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COUPLING THE IMAGE ANALYSIS AND THE ARTIFICIAL NEURAL NETWORKS TO PREDICT A MIXING TIME OF A PHARMACEUTICAL POWDER

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ABSTRACT

In recent years, different laboratories were interested in predicting the mixing time of a pharmaceutical powder. In fact, a nonhomogeneous mixture may lead to under dose and/or overdose of the active ingredient in the drug product. Our study is aimed toward using a new and revolutionary approach in the field of the processes "The Artificial Neural Networks" (ANN) by using the Neural Networks Toolbox™ derived from Matlab® software. The validation of the neural network was assumed by studying others mixing powders and then we compared the experimental results to the data obtained by the neural network calculations**.** Experimental results were obtained from a non-destructive method (Image Analysis) which was used in order to characterize the homogeneity of powder mixture in a V-Blender as well as a Cubic Blender which are most used in the pharmaceutical industry.

Keywords: ANN; Image analysis; Homogeneity; Back-propagation algorithm; multi-layer perceptron.

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1. INTRODUCTION

The divided solid mixture (powder, granular) is a key operation in many industrial fields (food, cement, plastics...). In the pharmaceutical industry, a tablet is obtained from the mixture of several components. Since the final powder mixture will be divided into several units which will contain with a certain tolerance the same amount of excipients and active ingredients; the mixing quality achieved will determine immediately the quality of the finished product [1].

The operation is indeed the primary responsible for the achievement of specifications and properties of the formulated products. But the notion of homogeneity of a mixture of solid, inseparable from those of scales observation and segregation, is difficult to achieve by measurement. In most cases, we must indeed resort to estimate by means of sampling, which causes problems of technical and statistical orders.

Powder mixing in the pharmaceutical industry is largely carried out by empirical methods. There are few controls on individual doses, where tablets containing 50 mg or less of drug substance must be individually tested for assay [2].

Different studies have been performed in order to characterize solid mixture. N. Abatzoglou et al. (2010) proposed an experimental method to measure the segregation tendency of flowing binary granular mixtures with NIRS methodology [3-5]; David Barling (2015) studied the mixing of a binary pharmaceutical powder using a colored tracer powder (sub-micronised iron oxide tracer) [6]; Carolyn Wightman et al. (1996) [7], Alvaro Realpe and Carlos Velázquez (2003) have used Image Analysis Method for characterizing mixtures of granular materials [8]; Ixchel Gijón-Arreortúa and Alberto Tecante (2015) have studied a mixing time of cohesive food powders with a horizontal helical double-ribbon impeller [9]; Luke A. Fullard and al. (2013) have developed a model of a powder mixing in mass flow discharge but not in the blender [10].

Despite these works, in our knowledge, we do not found enough studies about the exploitation of artificial neural networks to predict the mixing time of a pharmaceutical powder in a blender; also, in our study, we used also a non-destructive method (Image Analysis) that allows us to have the data about the mixture.

Artificial neural networks (ANNs) are a family of massively parallel architectures that solve difficult problems via the cooperation of highly interconnected but simple computing elements (or artificial neurons) [12].

Artificial neural networks (ANNs) have been successfully used in a number of diverse fields. Biosorption of methylene blue by dead leaves of posidonia oceanic, 2012 [11]; prediction of marten site fraction of micro alloyed steel, 2013 [12]; an efficient algorithm for automatic tumor detection in contrast enhanced breast MRI, 2013 [13]; explicit neural network in suspended sediment load estimation, 2013 [14]; modeling the correlation between heat treatment, chemical composition and bainite fraction of pipeline steels, 2013 [15].

The application of ANNs in pharmaceutical development has been assessed using theoretical as well as typical pharmaceutical technology examples [16]. Ibric et al. (2012) have been evaluating and optimizing the modified release solid dosage forms [17].

