DESIGN, FORMULATION AND EVALUATION OF PIROXICAM TABLETS USING ARTIFICIAL NEURAL NETWORK

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ABSTRACT

In the realm of pharmaceuticals, artificial intelligence (AI) denotes the application of automated algorithms to tasks traditionally associated with human cognitive abilities. An artificial neural network (ANN) serves as a simulation of the human brain, aiming to replicate both the structure and functionality of genuine neurons. Oral disintegrating tablets (ODTs), which can dissolve on the tongue in three minutes or less, are an unusual dosage form, particularly concerning the elderly and young patients. Formulation studies of ODTs face challenges, as they often depend on conventional laboratory trial-and-error methods and the expertise of pharmaceutical professionals. Unfortunately, this approach proves inefficient and time-consuming. The primary focus of the present research was to create an artificial neural network (ANN) prediction model tailored for ODT formulations employing the wet granulation technique. A literature review was carried out by collecting 307 formulation data set to train the data. For the ODT formulation, the ANN predicted and practically obtained values were compared. Formulations were subjected to pre-compression and post-compression parameters due to oral disintegration; the focus was on assessment of disintegration period and rate of *in vitro* dissolution. Notably, in the case of the PF7 formulation, the predicted disintegration time was precisely 48.476 seconds, closely aligning with the obtained result of 45.1 seconds. Additionally, the *in vitro* dissolution rate was accurately predicted at 92.34%, with the actual result being 93.74%. Besides, this dissolution rate stands out as the highest among all the formulations examined. Experimental data revealed, the almost identical estimate for ODT formulations compared to the ANN prediction. The application of this prediction model could efficiently reduce the time and cost required to produce a pharmaceutical and consequently facilitate the advancement of a potent drug product.

Keywords: Oral disintegrating tablets, artificial neural network, formulation prediction, input, hidden layer, output, piroxicam

INTRODUCTION

Introducing a new drug to the market is an immensely challenging, risky and resource-intensive process (time, money, and labour). Computer-Aided Drug Design (CADD) has become a popular new drug design strategy for minimizing time, cost and risk-borne components[1].

In pharmaceuticals, artificial intelligence employs automated algorithms for tasks traditionally requiring human intellectual capabilities, addressing industry challenges[2]. Artificial Neural Networks (ANNs) are often employed due to their ability to predict the effects of multiple variables simultaneously, making them one of the most accurate methods for predicting formulation parameters[3].

Artificial neural networks (ANNs) take inspiration from the neural networks found in the human brain. They are composed of interconnected neurons that process and transfer information. This enables ANNs to simulate the brain's ability to recognize patterns and solve problems. Working with ANNs entails taking on a variety of challenging tasks, including recognition, pattern association, simulation, and algorithm optimization[4].

The term "network" refers to the process through which neurons are synchronized, and a neural network might have a very large number of neurons. An ANN is most effectively compensated by three different types of layers as shown in Fig. 1[4].

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Table I: Pre-formulation studies of the piroxicam tablet and pre-compression parameters of all the PF1- PF7 formulation

Pre-formulation studies of the piroxicam tablet							
Standard calibration curve data using 0.1 M HCl	Max peak at 18 µg mL^{-1} about 0.922 ± 0.002 nm of absorbance at the wavelength of 334 nm						
Compatibility study using FTIR	Super-disintegrants and drugs were compatible						
Solubility study of piroxicam	The solubility showed increase in organic solvent chloroform 0.1179 mg mL^{-1}						
Pre-compression parameters of all the PF1- PF7 formulation							
Parameters	**Formulation code**						
	PF- 1	**PF- 2**	**PF-3**	**PF-4**	**PF-5**	**PF-6**	**PF- 7**
Bulk density (g mL^{-1})	0.383± 0.005	0.715± 0.006	0.617± 0.01	0.515± 0.005	0.679± 0.003	0.496± 0.002	0.547± 0.005
Tapped density (g mL^{-1})	0.46 ± 0.01	0.729± 0.007	0.633 ± 0.01	0.522± 0.008	0.700± 0.007	0.505± 0.006	0.648± 0.001
Hausner's ratio	1.196 ± 0.05	1.01 ± 0.009	1.025± 0.006	1.023± 0.006	1.031± 0.005	1.018± 0.005	1.014± 0.006
Carr's index (%)	16.54 ± 4.4	1.86 ± 0.8	2.465 ± 0.5	2.29 ± 0.6	3.041 ± 0.5	1.782 ± 0.5	1.946± 0.5
Angle of repose (°)	25.40 ± 1.8	27.19 ± 1.9	25.85 ± 0.6	23.12 ± 0.8	25.18 ± 4.3	26.03 ± 1.2	25.74 ± 1.8

