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From CCD to ANN: A Hybrid Statistical-Computational Framework for Optimization of Doxylamine Succinate Orally Disintegrating Tablets

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INTRODUCTION & AIM

Central Composite Design (CCD) is a popular statistical method for pharmaceutical formulation process optimisation. It is part of the Response Surface Methodology (RSM) used to implement Quality by Design (QbD). It is used to study how various variables affect a response. Because it models complex systems using linear and nonlinear effects. CCD is effective at finding optimal conditions for medication formulation and manufacturing [1,2].

Researchers in formulation development use neural networks because they can mimic brain function to memorise by experience. Despite poor or partial data, an Artificial Neural Network (ANN) makes decisions and draws conclusions for numerical and non-numerical computations. ANN is a more powerful and adaptable tool for multi-variable simultaneous optimisation of pharmaceutical formulations than Response Surface Methodology. Most pharmaceutical applications use the multi-layer perceptron (MLP) network. Input and output layers of MLP have processing units, known as nodes. One or more hidden layers link the nodes. The input and output layers have as many nodes as independent and dependent variables. The input layer receives external data, the hidden layer processes it, and the output layer outputs it [3].

Development of orally disintegrating tablets (ODTs) has improved patient compliance and adherence. For instance, improved bioavailability, enhanced stability, and immediate onset of action make them superior in specific patient types and conditions [4].

Doxylamine Succinate is known for its various pharmacological effects. It competitively antagonizes the H_1-receptors, situated in multiple locations in human body. Owing to its sedating effect, the drug is used for the short-term treatment of insomnia. Moreover, owing to its anti-emetic action, it is also utilized for morning sickness (a condition during pregnancy) [4].

Quality by Design is a risk-based methodology used by pharmaceutical manufacturers to ensure product quality. CCD and ANN both are used for the implementation of QbD. In this study, these two QbD techniques were employed to model the relationship between input and output variables. These tools were applied to optimise the development of Doxylamine Succinate ODTs via direct compression, creating a robust, adaptable methodology that aligns with ICH guidelines (Q8, Q9, Q11, Q19) [5].

METHOD

MATERIALS USED IN ODT FORMULATION: The formulation development included the use of Doxylamine Succinate (drug), Povidone, Crospovidone, Avicel PH 102, Sodium Saccharin, Mannitol, Aerosil, and Magnesium Stearate.

PREPARATION OF FORMULATION BLENDS: The ODT formulation of Doxylamine Succinate were developed using CCD approach. The approach was applied using the Design Expert® 13 (Stat Ease, Inc., Minneapolis MN 55413, USA). A rotatable CCD was applied with five center points and α value of 1.41421. The concentration of binder (Povidone) and superdisintegrant (Crospovidone) were used as the independent variables. Tablet friability, wetting time, and disintegration time were taken as the dependent variables (responses). The design proposed 13 formulations (F1-F13). All formulation ingredients were mixed, and the resulting formulation blends of Doxylamine Succinate ODT were directly compressed.

The compressed tablets were evaluated for their pre and post compression characteristics.

PRE & POST COMPRESSION PARAMETERS: Bulk density, tapped density, compressibility index, and Hausner's ratio were the pre-compression parameters. Weight variation, friability, hardness, thickness, wetting time, water absorption ratio, in vitro disintegration, and drug release (dissolution) were evaluated as the post compression tests.

DRUG RELEASE ASSESSMENT: Dissolution test was performed in an acidic medium (0.01N Hydrochloric Acid). The stock and sample solution were prepared, and calibration curve was constructed. All proposed formulations were assessed for their drug release.

ANN MODELING: The current study involved training and validating an ANN model utilising MLP to develop and optimise Doxylamine Succinate ODT. ANN modeling was performed using JMP® Pro 18 software (SAS Institute Inc., North Carolina, USA). The output responses of the CCD were used to train the ANN model.

TRAINING AND VALIDATION OF ANN MODEL: These output responses (dependent variables), which included wetting time, water absorption ratio, and in vitro disintegration, were labelled Y_1 to Y_3, respectively. Data training and testing were conducted using the Holdback input randomizing technique at a 70/30 (training/testing) ratio. After that, the tested formulations were cross-checked using the Central Composite Design (CCD).

NEURAL NODE SELECTION: The optimal number of nodes was determined with the trial-and-error method. By utilizing TanH (Tangent Hyperbolic) as an activation function, the nodes were tested in the range of 3 to 10. The node with the highest r^2 and minimum SSE (sum of square errors) value for each of the responses (Y_1-Y_3) was chosen as the optimum value for the simulated formulation.

SIMILARITY FACTOR TEST: The compressed ANN-optimized formulation was evaluated for the drug release through the in vitro dissolution test. The drug release profile of the ANN optimised formulation was compared with the CCD optimised formulation. The comparison was made through a model-independent approach, the similarity factor test (f_2 test). The similarity factor test was applied through DD Solver (Microsoft Excel® add-in program). Based on the results of the f_2 test, the presence or absence of similarity between the ANN and CCD-optimised formulations was determined.