Mixing of the pharmaceutical powders is a challenge that researchers are trying to understand and be able to model. In fact, the powder mixture depends on several parameters that affect the mixing time.

In this study, several low-dose binary mixtures were conducted while varying the parameters that most influence the mixing time (granulometry of excipients, concentration of the tracer, type of mixer and initial position of the tracer in the blender) to build the database that will serve as training neural network. Each mixture must satisfy several criteria in order to achieve a degree of homogeneity and which are: the coefficient of variation (CV), which must not be higher than 6%, all the individual dosages must be within the range of ± 15 % of the expected value and the average grade must be within the range of ± 7.5% [18].

2. MATERIALS AND METHODS

All mixtures have been obtained using a Cubic and a V-blender. The figure 1 shows a cubic mixer and a V-shaped rotating around an axis forcing the particles to roll relative to each other on the surface of the mixture powder.

Frequency converter equipment is mounted outside the mixer and connected to the mixer engine with adjustable rotational speed. The volume of each blender is 3000 cm^3.

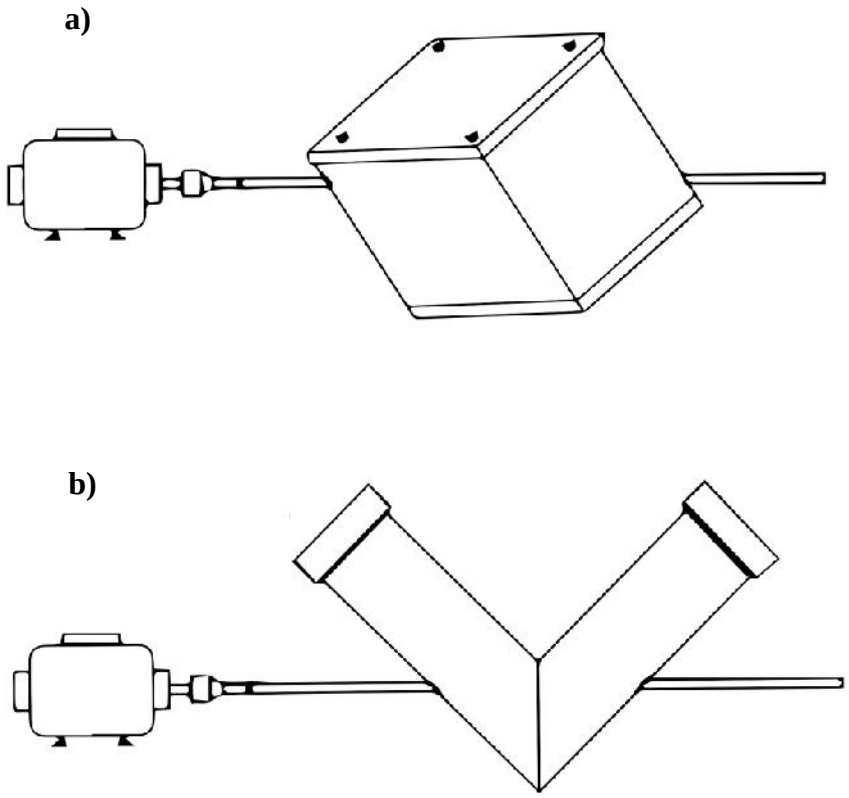

Fig. 1. Synoptic scheme of different blender: a) Cubic Blender, b) V- Blender.

2.1 Characterization of the products

The experimental studies were performed using the material described in Table.1 where the active substance of every material was in this case, a tracer (colored particle) with concentrations ranging from 1 to 6% (w/w). The particles of Starch were prepared in the laboratory with a fluid bed equipment (GLATT).

Table1. Particles used in the mixture.

Material used	Tracer
Big particle of Starch	Colored particle of Starch (same size) with Methylene blue
Small particle of Starch	Colored particle of Starch (same size) with Methylene blue

2.2 Study the homogeneity of a low-dose binary mixture

In order to establish a database that later will serve as a learning neural network, the powder mixtures were prepared in the laboratory by adjusting the parameters that affect the mixing time.

