



Prediction of Dissolution Profiles of Acetaminophen Beads Using Artificial Neural Networks (ANN)

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1. INTRODUCTION

The process of extrusion-spheronization, introduced by Reynolds^[1], and Connie and Hadley^[2], has become the method of choice for developing multiunit, pellet-based dosage forms. The major advantage of extrusion-spheronization is the ability to incorporate high levels of active compounds without producing excessively large particles. Moreover, extrusion-spheronization offers technological advantage of producing multiparticulates with a spherical shape, good flow properties, low friability, uniform particle size distribution, ease of coating and reproducible packing. The extrusion-spheronization is a labor intensive and time-consuming, multi-step process, which includes dry powder mixing, wet mixing, extrusion of the wet mass and spheronization of the cylindrical extrudate. The properties of the resulting beads are affected by the process conditions used during the bead manufacturing^[3-6].

Artificial neural networks (ANN) are computer programs that are designed to simulate some functions of the human brain using different learning algorithms, which can learn from experience^[7-8]. ANN have the remarkable information processing features of the human brain, such as nonlinearity, high parallelism, robustness, fault and failure tolerance, learning, ability to handle imprecise and fuzzy information, and their capability to generalize^[9]. Hence, ANN has been successfully applied to various pharmaceutical areas such as preformulation studies^[10], pharmaceutical process development^[11], formulation optimization^[12-13], *in-vitro-in-vivo* correlation^[14], and pharmacokinetic parameters prediction^[15]. The objectives of this study were to explore the applicability of ANN to predict the dissolution profiles of acetaminophen (APAP) from beads prepared with known extrusion-spheronization process variables, and to predict the optimal process variables, which can then be used to prepare APAP bead formulations that would yield the desired dissolution profiles.

2. MATERIALS AND METHODS

2.1. Experimental design

A 2³ full factorial (2 level 3 factor) design including one center point was adopted for the study. JMP[®] 5.1 software (SAS Institute, Cary NC) was used for designing the experiments. The process variables that were studied included screw speed, spheronization speed and spheronization time. The same process variables were used to manufacture different batches of APAP beads using two different extruder types, namely dome (Batch 10-18) and radial extruders (Batch 19-27). Total 18 batches of APAP beads were prepared using the process variables as shown in Tables 1. All the batches of APAP beads were prepared with 40% APAP (Mallinckrodt, St. Louis, MO) and 60% microcrystalline cellulose (MCC) (Avicel[®] PH 101, FMC Corporation, Newark, DE).

2.2. Extrusion-Spheronization process

The process of preparing beads using the extrusion-spheronization process involves five unit operations: dry-blending, wet-massing, extrusion, spheronization and drying. These processes are inter-related and hence affect the quality of the final product^[3]. The process used to prepare APAP beads was as follows: appropriate amounts of APAP and Avicel[®] PH 101 were mixed in Robot Coupe[®] (Model: 3VG, Robot-Coupe, Jackson, MS) high shear mixer-granulator in the reverse mode for 1 min at 350 rpm. The batch size (dry weight) for all formulations was 300 g. Purified water (200 g) was added to the bowl using Masterflex[®] peristaltic pump (Cole-Parmer Instrument Co., Vernon Hills, Illinois) at a flow rate of 240 mL/min to obtain the wet mass with 40% w/w moisture while stirring the mixture at 500 rpm in the forward mode. The wet mixture was not massed after complete addition of water. The resulting wet mass was extruded through either the dome or radial extrusion dies with 1 mm screen, using a single screw extruder (Multigranulator[®], Model: MG-55, LCI Corporation, NC) at specified screw speeds as shown in Table 1. The cylindrical extrudates were immediately spheronized using a Marumerizer[®] (Model: QJ-230T-1, LCI Corporation, NC) at specific speed and time as shown in Table 1. The resulting beads were dried in a tray-dryer at 50°C for 12 h.