Mean±SD(n=3)

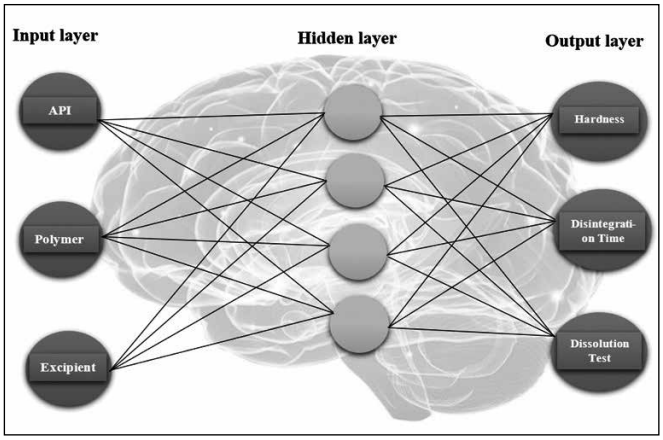

Fig. 1: Structure of artificial neural network

a) **Input layer**: Access the input values in the input layer.

b) **Hidden layer**: Between the input and output layers is a collection of neurons known as the "hidden layer". There may be one or many layers.

c) **Output layer**: It comprise a single neuron, it generates an output falling within the range of 0 to 1, that is between 0 and 1 and greater than or equal to 0. However, there may also be a variety of outputs.

ANNs IN TABLET MANUFACTURING

Artificial neural networks (ANNs) in tablet manufacturing can boost production efficiency and product quality by extracting patterns from large datasets, optimizing process parameters, monitoring operations, and identifying quality issues early on[4].

According to the U.S. Food and Drug administration (USFDA), orally dissolving tablets (ODTs) are designed to rapidly disintegrate in the mouth, usually within seconds to a minute, without water or chewing. They are particularly beneficial for drugs with a short duration of action or those needing quick onset, such as antiemetics, analgesics and antipsychotics. ODTs are especially popular among geriatric and paediatric patients who may have difficulty in swallowing conventional tablets or capsules.

Piroxicam, a nonsteroidal anti-inflammatory drug (NSAID) of the oxicam class, treats painful inflammatory conditions like arthritis by inhibiting the production of endogenous prostaglandins. Pfizer patented piroxicam in 1968, gaining medical use approval in 1979, and genericization occurred in 1992. Piroxicam is available as dispersible tablets and hard gelatin capsules. The absorption rate and bioavailability of piroxicam, especially

