANN	EXP
310	312	224	223	590	590
215	213	468	469	613	618
398	390	275	273	585	581
350	345	266	269	307	306
511	520	257	255	313	314
473	483	355	356	283	284
266	266	399	394	587	588
237	238	412	416	500	505
578	579	MSE	411	NMSE	0.001

Table 7.9: Test results of 9 test samples (efficiency = 90.9%)

ANN	EXP	ANN	EXP
418	428	491	464
561	544	560	554
434	423	238	238
327	337	545	542
515	527	560	516
385	374		

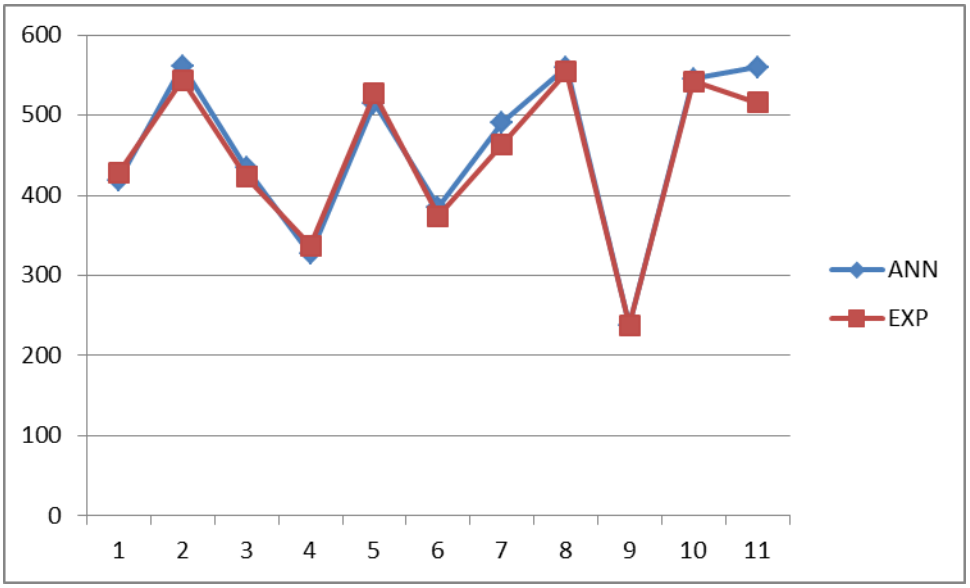

Figure 7.10: Test results of 9 test samples (efficiency = 90.9%)

The next tables (Table 7.10 and Table 7.11) present the results of training and test of the networks using arbitrary validation and test sets. MATLAB chooses randomly the samples of validation and test with the specified ratio. During the training, MATLAB uses the validation set to determine whether the training is successful or not.

Table 7.10: Training results with arbitrary validation set (efficiency 100%)

ANN	EXP	ANN	EXP	ANN	EXP
311.8	312.0	222.8	222.7	358.0	356.1
213.0	213.3	470.3	469.0	589.2	590.1
389.8	389.9	540.9	542.1	617.1	617.8
425.9	428.3	527.4	527.3	581.4	581.3
346.9	344.9	373.4	373.5	308.4	306.1
547.0	544.4	271.6	272.9	286.4	283.8
481.2	483.0	270.2	269.1	585.5	587.7
238.3	238.5	255.0	255.4	467.1	463.9

Table 7.11: Test results after validation (efficiency 75%)

ANN	EXP	ANN	EXP
571.1	519.7	543.0	505.2
113.8	266.3	308.4	313.6
449.6	423.1	771.5	578.6
331.7	337.2	510.0	515.8
420.8	394.3	268.0	238.5
560.9	416.4	559.3	554.4