The parameters studied are: the particle size of the excipients, the type of mixer, the concentration of the tracer and its initial position. In order to measure the homogeneity of the mixture, we use the method of Image processing, figure 2.

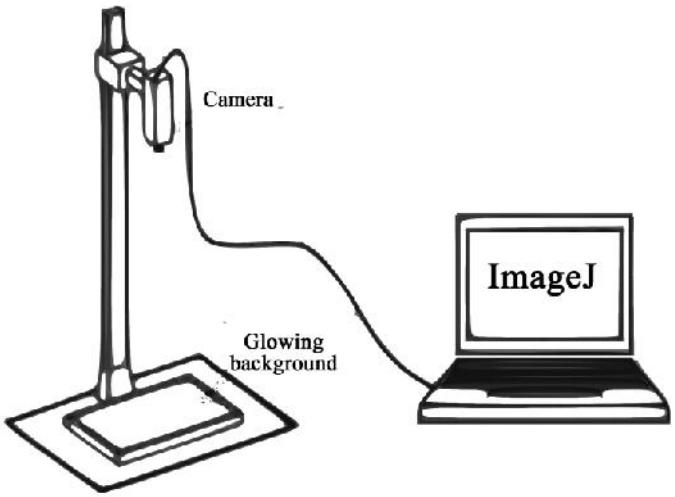

Fig. 2. Schematic diagram of the image acquisition setup

The pictures taken during the processes of mixture at the wall of the blenders have been analyzed using ImageJ software and have been validated with the results obtained by the UV-vis spectrophotometer testing.

The UV-Visible spectrophotometry was used as a reference method to perform the validation of the new method (Image Analysis). To this purpose, we used a spectral method in the objective to measure the assay of t h e colored particles contained in the samples. The assay of the active ingredient was performed with a UV-Visible spectrophotometer Optizen 2120 at the wave length λ = 650 nm

The obtained results are illustrated on the following regression, figure 3.

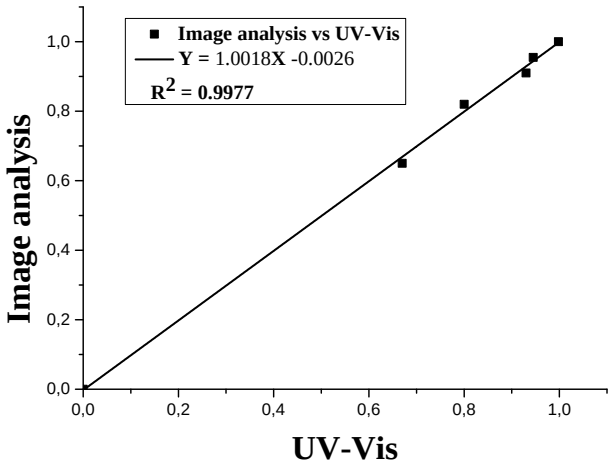

Fig. 3. Image analysis versus UV-Vis

3. RESULTS AND DISCUSSION

3.1 Mixing kinetic

In order to predict the mixing time by neural networks, a database is necessary. For this purpose, several experimental data will be done to build the neural network. The figure 4 shows the kinetic profile in a cubic blender for starch with a concentration of 2 % (w/w).

The coefficient of variation (CV) is defined as the standard deviation of the tracer sample divided to their average; kinetic of the mixture are analyzed by measuring the evolution of this coefficient versus time.