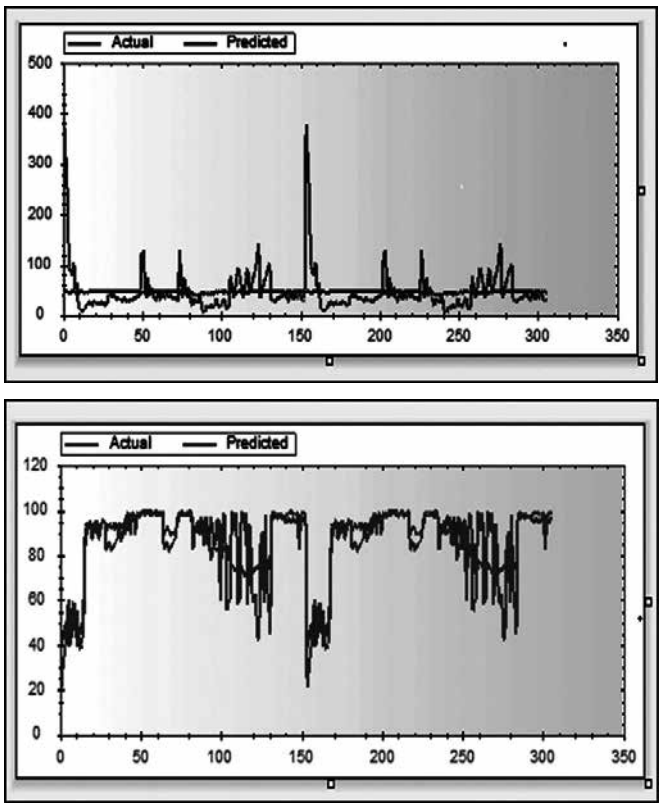

Fig. 2: Trained data graph of disintegration time and *in vitro* dissolution

as a poorly soluble and highly permeable drug (class II), depends on its dissolution rate in biological fluids. Solubility, dissolution behaviour, and permeability significantly influence oral bioavailability. Piroxicam's undesirable properties and potential for prolonged contact with the gastrointestinal mucosa makes it suitable for quick-release formulations like ODTs. ODTs can enhance patient compliance, particularly for those with swallowing difficulties. Offering medication without water may improve adherence to the prescribed regimen[5]. The primary aim of this work was to design, formulate and evaluate oral disintegrating tablets of piroxicam through the utilization of artificial neural networks[7,8].

MATERIALS AND METHODS

Piroxicam (API) was received as a drug sample from Shree Bhavani Pharmaceuticals, Rayapur, Hubballi. Excipients like sodium starch glycolate (SSG), sodium starch fumarate (SSF), talc and Aerosil® 200 were procured from VerGo Pharma Research Laboratories Pvt. Ltd., Goa. Lactose was procured from S D Fine Chem Ltd., Mumbai.

The relative impacts of polymer and super-disintegrants on disintegration time and *in vitro* dissolution were examined for 30 min using NeuroXL Predictor® software. In order to predict and analyze predictions, the software tool NeuroXL Predictor uses artificial neural networks, specifically, the focus is on employing multi-layer perceptron (MLP) neural networks for the design, formulation, and evaluation of oral disintegrating tablets. MLP neural networks are a sort of feed forward neural network design made up of numerous layers of interconnected nodes or neurons. There was a total of seven inputs with hidden levels, and one output. Surface reactions were produced about the significance of excipients showing *in vitro* drug release and disintegration time.

Disintegration time and *in vitro* dissolution rate can be considered as a continuous output variable that can be predicted using information from the input dataset containing samples of chemicals or materials and the times at which they disintegrate. The preprocessing of the data assists in training process improvement and prevents every feature from monopolizing learning due to its greater magnitude. The fed-forward network needs to be chosen. When an ANN has completed being trained, it is tested out on a different experimental data set[6] that wasn't applied for training and the outcomes evaluated[9,10].

Preparation of oral disintegrating tablets by wet granulation method

Wet granulation was used to formulate piroxicam oral disintegrating tablets. Seven different piroxicam oral disintegrating tablet formulations (PF1 to PF7) were designed using the super-disintegrant, sodium starch glycolate and diluent lactose in seven different concentrations.

Compatibility studies (IR) were conducted on the physical mixture, and pre-compression evaluation parameters such as bulk density, tapped density, Hausner's ratio, Carr's index, and the angle of repose of the prepared tablets were assessed. Post-compression studies followed accordingly.

RESULTS

Standard calibration curve of piroxicam

Calibration curve of piroxicam was obtained using 0.1M HCl as the solvent, mentioned in the Indian Pharmacopeia, at maximum wavelength of 334 nm and analyzed for regression analysis and standard calibration curve data as shown in Table I.

