Scale-Up of Agitation Fluidized Bed Granulation by Neural Network

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Received November 28, 1996; accepted March 17, 1997

Scale-up of wet granulation by agitation fluidized bed was conducted using a hierarchy neural network with a back-propagation learning. Scale-up characteristics of agitation fluidized bed granulation were self-learned using a developed neural network system, and properties of size, size distribution, apparent density and shape factor of granules prepared by the commercial scale under various operating conditions (moisture content, agitator rotational speed and fluidization air velocity) were predicted. To confirm the method's validity, the predicted properties were compared with the actual granulation data. Good correlation was obtained between the predicted and the experimental data of agitation fluidized bed granulation. It was found that the neural network could be a reliable tool to analyze the scale-up characteristics of granulation, and to predict granule properties being produced by the unknown larger scale granulator.

Key words neural network; scale-up; granulation; agitation fluidized bed; granule property; prediction; back-propagation learning

Fluidized bed granulation has become a key operation in pharmaceutical and other industries. It is applied to produce particulate materials of desired size and other physical properties. Use of the fluidized bed has attracted considerable attention, because the many different operations of mixing, granulation and drying can be conducted in a single vessel, thus preventing contamination and saving processing space, time and cost. However, the effects of process variables on granule properties are so complex that the design and scaling up of this process are very difficult. Only a few studies[1] have been reported on theoretical analyses of granulation scale-up, and a reliable tool to achieve this is strongly desired.

Neural Network,[2-8] which models the neuronal operation in the brain, is a data-processing method. It has become noted, because it has self-organization, *i.e.*, learning ability: it can easily change its structure to identify regularity among a vast amount of data. It can thus predict or recognize patterns of unknown data without constructing a mathematical model of the complicated non-linear relationships between each item of data.

In this study we applied this method to scale-up of agitation fluidized bed granulation,[9-12] in which modeling and theoretical approaches have been very difficult. The scale-up characteristics of the granulation were investigated using a hierarchy neural network with a back-propagation learning to predict properties of granules produced by the commercial scale granulator under various operating conditions. To confirm the method's validity, predicted granule properties were compared with the experimental data. The number of learning data required to analyze the scale-up characteristics accurately was also determined.

Experimental

Equipment A schematic diagram of the experimental apparatus is illustrated in Fig. 1.

For wet granulation, four sizes of agitation fluidized bed (NQ-125, 230, 500 and 750, Fuji Paudal Co., Ltd.),[2,9-18] of which the vessel diameter were 125, 230, 500 and 750 mm, respectively, were used. An agitator blade was equipped to give tumbling and compacting effects to granules, making the granules spherical and well-compacted. Under the blade, circular plates of different diameter were superimposed 0.5 mm

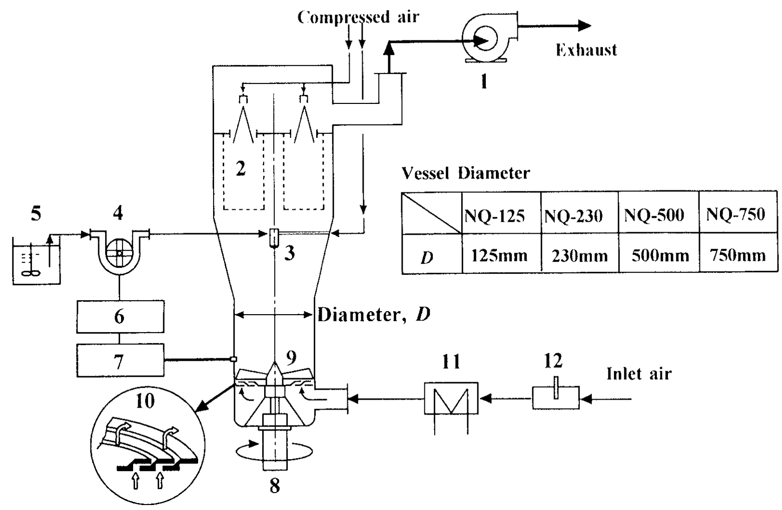

Fig. 1. Schematic Diagram of Experimental Apparatus Employed

1, blower; 2, bag filter; 3, spray nozzle; 4, pump; 5, binder liquid; 6, controller; 7, IR moisture sensor; 8, motor; 9, agitator blade; 10, slit plates; 11, heater; 12, hot-wire anemometer.