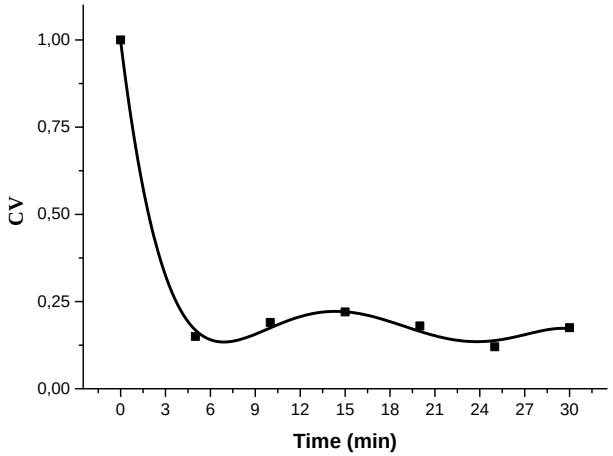

Fig. 4. Kinetics of the small particle of Starch with a concentration of 2% (w/w) in a Cubic mixer.

Indeed, the convective motions that allow rearrangements across the mixer have the immediate effect of important variance reductions, leading the shape observed for the first part of the curve.

Then the asymptotic part corresponds to the diffusional mechanism, much slower than the previous one; during this step, we think that there is a competition with the segregation by percolation, which explains the small oscillations amplitude [19].

We also note the absence of the shear mechanism on the kinetics of the mixture because the two mixers used are not equipped with a shearing tool [22].

3.2. Neural network

3.2.1. Building the neural network

Total of 72 experiments were realized in order to study the variation of mixing time as function of the excipient size particles (Starch), the type of mixer, the tracer concentration and the initial position of the tracer in the mixer.

Table 2. Database for learning of the neural network

N°	Size of the excipient (mm)	Type of mixer	Tracer concentration (%)(w/w)	Position of the tracer	Mixing time (s)
1	4	Cubic	1	Top	300
2	4	Cubic	1	Middle	600
3	4	Cubic	1	Bottom	600
4	4	V	1	Top	1800
5	4	V	1	Middle	600
6	4	V	1	Bottom	600
7	4	Cubic	2	Top	1200
8	4	Cubic	2	Middle	1500
9	4	Cubic	2	Bottom	1800
10	4	V	2	Top	300
11	4	V	2	Middle	1800
12	4	V	2	Bottom	1800
13	4	Cubic	3	Top	600
14	4	Cubic	3	Middle	1800
15	4	Cubic	3	Bottom	1800
16	4	V	3	Top	900
17	4	V	3	Middle	600

18	4	V	3	Bottom	1800
19	4	Cubic	4	Top	1800
20	**4**	**Cubic**	**4**	**Middle**	**300**
21	4	Cubic	4	Bottom	900
22	4	V	4	Top	1200
23	4	V	4	Middle	1200
24	4	V	4	Bottom	600
25	4	Cubic	5	Top	1200
26	4	Cubic	5	Middle	300
27	4	Cubic	5	Bottom	900
28	4	V	5	Top	600
29	4	V	5	Middle	900
30	4	V	5	Bottom	1500
31	4	Cubic	6	Top	600
32	4	Cubic	6	Middle	300
33	4	Cubic	6	Bottom	600
34	4	V	6	Top	300
35	4	V	6	Middle	600
36	4	V	6	Bottom	1500
37	0.894	Cubic	1	Top	1200
38	0.894	Cubic	1	Middle	600
39	0.894	Cubic	1	Bottom	900
40	0.894	V	1	Top	1200
41	0.894	V	1	Middle	1200
42	0.894	V	1	Bottom	600
43	0.894	Cubic	2	Top	1800
44	0.894	Cubic	2	Middle	300
45	0.894	Cubic	2	Bottom	300
46	**0.894**	**V**	**2**	**Top**	**1500**
47	0.894	V	2	Middle	1500
48	0.894	V	2	Bottom	600
49	0.894	Cubic	3	Top	900
50	0.894	Cubic	3	Middle	600
51	0.894	Cubic	3	Bottom	900
52	0.894	V	3	Top	1800
53	0.894	V	3	Middle	300
54	0.894	V	3	Bottom	1200
55	0.894	Cubic	4	Top	600
56	0.894	Cubic	4	Middle	1200
57	0.894	Cubic	4	Bottom	300
58	0.894	V	4	Top	1500
59	0.894	V	4	Middle	300
60	0.894	V	4	Bottom	1500
61	0.894	Cubic	5	Top	300