Table II: Post-compression parameters of all the PF1- PF7 formulation

Sl. No.	Parameter		Formulation code						
			PF - 1	PF - 2	PF - 3	PF - 4	PF - 5	PF - 6	PF - 7
1	Hardness (kg cm^{-2})		3 ± 0.1	2.966 ± 0.05	3.066± 0.05	3.033± 0.05	2.93± 0.11	3.022± 0.05	3.033± 0.05
2	Friability (%)		0.852 ± 0.05	0.631 ± 0.1	0.680± 0.1	0.502± 0.05	0.24± 0.4	0.676± 0.1	0.658± 0.1
3	Weight variation (mg)		0.105 ± 0.4	0.102 ± 0.2	0.101± 0.1	0.099± 0.1	0.103± 0.3	0.104± 0.4	1.01± 0.1
4	Drug Content (%)		97.82 ± 0.3	97.65 ± 0.3	97.94± 0.2	98.12± 0.2	99.02± 0.2	98.64± 0.2	99.37± 0.2
5	Wetting time (sec)		71.66 ± 14.5	70.33 ± 7.09	73.66± 1.5	71 ± 1	69.66± 0.5	72.14± 0.5	71.9± 1
6	Water absorption ratio		5.59 ± 4.6	16.16 ± 0.7	16.16± 0.7	20.91 ± 3.7	18.75 ± 3.7	19.58 ± 0.9	16.87 ± 0.8
7	Predicted disintegration time (sec)		50.901 ± 0.1	49.666 ± 0.1	49.429 ± 0.2	49.192 ± 0.2	48.954 ± 0.3	48.715 ± 0.3	48.476 ± 0.3
	Disintegration time (experimentally) (sec)		50.34 ± 0.4	49.87 ± 0.3	48.66 ± 0.2	47.6 ± 0.2	47.3± 0.1	46.6 ± 0.1	45.1 ± 0.1
8	Predicted *in vitro* dissolution (%)		88.987 ± 0.1	89.891 ± 0.1	90.086 ± 0.1	90.686 ± 0.1	91.176 ± 0.2	91.463 ± 0.2	92.344 ± 0.2
	In vitro dissolution (experimentally) (%)		87.81 ± 0.1	88.05 ± 0.2	88.49 ± 0.2	89.05 ± 0.06	89.48 ± 0.2	92.55 ± 0.2	93.74 ± 0.3
9	Stability study	Drug content (%)	96.72 ± 0.4	96.55 ± 0.4	96.84 ± 0.3	97.92 ± 0.3	98.92 ± 0.3	97.54 ± 0.3	98.27 ± 0.4
		Disintegration time (sec)	45.2 ± 0.5	45.6 ± 0.5	47.3 ± 0.3	47.5 ± 0.3	48.33 ± 0.2	48.67 ± 0.2	49.14 ± 0.2

Mean ±SD (n= 3)

Compatibility study using FTIR

Using IR spectroscopy, the IR spectra of the physical mixture of the pure drug and excipients was detected. Super-disintegrants and drugs were compatible, since the IR spectra of the drug and excipients exhibited no apparent shift in the distinctive peaks of the drug (Table I).

Solubility study of piroxicam

The solubility of piroxicam was studied by equilibrium method on different solvents. The solubility showed increase in organic solvents like ethanol and chloroform (Table I).

Pre-compression studies

The pre-compression parameters were assessed, and the obtained values were found to fall within the specified limits, demonstrating satisfactory free-flowing characteristics. These results are detailed in Table II.

Post-compression studies

All formulations performed excellent post-compression evaluations, and the resulting data are reported in Table II.

Disintegration time and *in vitro* dissolution studies values are mentioned in Table II, where the predicted values from artificial neural network, experimentally performed values of disintegration time and *in vitro* dissolution study are presented as shown in Fig. 2. The data had been collected from a literature survey, and the parameter that needed to be predicted was selected. The data was then collected, trained

and validated to obtain perfect prediction. For the testing data to acquire accurate predictions, the trained data must be loaded, and predictions must be made. The testing data will show the *in vitro* dissolution rate and disintegration time predictions.

In order to determine whether the predicted outcomes of the ANN were accurately produced, the formulations need to be developed experimentally. Almost all of the formulations from PF1 to PF7 coordinate with experimentally determined values to values predicted via the ANN.

Stability study

All oral disintegrating tablet formulations PF1–PF7 were packaged appropriately and kept in storage for 60 days at 37 °C ± 2 °C and RH 75%±5%. After 60 days, drug content and disintegration time of the tablets were assessed. Table II shows stability parameters for all formulations. Disintegration time and drug content did not alter much. All of the formulation's stability studies showed that they all met Indian Pharmacopoeia criteria and were stable (Table II).

DISCUSSION

Data extraction is a crucial step where experienced pharmaceutical researchers meticulously label reliable formulation datasets. However, the challenge lies in the scarcity of data in pharmaceutical research, making effective training of prediction models with minimal inputs a significant hurdle. For instance, in this formulation, a dataset of 307 was trained to achieve accurate predictions, but manual selection is time-consuming and requires expert knowledge. Regarding algorithm selection, feedforward networks are deemed appropriate for predicting outcomes like disintegration time and *in vitro* dissolution rate. It was found that artificial neural networks (ANN) provide accurate predictions, potentially reducing time, labor, and material resources required for ODT formulation development. This represents the beginning of an intelligent research approach for formulation development.

