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Validation of fluid bed granulation utilizing artificial neural network

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Abstract

Three innovative components (an annular gap spray system, a booster bottom and an outlet filter) have been developed by Innojet Technologies to improve fluid bed technology and to reduce the common interference factors (clogging of nozzles and outlet filters, spray loss, spray drying and fluidized bed heterogeneity). In a fluid bed granulator, three conventional components have been replaced with these innovative components. Validation of the modified fluid bed granulator has been conducted using a generalized regression neural network (GRNN). Under different operating conditions (by variation of inlet air temperature, liquid-binder spray rate, atomizing air pressure, air velocity, amount and concentration of binder solution and batch size), sucrose was granulated and the properties of size, size distribution, flow rate, repose angle and bulk and tapped volumes of granules were measured. To confirm the method's validity, the trained network has been used to predict new granulation parameters as well as granule properties. These forecasts were then compared with the corresponding experimental results. Good correlation has been obtained between the predicted and the experimental data. From these findings, we conclude that the GRNN may serve as a reliable method to validate the modified fluid bed apparatus.
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Keywords: Generalized regression neural network; Fluid bed granulation; Innovative components; Non-linear calculation methods

1. Introduction

Current good manufacturing practices as well as validation requirements, necessitate the development of predictable and controllable wet granulation procedures having as few processing steps as possible. Fluidized bed granulation as the economical, state-of-

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the-art method of granulating, offers the advantage of combining the various stages of conventional wet granulation in one process. It prevents contamination and saves processing space, time and cost. Development of other methods of fluidized bed technology enables the utilization of this technique also for coating, spheronization and layering (Funakoshi et al., 1980; Jäger and Bauer, 1982; Jones, 1988; Jozwiakowski et al., 1990; Egermann and Flögel, 1995; Achanta et al., 1997; Vertommen and Kinget, 1997; Bauer et al., 1998; Pisek et al., 2000).

The benefits of fluidized bed technology are well enough known to display the importance of innovative improvements to reduce the interference factors and to make fluidized bed processes more economic and safer. Some disadvantages have been discussed before. These include the high energy consumption, the enhanced risk of explosion due to the large amount of oxygen conveyed by the fluidizing air and the problem of air pollution by dust and solvents due to the structure of the standard fluidized bed equipments, where the fluidizing air is blown to the atmosphere. Different methods have been suggested to reduce these problems: methods of preventing explosions in fluidized bed granulators have been recommended by Külling (1977a, 1977b). In order to retain dust of highly toxic materials, a secondary high-efficiency filter has been suggested (Kristensen and Schaefer, 1987). Pollution of air by solvents can be prevented by using a specially constructed fluidized bed operating in a closed system, where the solvent is recovered by cooling (Kristensen and Schaefer, 1987). However, problems still exist: such as clogging of nozzles and outlet filters, spray loss, spray drying and fluidized bed heterogeneity especially with the use of the top spray method, which causes heterogeneous granulation with overwetting of some portions and underwetting of other portions of the feed material. The innovative components (spray system, booster bottom and outlet filter) have been developed by Innojet Technologies to reduce these interference factors. In a fluid bed granulator, the conventional nozzle, the outlet filter and the perforated base plate have been, respectively, replaced with the aforesaid novel devices. The aim of the presented study was the investigation of process and product parameters required to validate the modified apparatus.

In fluid bed granulation technology, the parameters that influence the granule properties have been classified as apparatus, process and product parameters (Kristensen and Schaefer, 1987). The process of size enlargement of particles in the fluidized bed is a complex interaction involving these parameters, which affect the final quality of the granules. Given such complex relationships, conventional data-processing methods are not suitable for investigation of the process of size enlargement. They often lead to unsatisfactory results due to non-linear relationships within the parameter set. This problem can be overcome by the use of non-linear calculation methods like artificial neural networks (Murtoniemi et al., 1994; Watano et al., 1994, 1997b).

Artificial neural networks have been formerly applied in different areas of studies (Veng-Pedersen and Modi, 1993; Klocker et al., 2002). They constitute a set of mathematical methods and algorithms designed to mime the functions (association, learning and generalization) of the human brain (Zupan and Gasteiger, 1999). From the large number of different network-learning processes, a generalized regression neural network (GRNN) has been selected for the presented study.