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Table 1. Dimensions and Operating Conditions

	Equipment	NQ-125	NQ-230	NQ-500	NQ-750
Dimensions	Diameter of vessel	125 mm	230 mm	500 mm	750 mm
	Powder load weight	0.36 kg	2.23 kg	22.9 kg	77.3 kg
Spray nozzle	Type of nozzle	655	3B	2B	2B × 2
	Nozzle insert diameter	i.d. 1.0 mm	i.d. 1.0 mm	i.d. 2.0 mm	i.d. 2.0 mm
	Air pressure	1.5×10^5 Pa	1.5×10^5 Pa	3.0×10^5 Pa	3.0×10^5 Pa
	Nozzle height	100 mm	200 mm	500 mm	800 mm
Granulation	Agitator rotational speed	300—900 rpm	150—600 rpm	75—300 rpm	50—150 rpm
	Fluidization air velocity	0.5—1.1 m/s			
	Moisture content	12—22%			
	Inlet air temperature	80 °C			
	Dampen time	Dampen to pre-determined moisture content in 20 min			
Drying	Agitator rotational speed	300 rpm	150 rpm	75 rpm	75 rpm
	Inlet air temperature	80 °C			
	Fluidization air velocity	0.7 m/s			

apart to function as air distributors. Heated air for particle fluidization was blown from the slit between each circular plate to create a circulating flow. Fine powders lifted up by the fluidization air were entrapped by bag filters, then brushed down by a pulsating jet of air.

Moisture content of granules during granulation was measured by an infrared (IR) moisture sensor (Wet-eye, Fuji Paudal Co., Ltd.).[9-13] Feedback control of the moisture content was conducted by regulating a liquid feed rate.

Fluidization air velocity was measured by a hot-wire anemometer (Ventcapter 3202.30, Weber Co., Ltd.), which was located at the center of the inlet air duct pipe to detect maximum air velocity. Inlet and outlet air temperatures and humidities were measured by ceramic sensors (HT20F, NTK).

The main operational variables of inlet air temperature, velocity, and agitator rotational speed were feedback controlled to maintain a stable operation. All the operational variables measured were on-line monitored *via* personal computer, then stored on a hard disk.

Powder Samples Starting material for granulation was a pharmaceutical standard formulation defined by the Working Group for Preparation of Standard Formulations,[19] which consisted of lactose and cornstarch (mixed at 7 : 3 by weight). Hydroxypropylcellulose (HPC EF-P, Shin-Etsu Chemical Co., Ltd.) was added to the above mixture at a level of 5 wt% before granulation.

Purified water was sprayed by a binary nozzle located at the top of the vessel (top spray method).

Operating Conditions Basic operating conditions for the scale-up experiments are summarized in Table 1.

Initial powder feed weight of each equipment was determined based on their geometric similarity (in proportion to vessel volume) to evaluate scale-up characteristics correctly.

Optimal spray conditions were preliminary optimized to spray water mist having a median diameter of 40 μm and to maintain a constant ratio of spray area to vessel sectional area (30—35%), regardless of spray nozzle type.

Scale-up experiments were conducted as follows: i) Premixed powder samples were fed to the vessels and agitated with fluidized air for 300 s. ii) Granulation experiments started with spraying water. To avoid the effect of granulation time on granule growth, damping speed was controlled so as to dampen to any predetermined moisture content within 20 min. These procedures were the same as those previously reported.[18] iii) After the granulation, granulated products were dried with fluidization air in the vessel until the measured moisture content decreased below 0%. The fluidization air was kept constant at 80 °C regardless of vessel scale. In preliminary experiments, we had confirmed that the effect of drying time increase on granule properties such as attrition could be almost ignored if vessel scale increased. This was because the drying time was considerably short and granules were so spherical and well-compacted that attrition rarely occurred.

Evaluation of Produced Granules Particle size distribution of granules was determined by a sieve analysis with a row-tap shaker. Based on the log-normal distribution, mass median diameter and geometric standard deviation were obtained using a personal computer.

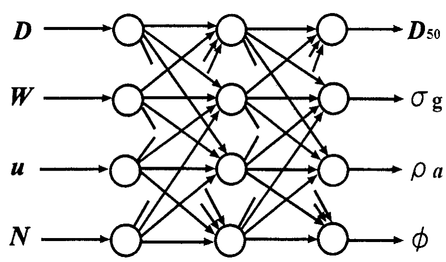

Fig. 2. Structure of Three-Layer Neural Network Applied

Apparent density of granules was measured using a powder tester (Hosokawa Micron Co., Ltd.).