62	0.894	Cubic	5	Middle	900
63	0.894	Cubic	5	Bottom	300
64	0.894	V	5	Top	1200
65	**0.894**	**V**	**5**	**Middle**	**900**
66	0.894	V	5	Bottom	1800
67	0.894	Cubic	6	Top	1200
68	0.894	Cubic	6	Middle	1500
69	0.894	Cubic	6	Bottom	1500
70	0.894	V	6	Top	1500
71	0.894	V	6	Middle	1800
72	0.894	V	6	Bottom	1200

The excipients particle size, the mixer type, the tracer concentration and the initial position of the tracer in the mixer are considered the inputs of the neural network, while the mixing time is its output. The multilayer perceptron will include three layers, Figure 5:

The first include four inputs variables.

The second will contain a number of hidden neurons.

The third consists of a single output neuron.

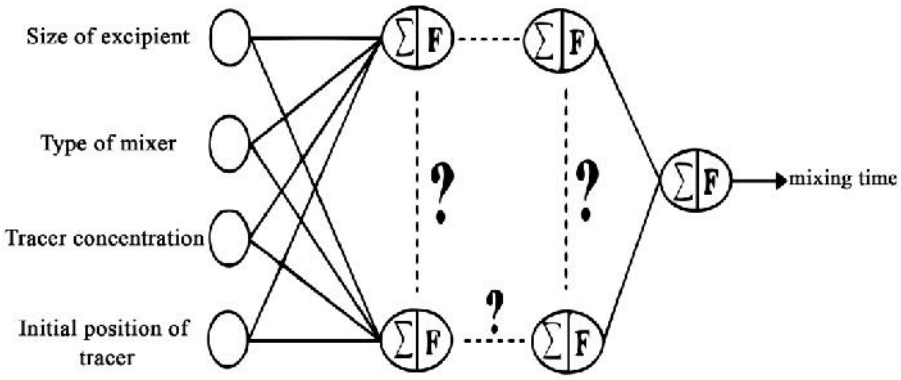

Fig. 5. Building the neural network

The primary goal was to determine the network optimal structure, in another way the optimal number of hidden neurons, which allows the best approximation of mixing time, while ensuring a good generalization to see if the network can predict a mixing time with values that were not used in the learning phase.

The determination of the optimal structure of the model is performed by an iterative manner.

To ensure optimal network structure, we chose an activation function of hidden layer and the output layer a "log-sigmoid" function, equation 1 and the x is the sum of the inputs.

$$f(x) = \frac{1}{1+e^{-x}} \quad (1)$$

This function allows the output amplitude limiting between 0 and 1, it is designated in MATLAB® by "logsig".

Learning of the considered Multilayer Perceptron, is done using the backpropagation algorithm, the modification of network weights is done by the Levenberg-Marquardt method, it is designated in MATLAB® by TRAINLM [20, 21].

When the number of iterations exceeds 1000, or the mean square error becomes equal to 0, or the gradient reaches a minimum value of $1e^{-10}$, or the step μ reaches a maximum value of 10, the algorithm stops and does not evolve. μ is the number of validation checks and represents the number of successive iterations that the validation performance fails to decrease. If this number reaches 10, the training will stop.

Our strategy is to vary the number of neurons in the hidden layers. Several networks of different structures will be tested. Then, we select the optimal network that gives a test error as small as possible [20].

The initialization of weights and biais occurs randomly between -1 and +1. It is therefore necessary, for a fixed number of hidden neurons, making several attempts to set parameters in order to optimize the model.

We varied the number of neurons in the hidden layers from 1 to 10. For each number of hidden neurons, several trials initialization parameters were made and then we notice which configuration gives the smallest mean square error (MSE).