2. Materials and methods

2.1. Equipment

For wet granulation, (a) the “Innojet annular gap spray nozzle Rotojet type IRN 2” with 2 mm annular gap diameter, 6.28 mm developed length, 0.25 mm gap width, 1.57 mm^2 free spraying cross-section and 2.09 nl/s air consumption at 1 bar spraying pressure, (b) the “Innojet booster Opojet type ITS 140” with 140 mm diameter, four dividing gaps, 1.5 mm gap length and 80–160 m^3/h air velocity, and (c) the “Innojet filter Sepajet type 280” have been incorporated into a laboratory fluid bed granulator with a product container of 5 l feed material capacity.

The annular gap spray nozzle consists of rotating annular gaps. Each rotating annular gap liquid cross-section is both internally and externally surrounded by additional annular gap cross-sections for spraying and supporting air. The three media gap widths were defined or dimensioned at a constant ratio to each other (Fig. 1).

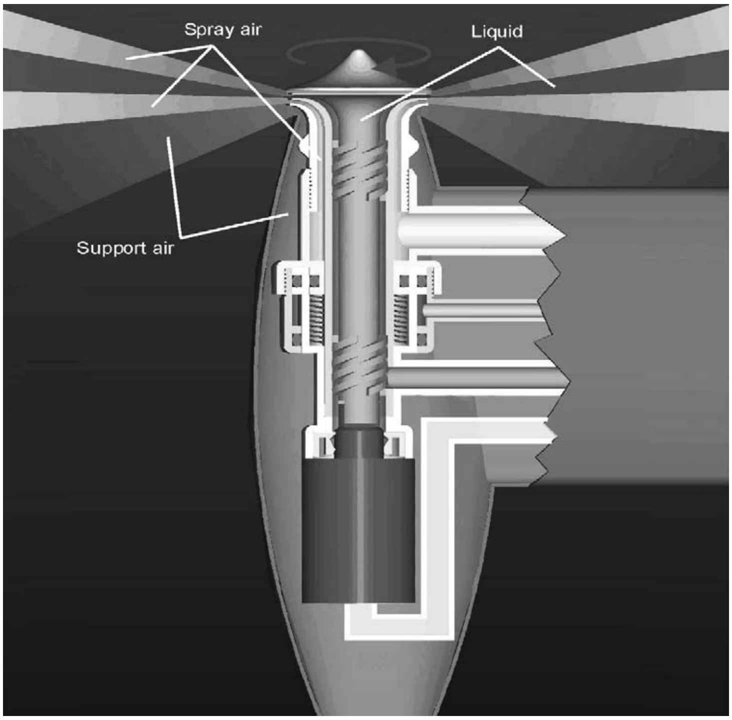

Fig. 1. The design of the Innojet gap spray nozzle Rotojet type IRN 2.

The base plate, which refers to its function is called “booster”, consists of two semicircular surfaces that create two currents directed towards each other. The horizontal air and product streams are diverted vertically at the dividing centre line (Fig. 2).

The filter is of a special folded configuration, with an uninterrupted self-dependent cleaning system. The special folded design which causes an enlargement in the filter surface is intended to increase the air transition capacity of the filter (Fig. 3).

The gap spray nozzle has been installed in the booster bottom to enable the use of the bottom spray method.

The inlet air temperature together with the outlet temperature and the temperature of the product container have been monitored by an industrial controller Philips model KS 90.

2.2. Granulating materials

Sucrose (Ph E 97, Agrana International) has been granulated using glucose syrup as a feed material.

The batch size, the amount and concentration of binder solution have been investigated as product parameters, while the inlet air temperature, atomizing air pressure, liquid-binder spray rate and air velocity have been investigated as process parameters.

To investigate individual aforesaid parameters, a series of granulation processes have been performed and each investigated parameter was set at different values, while keeping the other investigated parameters constant.

2.3. Evaluation of produced granules

Following each granulation, the statistical granule size, the size distribution, the bulk and the tapped volumes, the flow rate and the repose angle of the granules have been determined.