Shape factor of granules was computed using an image processing system[9] (Image Eye, Fuji Paudal Co., Ltd.).

Results and Discussion

Determination of Optimum Structure of Neural Network Figure 2 illustrates the three-layer neural network applied in this study. For the input-layer, four units composed of vessel diameter D, moisture content W, fluidization air velocity u, and agitator rotational speed N were used. For the middle-layer, we used one layer, considering that convergence time increased with the middle layer number and that a three-layer neural network is sufficient.[20] Unit number for the output-layer was four, which generated the predicted granule properties of granule mass median diameter D_{50}, geometric standard deviation σ_g (size distribution), apparent density ρ_a and shape factor ϕ.

Table 2 gives a list of learning data consisting of granule properties under various operating conditions and vessel scales.

Learning was conducted using the back-propagation,[2,8] which is a learning algorithm to update the weight and the threshold value by making the error function (Eq. 1) minimum.

$$E = \frac{1}{2} \sum_{i=1}^{N_M} (y_i^{(M)} - d_i)^2 \qquad (1)$$

Practically, learning is conducted using the following equation to update the weight

$$\omega_{ij}^{(m)}(t+1) = \omega_{ij}^{(m)}(t) - \eta \frac{\partial E}{\partial \omega_{ij}^{(m)}} \qquad (2)$$

Table 2. List of Supervised Learning Data Obtained by Laboratory Scale Granulator (NQ-125, -230 and -500)

Input data				Result			
D (mm)	W (%)	u (m/s)	N (rpm)	D_{50} (μm)	σ_g (—)	ρ_a (kg/m³)	ϕ (—)
125	12	0.7	300	165	1.79	520	0.767
125	12	0.7	600	157	2.02	540	0.720
125	14	0.7	300	200	1.77	545	0.758
125	14	0.5	600	182	1.79	562	0.778
125	14	0.7	600	188	1.92	545	0.761
125	14	0.9	600	196	1.79	537	0.761
125	14	0.7	900	180	1.73	572	0.783
125	16	0.5	600	220	1.67	565	0.772
125	16	0.7	600	228	1.66	554	0.762
125	16	0.9	600	238	1.67	554	0.758
125	16	0.5	900	211	1.65	548	0.781
125	16	0.7	900	216	1.66	530	0.767
125	16	0.9	900	229	1.71	532	0.777
125	18	0.7	600	303	1.55	562	0.768
125	18	0.7	900	216	1.48	570	0.777
230	18	0.7	300	233	1.70	593	0.820
230	18	0.7	450	166	1.63	600	0.830
230	16	0.5	300	169	1.82	594	0.820
230	16	0.7	300	175	1.81	582	0.813
230	16	0.9	300	183	1.82	582	0.813
230	16	0.5	450	162	1.80	575	0.834
230	16	0.7	450	166	1.81	556	0.818
230	16	0.9	450	176	1.86	556	0.828
230	14	0.7	150	154	1.92	572	0.798
230	14	0.5	300	140	1.94	591	0.816
230	14	0.7	300	145	2.07	572	0.802
230	14	0.9	300	151	1.94	563	0.801
230	14	0.7	450	139	1.88	602	0.826
230	12	0.7	150	127	1.94	544	0.770
230	12	0.7	300	121	2.17	550	0.782
230	20	0.7	300	340	1.60	600	0.840
500	12	0.7	150	110	2.60	570	0.803
500	14	0.7	75	130	2.61	580	0.780
500	14	0.7	150	119	2.54	596	0.819
500	14	0.9	150	122	2.48	604	0.797
500	16	0.7	150	140	2.42	613	0.822
500	18	0.7	75	215	2.16	617	0.798
500	18	0.5	150	178	1.83	630	0.840
500	18	0.7	150	188	1.96	625	0.832
500	18	0.9	150	234	2.14	610	0.831
500	20	0.7	150	280	1.80	617	0.837

where η is the learning rate determining speed of learning convergence and t is the learning cycle. Based on the behavior of error convergence during the learning, the number of middle-layer units, learning cycles t and learning rates η were determined.