RESULTS & DISCUSSION

All the CCD proposed Crospovidone formulations passed the pre and post compression tests. Among the 13 formulations, F7 formulation gave the best results with a highest drug release. The results of the optimized formulation are presented in **Table 1 and 2**. A higher water absorption ratio was linked to a shorter wetting time and faster disintegration. This ratio is a key measure of a disintegrant's capacity to swell upon contact with water, a process that directly facilitates drug dissolution.

Table 1: Pre-compression results for F7 formulation

PRE-COMPRESSION PARAMETERS			
Bulk Density	Tapped Density	Carr's Index	Hausner's Ratio
0.387 g/ml	0.441 g/ ml	12.284 %	1.140

The CCD suggested that Crospovidone has high influence in decreasing the formulation's disintegration time and wetting time. The presence of Povidone demonstrated no significant impact, highlighting its ineffective action on disintegration and wetting time.

Table 2: Post-compression results for F7 formulation

POST- COMPRESSION PARAMETERS	
Hardness	3.5 N
Thickness	3.7 mm
Diameter	5.90 mm
Friability	0.67%
Weight Variation	Passes
Wetting Time	9.89 seconds
Water Absorption Ratio	101.5
In vitro Disintegration	27.00 seconds
In vitro Dissolution	100.76%

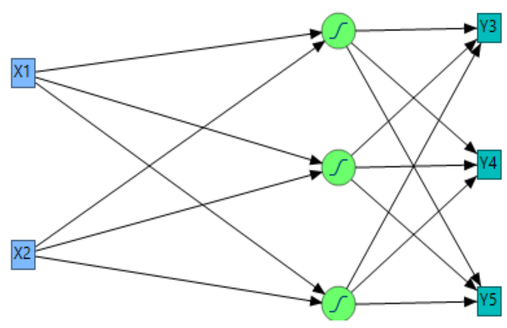
Previous research findings compared the disintegration strength of Crsopovidone with other superdisintegrants. Crospovidone showed the highest efficiency [6].

Artificial Neural Network is used in the current study for optimization of Doxylamine Succinate ODT. ANN has been utilized as a predictive and optimisation tool in past to develop a pH-dependent Mesalamine matrix tablet targeted for colonic delivery [7]. As the performance of the ANN model is directly related to the selection of the optimal number of nodes, therefore, the model was trained using the Random Holback method, with TanH values ranging from 3 to 10. The values recorded in **Table 3** revealed that node value 5 (highlighted in blue) is the best activation node for formulations containing Crospovidone. **Figure 1** showed the input layers connected with the responses in the output layer in an ANN model. Between these were the hidden layers of nodes.

Table 3: Selection of optimal node value

Nodes	Generalized r^2 (Training)	r^2, SSE		
		Y_1	Y_2	Y_3
3	0.998	0.859, 0.232	0.328, 0.416	0.832, 0.441
4	0.988	0.812, 0.309	0.104, 0.555	0.790, 0.551
5[a]	**1.000**	**0.979, 0.034**	**0.449, 0.341**	**1.000, 0.000**
6	0.989	0.813, 0.308	0.104, 0.554	0.792, 0.544
7	0.997	0.835, 0.272	0.181, 0.507	0.814, 0.487
8	0.987	0.814, 0.306	0.103, 0.556	0.790, 0.550
9	0.984	0.812, 0.310	0.098, 0.558	0.792, 0.545
10	0.987	0.814, 0.305	0.102, 0.556	0.793, 0.544

Figure 1: MLP architecture



Prediction profiler proposed an optimized formulation which was compressed, and dissolution studies were performed. Similarity factor test was performed on CCD and ANN proposed formulation and a f_2 value above 50 indicated similarity between two formulations. A comparison between the CCD and ANN optimized formulations has been performed in different formulation development research. Khan et al (2023) used one-way ANOVA to analyze the percentage drug release variance between ANN and CCD optimized Moxifloxacin ODTs [3]. The results revealed no statistically significant difference. Another group of researchers who formulated Pyrazinamide ODTs tablets used one-way ANOVA to compare ANN and CCD optimized formulations. The comparison revealed no statistical difference between the two formulations [8].

CONCLUSION

The integration of Central Composite Design and Artificial Neural Network provided a robust hybrid framework for the optimisation of Doxylamine Succinate orally disintegrating tablets. The ANN-predicted formulation demonstrated comparable performance to the CCD-optimized formulation, confirming the reliability of both models. This study highlights that ANN can serve as a powerful complementary tool to traditional statistical designs for multi-variable optimization in pharmaceutical formulation development.

FUTURE WORK / REFERENCES

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