Particle size analysis ($n = 5$) was performed on a laboratory sieve machine Retsch type VE 1000 with amplitude 0.2 for 6 min. The particle size distribution obtained was plotted on a Rosin, Rammler, Sperling, and Bennet (RRSB) nomogram. The size corresponding to

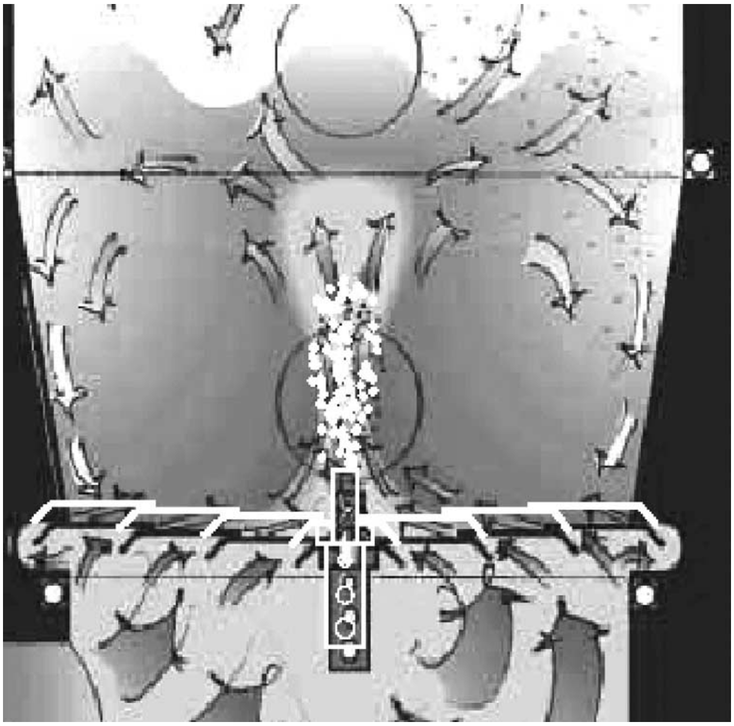

Fig. 2. The functioning of the Innojet booster Opojet type ITS 140.

63.2% on the passage percentage axis was taken as the statistical diameter. The geometric mean granule size, d_{50}, was taken by the use of log normal distribution. The particle size distribution was taken by calculating the geometric standard deviation (σ_g).

The flow rate ($n = 5$) was measured as the required time (s) for granule samples (100 g) to flow through a 9.5 mm orifice.

The bulk volume of each sample (50 g) was measured in a 100 ml graduated cylinder ($n = 5$).

After each granulation process, the residual moisture of granules was determined using an electronic moisture analyzer Scaltec type SMO 01, which uses thermogravimetric principles. At the end of the granulation process, the granules have been dried for 5 min. During the drying process, samples were taken when the bed temperature had risen 20% beyond the final granulation temperature ($n = 3$). A sample weighing approximately 5 g was spread onto an aluminium pan and was placed in the analyzer. The sample was heated to 100 °C and evaporative moisture losses were recorded and automatically reported as percent moisture content.

2.4. Computational methods

A generalized regression neural network (GRNN) was trained for the studied granulation process.

GRNNs were introduced by Specht in 1991 and estimate the most probable value for continuous dependent values of a given dataset. They compute the probability density functions of the given patterns and finally attribute them to the value to which they most likely belong (Specht, 1991). GRNNs are feed-forward networks which are comprised of four layers (Fig. 4). The input layer is constituted by a varying number of neurons, which is equal to the number of independent features the network is trained on. The normalized input vector is copied onto the pattern units in the pattern layer, each representing a training case. An exponential activation function is applied and the corresponding activation level is forwarded to the summation unit, where the density estimate on each pattern of each group or possible value is summarized. Finally, a decision with Bayesian theory is established in the fourth layer (decision layer)