2.3 Moisture content determination

Moisture content of the beads was determined using AND[®] Infrared moisture balance (Model: AD-4714 A), which was operated at 90°C for 20 minutes. Approximately 5-6 g of beads were used to determine the moisture content in the beads.

2.4. In vitro dissolution testing

Dissolution studies from the beads were performed using USP 27 dissolution Apparatus II (Hanson SR8-Plus[®], Hanson Research Corporation, CA) at 50 rpm. Purified water (900 mL) at 37 ± 0.1°C was used as the dissolution medium. Samples were taken every 5 min using a peristaltic pump auto-sampler and the APAP concentration in the withdrawn sample was determined using Perkin-Elmer double beam UV-Spectrophotometer (Perkin Elmer Corporation, Norwalk, CT) at 243 nm. Data processing (calculation of the percentage of drug released versus time) was performed using Perkin Elmer UV DissLab[®] software (Version 1.0, Perkin Elmer Corporation, Norwalk, CT).

2.5 ANN model development

A commercially available ANN software, AI Trilogy[®] (NeuroShell[®] Predictor, Release 2.1; NeuroShell[®] Classifier, Release 2.1; and GeneHunter[®], Release 2.4, Ward System Group Inc. Federick, MD.) was used for this study. The process variables, namely, screw speed, spheronization speed, spheronization time, and type of extruder (dome and radial) were used as inputs. The percentage of drug released from each batch of APAP beads at ten different time points were used as the outputs. The ANN models were developed using neural and genetic training strategies. These developed ANN models were then validated using the validation batch, which was left out during the ANN model development process. The final trained ANN model was selected from the two ANN models based on the validation results.

The validation criteria for selecting final trained ANN model included correlation coefficients, average errors, mean squared errors (MSE), and root mean squared errors (RMSE) between the actual percent drug dissolution data and the drug dissolution data predicted by either of the two ANN models.

2.6. Prediction of dissolution profiles of new batches prepared with known process variables

Two new batches (Batches 28 and 29) of APAP beads were prepared with known extrusion-spheronization process variables (Table 1) that were not included in the ANN model training procedure. However, these process variables were within the confines of the process variables used during the ANN model development. Drug dissolution test was performed on the two new batches of APAP beads as described in Section 2.4, and the validated final ANN model was used to predict the dissolution profiles of these two batches. The similarity between the actual dissolution profiles and the dissolution profiles predicted by the final selected ANN model was evaluated using the similarity factor (f_2), which has been adopted by the Food and Drug Administration (FDA) to compare *in vitro* dissolution profiles^[16]. The f_2 value was calculated using the following equation:

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^n w_t (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\}$$

n: number of sampling time points used.

R_t: actual cumulative percentage of acetaminophen released from the beads at each of the selected n time points.

T_t: ANN model predicted cumulative percentage of acetaminophen released from the beads at each of the selected n time points.

w_t: optional weight factor. In this study, w_t = 1.

When the two profiles are identical, $f_2 = 100$. A f_2 value is equal to 50 when an average difference of 10% in the dissolution profiles is observed at all time points used for the calculation of the f_2 value. The FDA has set a public standard of f_2 value between 50 and 100 to indicate similarity between two dissolution profiles.