Results revealed that for the formulated piroxicam oral disintegrating tablets, the pre- formulation studies showed calibration curve equation of Y= 0.00516x + 0.005 at maximum wavelength of 334nm and analyzed $R^2 = 0.9968$ for regression analysis. Equilibrium solubility method was studied where chloroform shown 0.1179 mg mL^{-1} of solubility. Pure drug peak and physical mixture peak were found to be compatible by IR spectroscopy. In the pre-compression, bulk density was found in range of 0.383- 0.715 g mL^{-1}, tapped density was in the range of 0.46- 0.729 g mL^{-1}. In the Hausner's ratio, PF1 shown fair flow property, whereas PF2-PF7 shown excellent flow property. Carr's index PF1 has shown fair passable, whereas PF2-PF7 has shown excellent flow property. Angle of repose for prepared granules PF1-PF7 shows excellent flow. In the post-compression studies, hardness was found in the range of 2.933 to 3.066 kg cm^{-2}, while friability was found in the range of 0.24%- 0.852%. Weight variation was in the range of 0.099-0.105 mg. Drug content was in the range of 97.65-99.37%. Wetting time was in the range of 69.66-73.66 sec and wetting absorption ratio in the range of 5.59-20.91. The PF7 formulation showed disintegrating time which has been accurately predicted to be 48.476 seconds and obtained to be 45.1 seconds and *in vitro* dissolution rate has been accurately predicted to be 92.344% and obtained to be 93.74% which is found to be highest among all the formulations.

CONCLUSION

The conventional 'trial-and-error' approach to formulation development is expensive in terms of time, money, and labor. Oral disintegrating tablets have emerged as a convenient and efficient formulation form. To predict disintegration time and *in vitro* dissolution of ODT formulations reliably, current research developed an ANN, demonstrating effective deep learning on limited data. This predictive method considers ODT formulations and tablet characteristic variables, assessing crucial formulation quality control parameters and driving research. This deep-learning model may find applications across pharmaceutical research areas and dosage forms, potentially minimizing resources required for medicine development and aiding in reliable drug product development.

REFERENCES

1. Surabhi S. and Singh B.: Computer Aided Drug Design: An overview. **J. Drug Deliv. Ther.,** 2018, 8(5), 504–509.
2. Ch. K. and Arvapalli S.: Artificial Intelligence in Pharma Industry- A Review. **IJIPSR**, 2019, 7(10), 37-50.
3. Guler G. K. and Eroglu H.: Development and formulation of floating tablet formulation containing rosiglitazone maleate using Artificial Neural Network. **J. Drug Deliv. Sci. Technol.,** 2017, 39, 385–397.
4. Ananthu M. K. and Chintamaneni P. K.: Artificial neural networks in optimization of pharmaceutical formulations. **Saudi J. Med. Pharm. Sci**., 2021, 7(8), 368–378.
5. Panwar A. S. and Nagori V.: Formulation and evaluation of fast dissolving tablets of piroxicam. **Am. J. Pharmtech. Res**., 2011, 1(3), 255-273.
6. Han R. and Yang Y.: Predicting oral disintegrating tablet formulations by neural network techniques. **Asian J. Pharm. Sci**., 2018, 13(4), 336–342.

7. Aksu B. and Paradkar A.: Quality by design approach: Application of artificial intelligence techniques of tablets manufactured by direct compression. **AAPS PharmSciTech**., 2012, 13(4), 1138–1146.
8. Hussain A. and Syed M. A.: Development of an ANN optimized mucoadhesive buccal tablet containing flurbiprofen and lidocaine for dental pain. **Acta Pharm**., 2016, 66(2), 245–256.
9. Patel A. D. and Agrawal A.: Investigation of the effects of process variables on derived properties of spray dried solid-dispersions using polymer based response surface model and ensemble artificial neural network models**. Eur. J. Pharm. Biopharm**., 2014, 86(3), 404–417.
10. Yang Y. and Ye Z.: Deep learning for *in vitro* prediction of pharmaceutical formulations. **Acta Pharm. Sin B,** 2019, 9(1), 177–185.