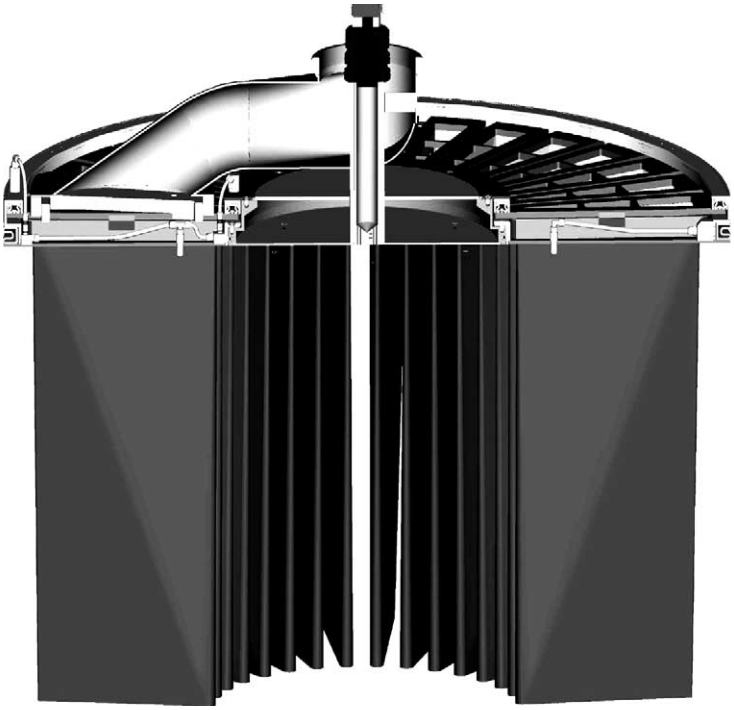

Fig. 3. Innojet filter Sepajet type 280.

(Specht, 1990; Young et al., 1999; Simon and Nazmul, 2001).

A principal advantage of GRNNs is that they involve a one-pass learning algorithm and are consequently much faster to train than the well-known backpropagation paradigm (Specht, 1990; Specht, 1991). Furthermore, they differ from classical neural networks in that every weight is replaced by a distribution of weights. This leads to the exploration of a large number of combinations of weights and is less likely to end in a local minimum (Bruneau, 2001). Therefore, no test and verification sets are necessary, and in principle all available data can be used for the training of the network. To ensure that the results of the trained network are real and no artefacts of the training process, an external validation can be done by predicting new granulation parameters for experiments. The experimentally obtained granule properties may then be compared to those predicted by the network.

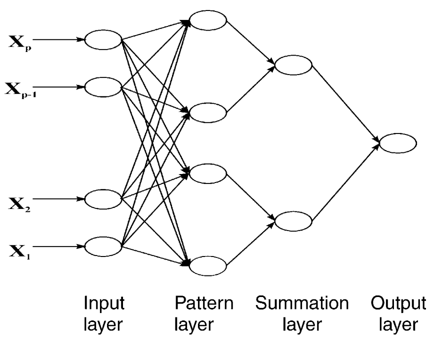

Fig. 4. Architecture of generalized regression neural networks.

3. Results and discussion

The presented GRNN has been trained by the Trajan software package (Trajan Neural Networks 5.0, 1999). As input, the seven product and process parameters have been used, namely batch size, amount and concentration of binder solution, liquid-binding spray rate, atomizing air pressure, inlet air temperature and air velocity. The output has been defined as the corresponding granule properties such as the statistical granule size, the granule size distribution, the flow rate, the re-

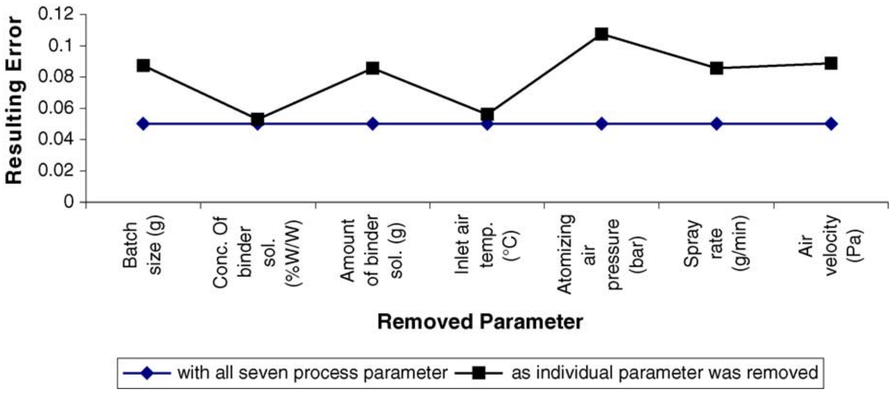

Fig. 5. Prediction accuracy of the GRNN for the training set when individual parameters are excluded.