2.7. Prediction of the optimal process variables for desired drug dissolution profiles

The applicability of ANN software's potential of predicting optimal process variables that can be used to make APAP beads, which would yield the hypothetical target dissolution profiles, was explored as follows: two hypothetical drug dissolution profiles were obtained by calculating the average of nine drug dissolution profiles generated from APAP beads prepared by either the dome or radial extruder. These hypothetical dissolution profiles were then employed as the desired drug dissolution profiles. GeneHunter[®] (one of the components from AI Trilogy[®] ANN software) software was then used to predict the process variables, which can be employed to prepare APAP beads capable of generating the desired dissolution profiles. The parameters used by the GeneHunter[®] software to predict the process variables are shown in Table 3. The procedure to obtain the optimum process variables by GeneHunter[®] software was as follows: the initial process variables generated by the GeneHunter[®] software were provided to the trained ANN model to obtain the predicted drug dissolution profiles. These predicted dissolution profiles were subsequently compared to the hypothetically desired dissolution profiles, and the mean squared errors (MSE) between the predicted and the hypothetically desired dissolution profiles were calculated. The aforementioned procedure of generating process variables was automatically continued by GeneHunter[®] software (with the help of the trained ANN model) until there was no more change in the MSE for at least 75 generations. Two sets of optimized process variables (one for the dome and the other for the radial extruder) were obtained based on the aforementioned optimization procedure using the GeneHunter[®] software (Table 1). Two batches of APAP beads (Batches 30 and 31) were then prepared using the optimal process variables predicted by GeneHunter[®] software and the validated ANN model. Drug dissolution from these two batches was carried out using the USP dissolution Apparatus 2 as described in Section 2.4. The similarity of the actual drug dissolution profiles and the hypothetically desired drug dissolution profiles were then evaluated using the f_2 values.

3. RESULTS AND DISCUSSION

3.1 Drug Dissolution profiles

In vitro drug dissolution profiles of the APAP bead formulations obtained using the dome extruder (Batches 10 to 18) and radial extruder (Batches 19 to 27) are depicted in Figure 1. Each data point represents the mean of three measurements for each formulation. The data showed that more than 80% of the drug was released in 30 minutes from all the 18 batches. However, the percentage of drug released in the first 5 minutes and the overall drug release rates were different when the process variables were changed.

3.2 ANN model development

Two ANN models were developed using neural or genetic training strategies based on the dissolution data obtained from 17 batches. One batch (Batch 22) was left out to validate the prediction capability of the developed ANN models. The mean squared errors (MSE) of the ANN model developed with neural and genetic training strategies are shown in Figures 2A and 2B, respectively. Different numbers of hidden neurons were used to train the ANN model using the neural strategy, whereas different generations were used to train the ANN model using the genetic strategy.

The plots of the predicted versus the actual drug dissolution data of the 17 batches of APAP beads (included in the training set), are shown in Figures 3A and 3B for neural and genetic training strategies, respectively. A comparison of the percent error between the actual dissolution data and dissolution data predicted by the ANN model developed with neural or genetic training strategy is shown in Figure 4. The evaluation results of the developed ANN models using the two different training strategies are shown in Table 2. It is evident from the results that both the ANN models trained with either the neural or genetic strategy have good prediction capability for the drug dissolution data that were included in the training set. Prediction of drug dissolution profiles for the training set was slightly better by the ANN model trained with the neural strategy than those predicted by the ANN model trained with the genetic strategy. However, prediction of drug dissolution profile of the validation batch (which was not included in the ANN model training set) using the ANN models trained by both the neural and the genetic strategies was dramatically different (Figures 5). The predicted drug dissolution profile of the validation batch by the ANN model trained by the genetic strategy more closely resembled the actual drug dissolution profile of the validation batch. The validation criteria such as correlation coefficients, average errors, mean squared errors, and root mean squared errors between the actual percent drug dissolution data and the drug dissolution data predicted by either of the two ANN models are shown in Table 2. It is evident from these results that the ANN model trained with the genetic training strategy was better to predict the drug dissolution data of the validation batch. This was further confirmed by the similarity factors (f_2); the f_2 between the actual and predicted drug dissolution profiles was 51.7 for the ANN model trained with the neural strategy and 89.8 for the ANN model trained with the genetic strategy. Therefore, the validated ANN model trained with genetic strategy was selected as the final ANN model for further studies.

3.3. Prediction of drug dissolution profiles of new batches prepared with known process variables

Two new batches (Batches 28 and 29) of APAP beads were prepared using given process variables (Table 1) that were not included in the ANN model training step. However, these process variables were within the confines of the process variables used during the ANN model development. The selected ANN model trained with genetic training strategy was used to predict the drug dissolution profiles of these two batches of APAP beads. A comparison of the predicted drug dissolution profiles versus the actual drug dissolution profiles are shown in Figures 6 A and 6 B for Batches 28, and 29, respectively. It is evident from the figures that the actual drug dissolution profiles are similar to the predicted drug dissolution profiles for both Batch 28 (f_2 values of 75.9) and Batch 29 (f_2 values of 72.9).