Figures 3 indicates the behavior of error convergence under various numbers of middle layer units.

As seen in the figure, each final error after 10000 learnings was prone to decrease with the increase in number of middle-layer units. Moreover, if the unit number was four or five, there was no significant difference in the final error. It is commonly said that the neural network can express more complicated functions as the number of middle-layer units increases. However, with a large unit number, there is a possibility of over-learning and a tendency for a remarkable increase in convergence time.[20] We therefore determined that the optimum unit number for the middle-layer was four.

For the learning cycles, an error over 10000 learnings

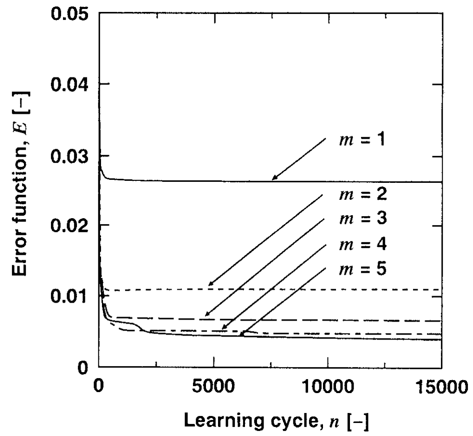

Fig. 3. Behavior of Error Convergence at Various Numbers of Middle-Layer Units

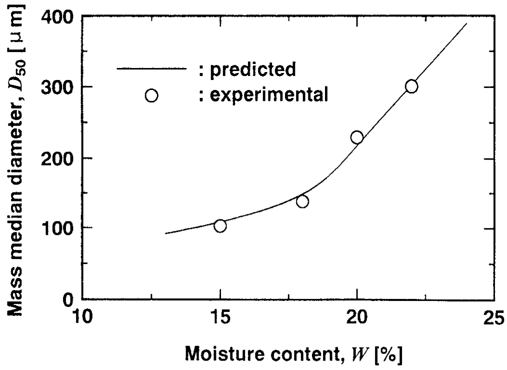

Fig. 4. Granule Mass Median Diameter against Moisture Content in the Commercial Scale Equipment (NQ-750, N = 100 rpm, u = 0.7 m/s)

indicated almost constant value. Since an increase in the number of learning cycles resulted in an increase in learning time, the optimum learning cycles in this study was determined to be 10000.

We conducted the same optimization concerning the learning rate η: the optimum learning rate was determined to be $\eta = 0.8$.

Prediction of Granule Properties Figures 4—7 show mass median diameter D_{50}, geometric standard deviation σ_g apparent density ρ_a and shape factor ϕ of granules produced by commercial scale equipment (NQ-750) at various levels of moisture content. Plots in the figures indicate the experimental data and lines show predicted results using the neural network.

As seen in Fig. 4, there was close agreement between predicted and experimental data. The granule mass median diameter of both predicted and experimental data showed an increase with moisture content. As described earlier,[14—17,21] granule size was determined by adhesion force of a liquid bridge formed between the granules and a separation force experienced to the granules to separate each other. With moisture variation at the same agitator rotational speed and fluidization air velocity (*i.e.*, constant separation force), the granule size was influenced only by the moisture content, because the adhesion force by the liquid bridge was closely connected with the water volume of the bridge.

As a result, the effect of moisture content on granule size could be well predicted using the neural network

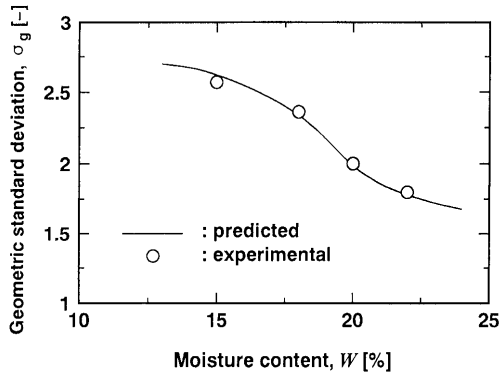

Fig. 5. Geometric Standard Deviation against Moisture Content in the Commercial Scale Equipment (NQ-750, $N=100$ rpm, $u=0.7$ m/s)