pose angle and the difference between bulk and tapped volumes. Consequently, the obtained network architecture consisted of seven units in the input layer, 45 pattern neurons, six neurons in the summation layer and five output units. The averaged absolute error for the prediction of the granule properties from the granulation parameters was found to be 0.050, whereby the error has been defined as the sum of the squared differences between the predicted and actual output values on each output unit.

The contribution of each parameter to the prediction of the granule properties has been estimated by a sensitivity analysis. During this analysis, it has been tested how the GRNN would cope if each of the process parameters in turn were unavailable. Therefore, the experimental data has been submitted to the network repeatedly, with each process parameter in turn treated as missing, and the resulting network error has been reported. If an important parameter was deleted in this fashion, the error increased significantly; whereas if an unimportant one has been removed, the error was only slightly influenced. The results of this sensitivity analysis are illustrated in Fig. 5. It can be seen that the most important descriptor contributing to the final network was the atomizing air pressure. Its removal from the input variable resulted in an increased error of 0.11. The other most important descriptors were the air velocity, the spray rate and the amount of binder solution. Their removal from the input variable resulted in an increased error of 0.09, 0.07 and 0.085, respectively.

This is confirmed by the analyses of the properties of the corresponding test granules. These analyses have shown that the moisture content of granules is significantly affected by varying the amount of binder solution, the binder spray rate and the atomizing air pressure. On the one hand, an increase of the amount of binder solution and the spray rate, and on the other hand, a decrease of the atomizing air pressure resulted in increased moisture levels causing size enlargement of the produced granules. Granules with a wide size distribution are caused by too high or not sufficient moisture levels in the bed. Therefore, achieving the optimal moisture content during the granulation process is the key for obtaining granules with a narrow size distribution. Surprisingly, there have been no significant correlations between the inlet air temperature and the mean granule size. Correlations of atomizing air pressure, spray rate and amount of binder solution with mean granule size, granule size distribution and residual moisture of granules are illustrated in Fig. 6. The important role of the moisture content in size enlargement of particles was previously described (Kristensen and Schaefer, 1987; Watano et al., 1991, 1997a; Frake et al., 1997; Rantanen et al., 1998; Abberger, 2001).

The bulk and tapped volumes have been significantly affected by increasing the amount of binder solution (Fig. 7) and the flow rate has been correlated to the amount of binder solution (Fig. 8).

The standard Pearson's R correlation coefficients between the experimentally measured and by GRNN predicted output values are depicted in Table 1. Furthermore, the corresponding prediction accuracy for the different granule properties is summarized which has been evaluated by considering ±10% cut-offs of