3.4. Prediction of the optimal process variables for the desired dissolution profiles

The optimal process variables predicted by the trained ANN model for the hypothetical 1 (Dome) and hypothetical 2 (Radial) APAP beads formulations are shown in Table 1. Two new batches (Batches 30 and 31) were prepared according to the predicted optimal process variables. The desired and actual drug dissolution profiles of Batches 30 and 31 are shown in Figures 7 A and 7 B, respectively. The similarity factor f_2 was 61.1 between the dissolution profile of Batch 30 and the hypothetical drug dissolution profile 1 (Dome). Similarly, f_2 was 78.6 between the dissolution profile of Batch 31 and the hypothetical drug dissolution 2(Radial). Thus, it is evident from the results that GeneHunter[®] was able to predict the optimal process variables (inputs) based on the hypothetically desired drug dissolution profiles (outputs) of APAP beads. This is because the GeneHunter[®] software also uses a similar strategy as the genetic training strategy to select and optimize the inputs to achieve the desired outputs. It allows the less fit process variables to be eliminated from the data set, thus selectively breeding the most fit process variables in the data set. This process is called "selection", as in selection of the fittest. GeneHunter[®] software also takes two fit process variable sets and mate them. This process is called crossover. Occasionally, GeneHunter[®] also generates mutations in its data set. The new data set then consists of an "offspring data" plus a few of the older data, which are allowed to survive to the next generation because they are the fittest in the data set. After dozens or even hundreds of generations, the fittest data set is considered as the optimum or close to the optimum inputs for the desired output.

Figure 1: Dissolution profiles of the APAP beads prepared with the dome extruder (Batches 10 to 18) and radial extruder (Batches 19 to 27)