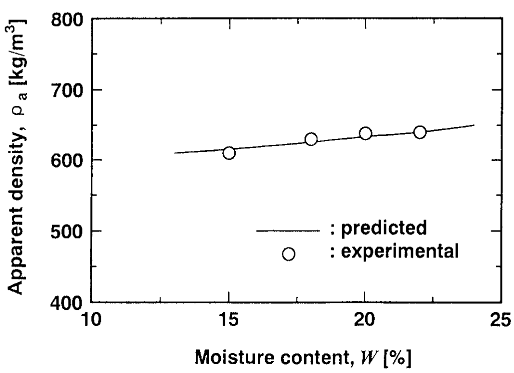

Fig. 6. Granule Apparent Density against Moisture Content in the Commercial Scale Equipment (NQ-750, $N=100$ rpm, $u=0.7$ m/s)

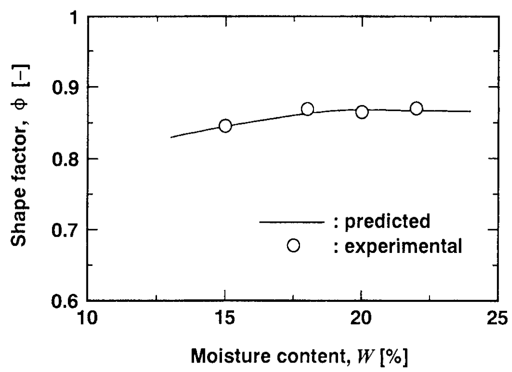

Fig. 7. Granule Shape Factor against Moisture Content in the Commercial Scale Equipment (NQ-750, $N=100$ rpm, $u=0.7$ m/s)

system with a back propagation learning.

Also, as shown in Figs. 5—7, each predicted data point agreed well with the experimental data. In this case, increase in moisture content resulted in a decrease in particle size distribution and increase in apparent density and shape factor, indicating granules were spherical and well compacted, and their size distribution was narrower. These characteristics were also well understood by the neural network with the back-propagation learning.

We also confirmed here that granule properties of the commercial scale equipment (NQ-750) under various agitator rotational speeds and fluidization air velocities showed good agreement with the experimental data.

Based on the results obtained, it was concluded that granule properties in larger scale equipment under various operating conditions could be easily and accurately pre-

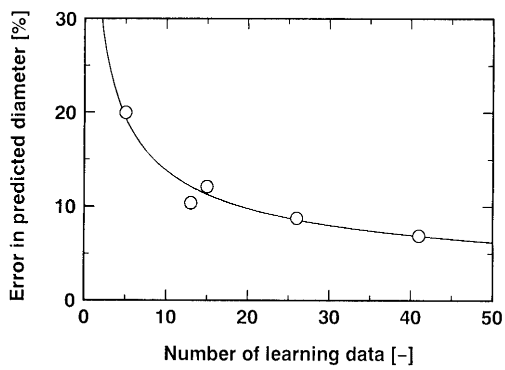

Fig. 8. Effect of Learning Data Number on the Accuracy of Prediction (Mass Median Diameter)

dicted by means of the neural network with back-propagation learning. It was also found that the neural network could predict or recognize patterns of unknown data without constructing a mathematical model of complicated non-linear relationships of vast experimental data.

Figure 8 is an example of the effect of number of learning data on the accuracy of the predicted properties. In this case, the accuracy of the prediction was investigated using the deviation (error) between the predicted and experimental data of mass median diameter.

By selecting all the data of NQ-500 and some data of other scale equipment (NQ-125 and -230), the number of learning data could be decreased and a good accuracy retained. When the number of learning data dropped below 12 or 13, however, the accuracy of the prediction decreased markedly with a decrease in the number. The number of learning data thus could be reduced, however, for good accuracy in prediction, a larger number of learning data is preferable.

Conclusion

Application of neural network to scale-up of granulation by an agitation fluidized bed was described. Optimum structure of the neural network was determined by the behavior of error convergence, and the learning of the scale-up characteristics was conducted adopting supervised learning data obtained by smaller laboratory scale equipment of three sizes (vessel diameter were 125, 230 and 500 mm, respectively). The granule properties of granule mass median diameter, geometric standard deviation, apparent density and shape factor obtained in the commercial scale equipment (vessel diameter was 750 mm) at various moisture contents, agitator rotational speeds and air flow rates were predicted. There was close agreement between the predicted and the experimental data, and scale-up characteristics were well understood by the neural network with back-propagation learning. The effect of learning data number on the accuracy of prediction was also investigated.

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