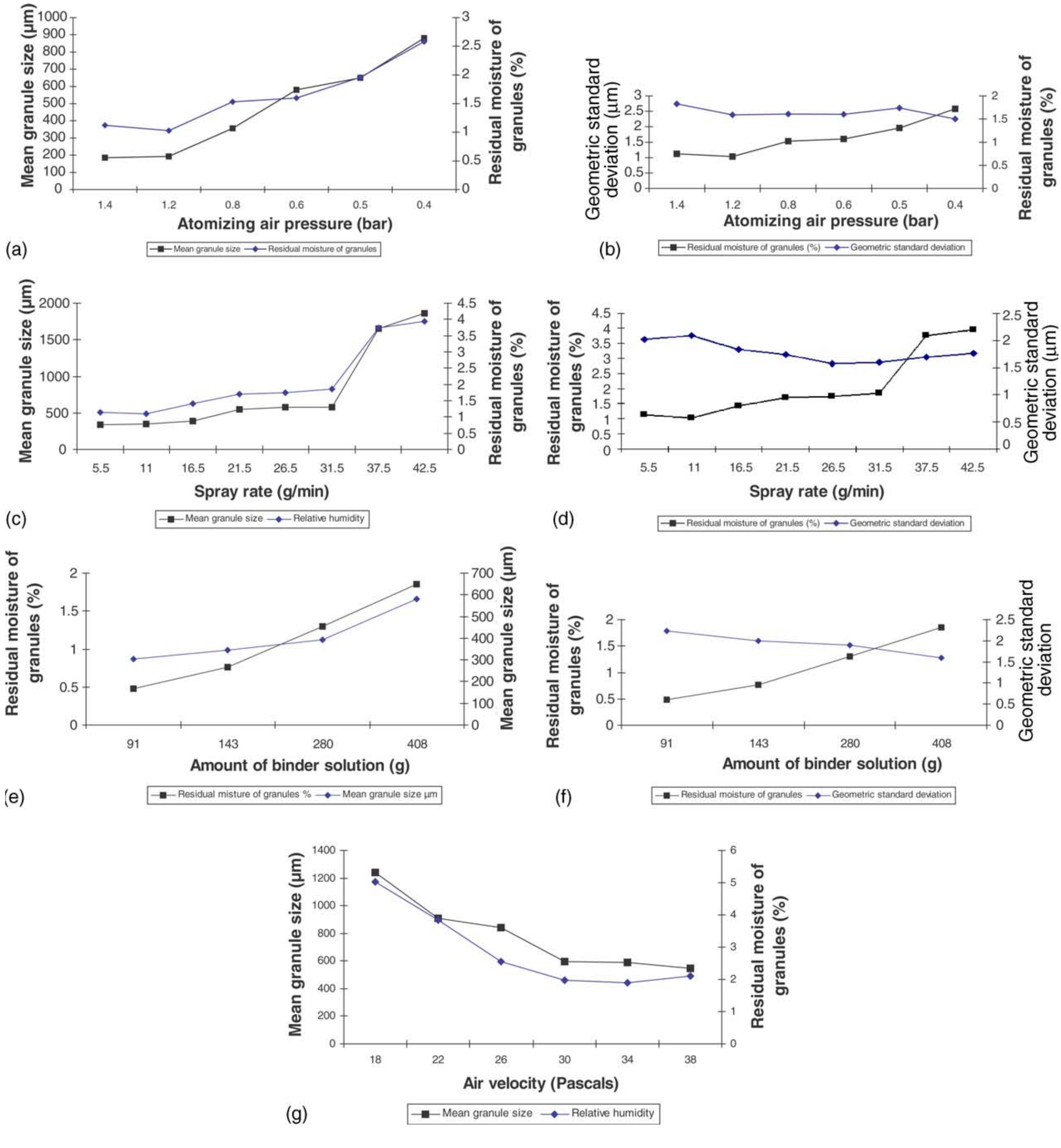

Fig. 6. Correlations of atomizing air pressure, spray rate, amount of binder solution and the air velocity to mean granule size, granule size distribution and the residual moisture of granules. (a) Correlation of atomizing air pressure with either mean granule size or residual moisture of granules. (b) Correlation of atomizing air pressure with either granule size distribution or residual moisture of granules. (c) Correlation of spray rate with either mean granule size or residual moisture of granules. (d) Correlation of spray rate with either granule size distribution or residual moisture of granules. (e) Correlation of amount of binder solution with either mean granule size or residual moisture of granules. (f) Correlation of amount of binder solution with either granule size distribution or residual moisture of granules. (g) Correlation of air velocity with either mean granule size or residual moisture of granules.

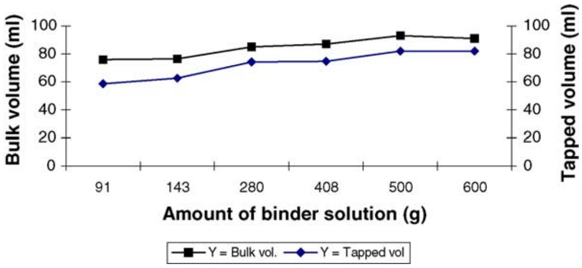

Fig. 7. Correlation of amount of binder solution with either bulk or tapped volumes.