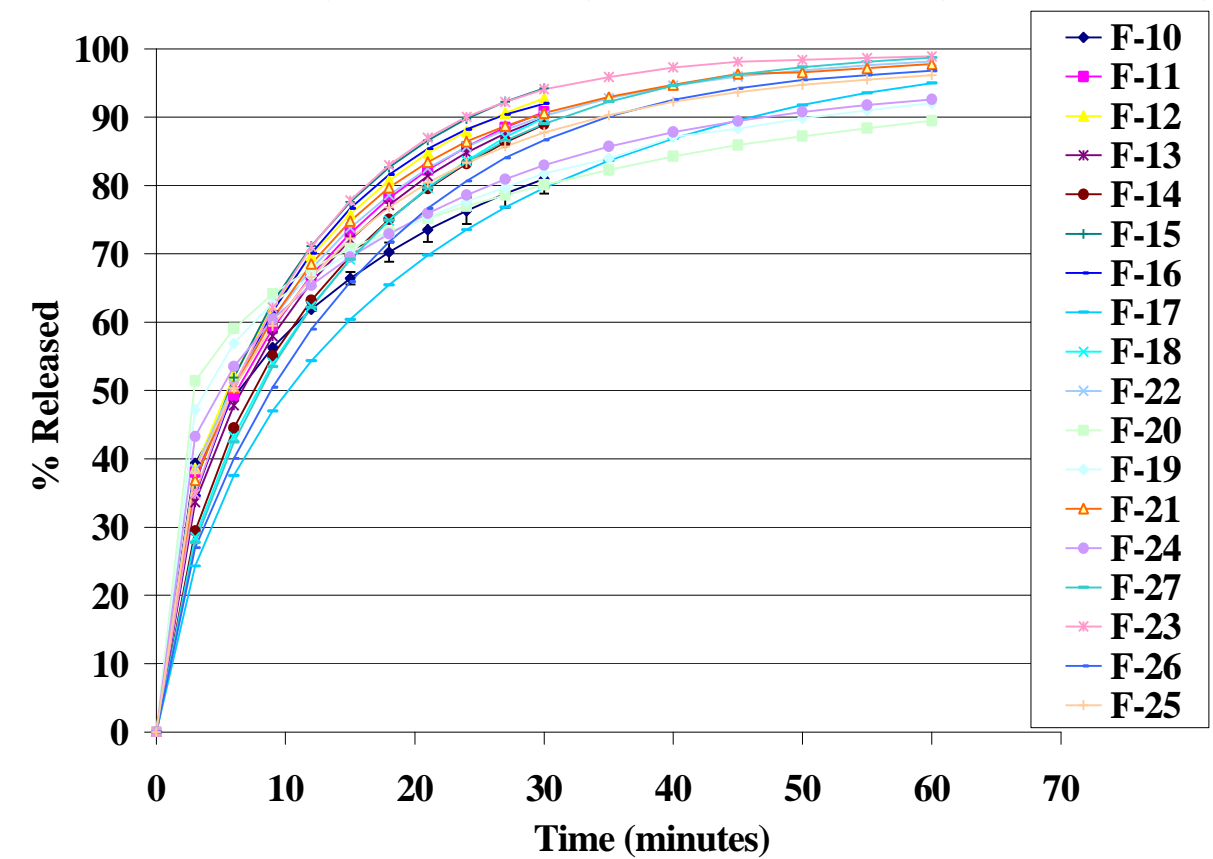


Table 1: Process variables of extrusion-spheronization used to prepare APAP beads

Batch Code	Screw Speed (rpm)	Spheronization Speed (rpm)	Spheronization Time (min)	Type of Extruder
10	25	600	1	Dome
11	75	600	1	Dome
12	25	1400	1	Dome
13	75	1400	1	Dome
14	50	1000	5.5	Dome
15	25	600	10	Dome
16	75	600	10	Dome
17	25	1400	10	Dome
18	75	1400	10	Dome
19	25	600	1	Radial
20	75	600	1	Radial
21	25	1400	1	Radial
22	75	1400	1	Radial
23	50	1000	5.5	Radial
24	25	600	10	Radial
25	75	600	10	Radial
26	25	1400	10	Radial
27	75	1400	10	Radial
28	35	1200	7.5	Radial
29	65	800	3.5	Dome
30	30	1026	2.7	Dome
31	28	957	8.7	Radial

Table 2: Evaluation results of the developed ANN models using neural or genetic training strategy

Evaluation Criteria	Model developed with Neural training strategy		Model developed with Genetic training strategy	
	Batches used for Training	Validation Batch	Batches used for Training	Validation Batch
R-squared	0.999	0.680	0.974	0.996
Average Error	0.252	7.496	1.973	0.605
Correlation coefficient	0.999	0.997	0.989	1.000
MSE	0.114	84.773	7.485	1.025
RMSE	0.337	9.207	2.736	1.012