The criterion for choosing between different models (number of hidden layers and number of neurons in the hidden layers) is obviously the mean square error on the training set.

We noted that the network with two hidden layers (eight neurons in the first layer and four neurons in the second), present the smallest mean square errors on the training sets (6.1989

10^{-08}) at 300 iterations. This model is considered optimal and allows us to obtain the best approximation of mixing time, Figure 6.

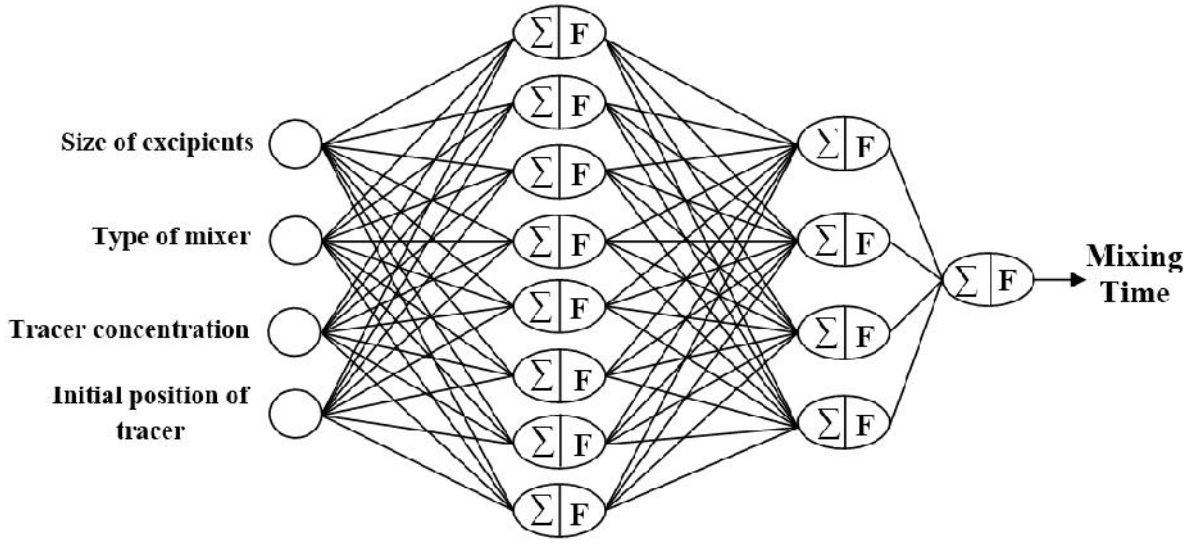

Fig. 6. Neural network used for the calculation of the mixing time

3.2.2. Performance Evaluation Model

The predicted mixture time values were obtained using Matlab® with the command 'S*=sim (net, inputs)'. With 'net', the name assigned to the Neural Network and 'inputs', the input matrix.

The points in Figure 7 represents the mixing time predicted by the Neural Network as a function of mixing time obtained experimentally by Image Analysis.

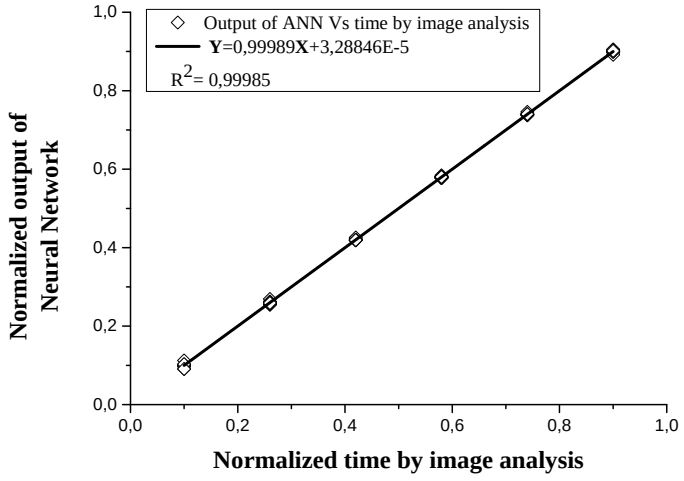

Fig. 7. Mixing time predicted by mixing time with image analysis

The straight line confirms that the neural network is agreed with the results obtained by the image analysis.