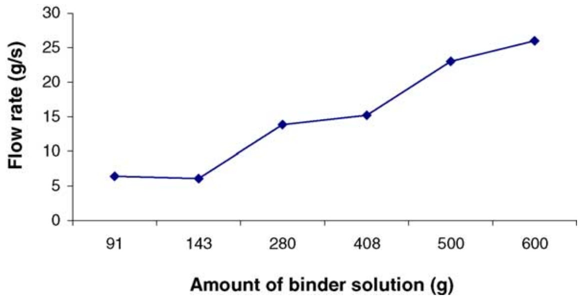

Fig. 8. Correlation of amount of binder solution with flow rate.

the highest experimentally measured values. The overall prediction accuracy is very impressive (93.8%), only 6.2% of the predictions lie outside the applied ±10% regions.

To confirm the network's ability to predict granule properties, the trained GRNN has been used to predict granulation parameters resulting in defined granule properties. For this process, mean granule sizes between 250 and 800 μm have been chosen. The properties of the mathematically forecasted and experimentally obtained granules have then been compared and were all found to be within the ±10% cut-offs.

Table 1
Correlation coefficients and prediction accuracy for the studied granule properties

Granule property	Correlation coefficient	Prediction accuracy (%)
Mean granule size	0.94	91.1
Size distribution	0.96	91.1
Flow rate	0.97	95.6
Angle of repose	0.95	97.8
(Bv − Tv)[a]	0.92	93.3

[a] (Bv − Tv) = difference between bulk and tapped volumes.

Table 2
Values of predicted granulation process parameters and their corresponding artificial and experimental results

Granulation process parameters								Granule properties as predicted by GRNN					Granule properties as obtained by experiment ± S.D.				
Batch number	Batch size (g)	Concentration of binder solution (%, w/w)	Amount of binder solution (g)	Inlet air temperature (°C)	Atomizing air pressure (bar)	Spray rate (g/min)	Air velocity (m/s)	Mean granule size (μm)	Granule size distribution (μm)	Flow rate (g/s)	Repose angle (°)	(Bv − Tv)[a] (ml)	Mean granule size (μm)	Granule size distribution (μm)	Flow rate (g/s)	Repose angle (°)	(Bv − Tv)[a] (ml)
1	1400	30	400	60	1.1	20	20	298	1.57	10	26.1	14.1	309 ± 3.52	1.62 ± 0.016	10.5 ± 0.97	27.91 ± 0.84	13.0 ± 0.66
2	1400	30	200	60	0.6	30	22	350	1.61	6.1	26.7	14	345 ± 15.26	1.58 ± 0.014	6.3 ± 0.91	27.10 ± 1.03	14.3 ± 0.50
3	1400	30	400	60	0.6	20	20	418	1.7	17.6	32.2	17.4	403 ± 9.22	1.82 ± 0.020	16.8 ± 0.63	31.38 ± 1.20	17.5 ± 0.50
4	1400	30	408	60	0.5	25	20	630	1.85	19	28.6	15	645 ± 6.44	1.72 ± 0.013	18.3 ± 0.06	27.10 ± 0.92	15.5 ± 0.47
5	1400	32	408	50	0.6	30	22	781	2.1	21	26.5	13	790 ± 10.11	1.95 ± 0.018	20.6 ± 1.30	28.00 ± 1.01	13.5 ± 0.54

[a] (Bv − Tv) = difference between bulk and tapped volumes.

The forecasted values from GRNN for five batches are given in Table 2 together with the corresponding experimental results.

4. Conclusions

The GRNN analysis enabled us to investigate the complex relationship between the individual parameters affecting size enlargement and granule properties and to predict granule properties such as, size, size distribution, bulk and tapped volumes and flow rate from different process and product parameters. Good correlation has been obtained between predicted and experimental data.

Investigations of the particle size and particle size distribution of granules, produced by adjusting different process and product parameters, showed the key role of the atomizing air pressure in the size enlargement of particles. The other important parameters were the spray rate, the amount of binder solution and the air velocity.

The innovative modifications provided the possibility to produce granules with compact structures, low porosity and narrow particle size distributions.

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