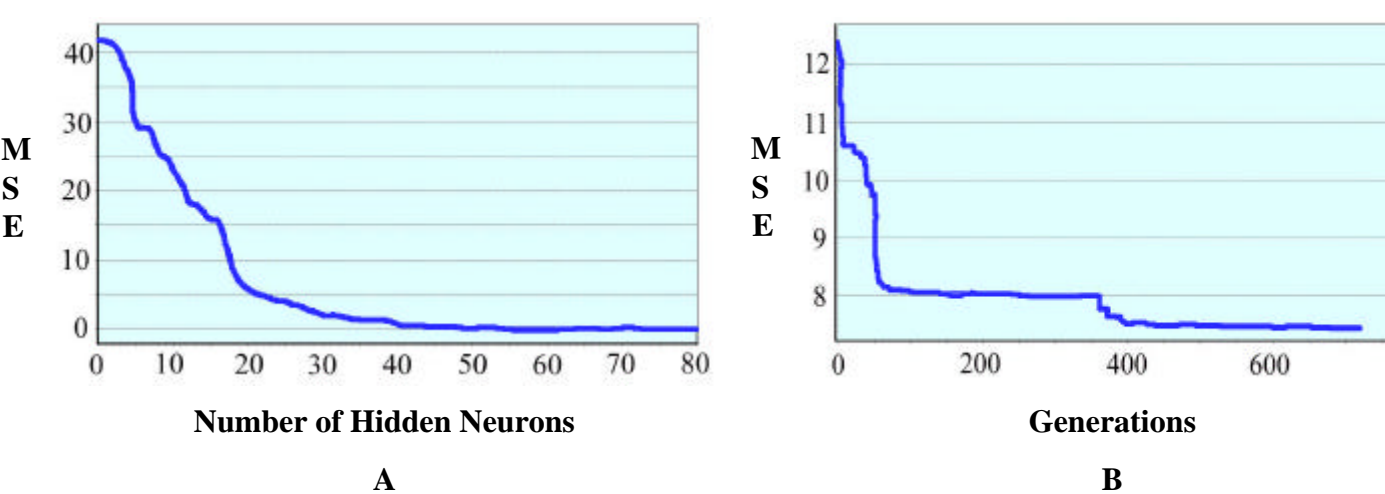


Figure 2: Mean squared error (MSE) between the dissolution profiles of actual and predicted by the ANN models developed with (A) neural or (B) genetic strategy

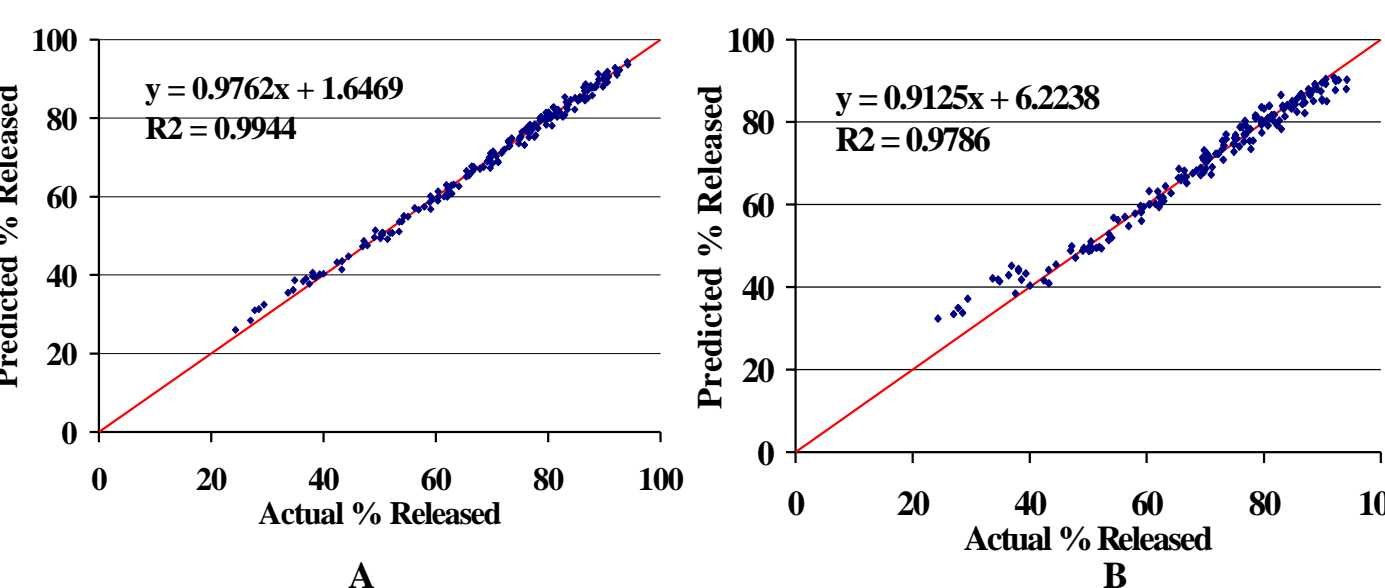


Figure 3: Plots of actual dissolution profiles versus predicted dissolution profiles by the ANN models developed with (A) neural or (B) genetic strategy