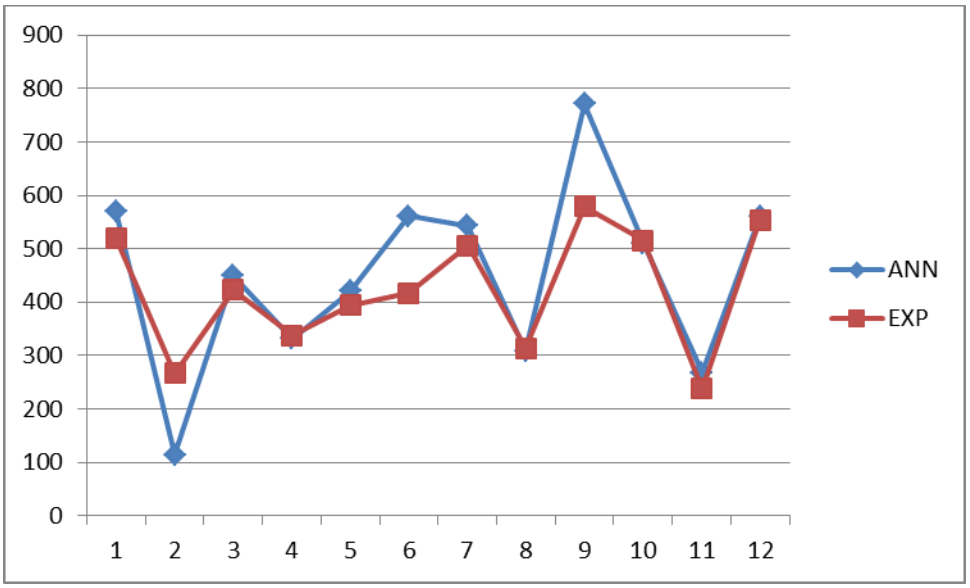

Figure 7.11: Test results after validation (efficiency 75%)

The training results show a high efficiency while in the test (Figure 7.11) and validation results three of the samples were not correctly predicted. The test performance was then 75%. The performance curve of this experiment is presented in Figure 7.12 where training, validation, and test errors are presented.

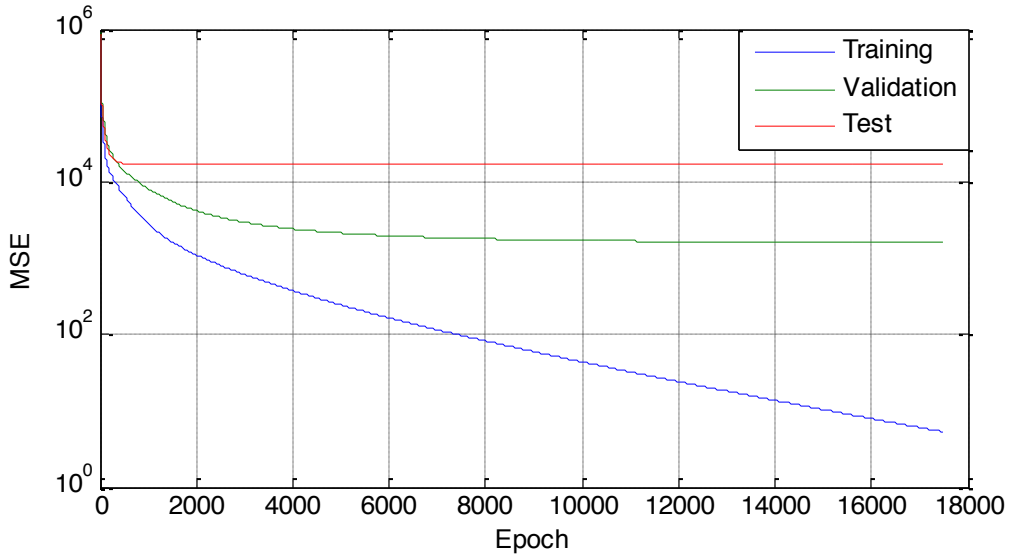

Figure 7.12: Training, validation, and test curves

CHAPTER EIGHT

CONCLUSIONS AND FUTURE WORKS

8.1 Conclusions

In this the study, the prediction of the effect of conical milling operation parameters on the mean particle size was shown by applying an artificial neural network. Milling process is a very commonly used unit operation in pharmaceutical production. Conical milling has become one of the most commonly used milling methods in recent years. In addition to the type of model, the main parameters of conical milling are the impeller type, screen opening and the operation speed. This study showed that these parameters have significant impact on the particle size distribution as well as the mean particle sizes of the milled product (sodium chloride) at different levels. It was shown that the machine type had the minimum impact on the particle size distribution and the mean particle size. This is important in terms of scale up process as the formulation scientist desire the same results as they increase the size of the equipment. Impeller type showed greater impact than that of the model on the particle size distribution and the mean particle size of the milled material. This shows the importance of the correct impeller type according to the material. As only sodium chloride was used in this study, it can be suggested to use other materials for future work.

The most significant impact on the particle size distribution and the mean particle size was, as expected, due to the screen size and the rpm of the operation speed. The prediction of the mean particle size of the milled products is always critical and important.

8.2 Recommendations for Future Work

This study showed that artificial neural network can successfully employed for this purpose. This is of importance, as ANNs are increasingly employed for the determination of design space as part of the quality by design (QbD) studies. It can also be deduced from this work that ANNs can be utilized in other type of unit processes (such as mixing, granulation, compression) and this is suggested as the future work as well.

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