Table 3. Definitive values of the weights and the biais in different layers

Input layer							
Weights Matrix							
1.1503	-1.308	-3.0913	-3.4285				
24.89	28.246	30.0681	-19.2073				
-21.4874	-1.5601	-19.0579	-19.1107				
-10.0358	15.4421	-24.6645	8.2698				
1.5647	-2.4426	20.1537	14.1818				
-4.4565	-4.4983	1.5558	-10.7458				
0.36567	-1.8128	-11.1023	-4.0781				
-27.2842	-6.8954	13.1096	-13.358				
First hidden layer							
Weights Matrix							
8.7305	2.8032	10.8135	-10.8197	2.8067	-5.1048	0.88891	-9.5202
-7.0901	20.8131	-17.5945	8.5084	-1.0856	11.9507	-9.8859	12.2046
18.6689	8.1902	-4.0267	-0.07999	6.0855	-5.793	-2.0112	4.9468
2.3955	-13.5684	-16.3516	32.3865	12.9966	12.9811	-29.5976	8.2158
First hidden layer							
Biais Vector							
1.0513							
-13.5656							
23.7127							
-2.8504							
-13.295							
9.4513							
12.9711							
4.6258							
Second hidden layer							
Weights Vector							
-8.1843	-3.5484	28.6687	-4.5922				
Second hidden layer							
Biais Vector							
-3.5794							
6.2299							
-14.6853							
12.3115							
Output layer							
Biais Vector							

5.8994

3.2.3. Generalization phase

In order to generalize the network, other mixtures were made with other values to check if the network can predict a mixing time with values that were not used in the learning phase.

Mixtures prepared are:

1. Big particles of Starch and colored particles (concentration at 4%) in a Cubic blender (experiment number 20 in the table 2)
2. Small particles of Starch and colored particles (concentration at 2%) in a V-blender (experiment number 46 in the table 2)
3. Small particles of Starch and colored particles (concentration at 5%) in a V-blender (experiment number 65 in the table 2)

Table 4. Comparison between experimental results and results obtained with neural network

N° of experience	Mixing time with image analysis (s)	Mixing time with neural network (s)	Relative error (%)
1	300	307.1	2.37
2	1500	1450.6	3.29
3	900	898.04	0.22

Table 4 confirms that the neural network with two hidden layers (8 in the first and 4 in the second) can predict the mixing time of any experience even if it not contained in its learning database with an error less than 4%.

4. CONCLUSION

The mixing of pharmaceutical powders is a challenge that researchers are trying to understand and be able to model. The powder mixture depends on several parameters that affect the mixing time.

In this study we varied the parameters that influence the mixing time, which are the particle size of the excipients, the type of mixer, the concentration of the tracer and the initial position of the tracer in the blender.

A neural network has been realized with the neural networks toolbox of Matlab® software.

The parameters which influence the mixing represent the input of the neural network and in the output, the mixing time.

The overall results were obtained by a non-destructive method, the image analysis with the ImageJ software and the neural network with two hidden layers (eight in the first and four in the second) gave the lowest mean square error for the learning of 6.19 after 300 iterations.

In this paper, we have validated one method of characterization of mixture image analysis which is a non-destructive method by the UV-Visible spectrophotometric method. The application of ANN allows predicting the mixing time in two types of mixers: Cubic and V-Blender with low concentration of a binary mixture in different initial positions of the tracer in the blender. The neural networks model can predict correctly the mixing time experiments with an error less than 4%.

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