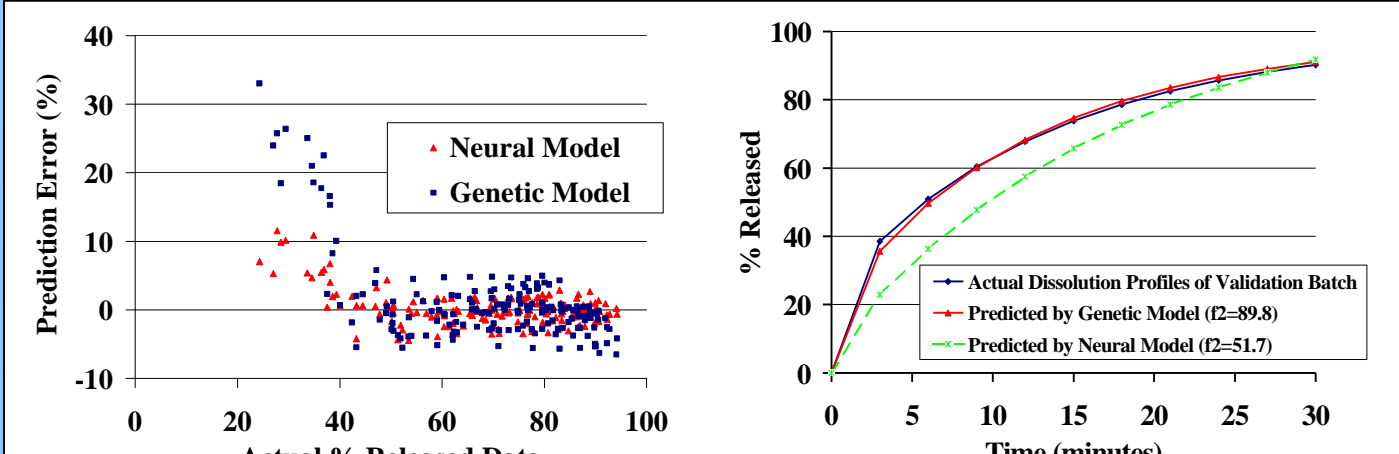


Figure 4: A comparison of the prediction errors of the ANN models developed with two different training strategies

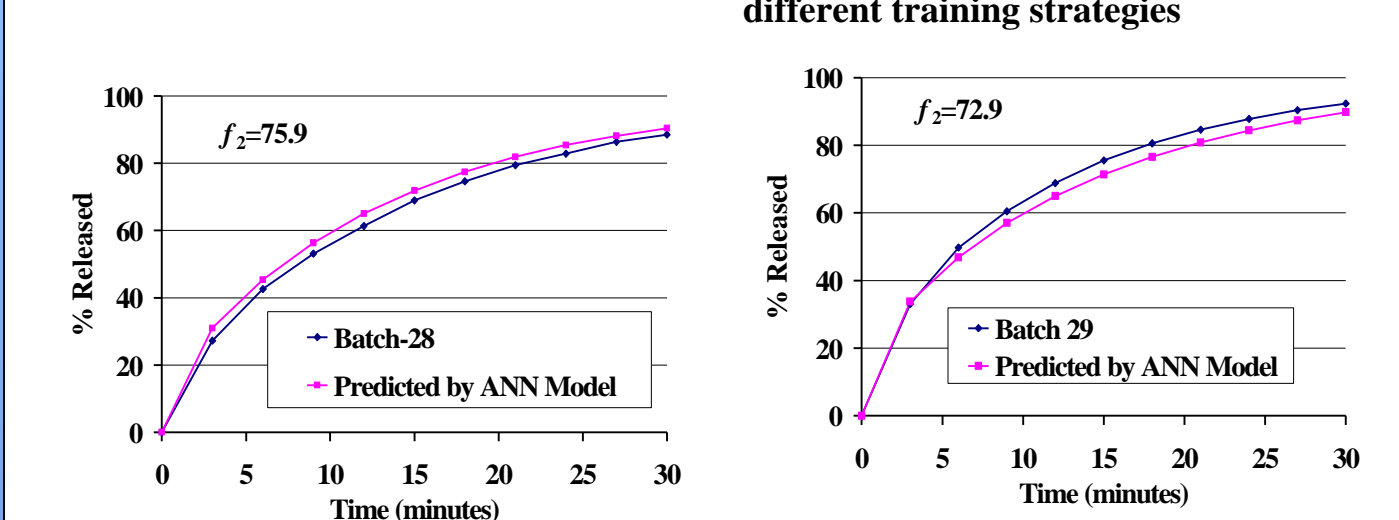


Figure 5: A comparison of the actual dissolution profile of the validation batch versus the dissolution profiles predicted by the ANN models developed with two different training strategies

Table 3: Parameters used in the GeneHunter[®] software

Population size	50
Chromosome length	8 bits
Crossover rate	90%
Mutation rate	1%
Generation gap	0.98
Evolution stop criterion	The best fitness unchanged after 75 generations

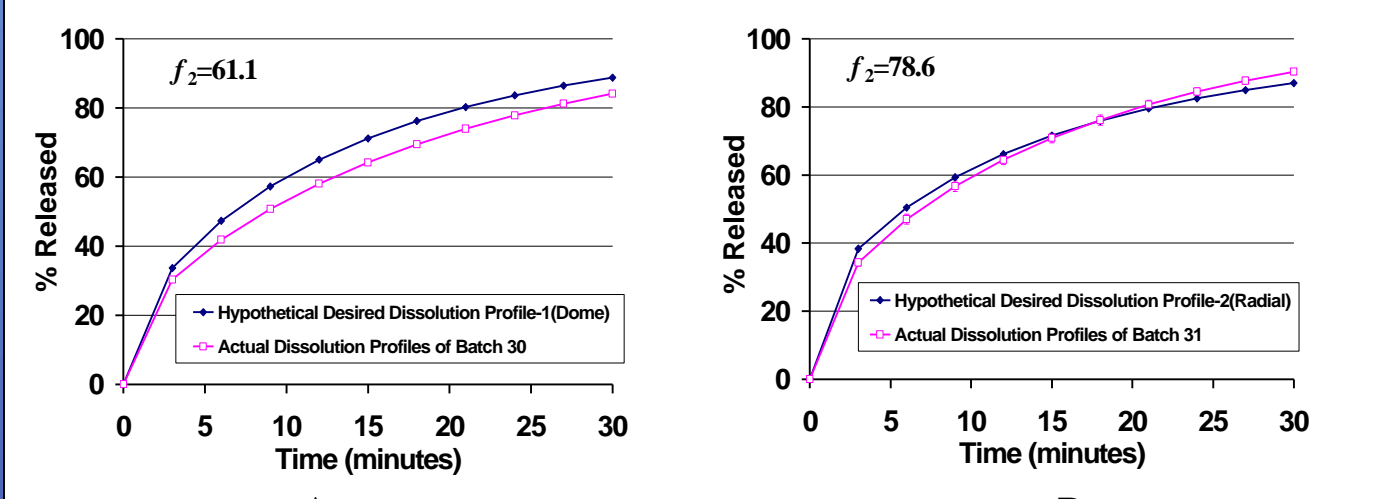


Figure 7: A comparison of the hypothetical desired dissolution profile versus actual dissolution profile for (A) Batch 30 and (B) Batch 31

4. CONCLUSION

The results of the study showed that an ANN model trained with the genetic strategy was better than the one trained with the neural strategy in predicting the release profiles of APAP from the beads. Moreover, the trained ANN model can predict the dissolution profile of APAP beads manufactured using known process variables, as well as it can be employed to predict the optimal process variables (inputs) that will produce a formulation with the desired dissolution profile (outputs).

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