



Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Pharmaceutics, Drug Delivery and Pharmaceutical Technology

Artificial Intelligence Tools for Scaling Up of High Shear Wet Granulation Process

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ARTICLE INFO

Article history:

Received 5 August 2016

Revised 20 September 2016

Accepted 21 September 2016

Keywords:

granulation
simulations
solid dosage form
tableting
wetting

ABSTRACT

The results presented in this article demonstrate the potential of artificial intelligence tools for predicting the endpoint of the granulation process in high-speed mixer granulators of different scales from 25L to 600L. The combination of neurofuzzy logic and gene expression programming technologies allowed the modeling of the impeller power as a function of operation conditions and wet granule properties, establishing the critical variables that affect the response and obtaining a unique experimental polynomial equation (transparent model) of high predictability ($R^2 > 86.78\%$) for all size equipment. Gene expression programming allowed the modeling of the granulation process for granulators of similar and dissimilar geometries and can be improved by implementing additional characteristics of the process, as composition variables or operation parameters (e.g., batch size, chopper speed). The principles and the methodology proposed here can be applied to understand and control manufacturing process, using any other granulation equipment, including continuous granulation processes.

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Introduction

Scaling up of high shear granulation process is of high relevance within the pharmaceutical and food industry. There is an extensive work about the control of wet granulation processes and the scale-up methodologies in the literature.¹⁻³ Scale-up methodologies can be classified into 2 main categories⁴: (a) methods based on engineering principles that apply fixed mathematical rules to process parameters and (b) empirical methods that adjust process parameters in order to maintain the granule attributes across scales.

It has been pointed out that the scale-up granulation process is facilitated by maintaining geometric, dynamic, and kinematic similarity. Based on this premise, the companies design the equipment (bowl height/diameter ratio, impeller design) to achieve geometric similarity. On the other hand, the dynamic and kinematic similarities are directly related to the control of impeller speed, which determines the forces and collision energy experienced by the granules, and the particle velocity inside the granulator, respectively.

Several authors⁵⁻⁸ have followed the method proposed by Cliff and Parker⁹ for predicting the behavior of plant scale equipment

from the information generated from laboratory scale apparatus. The approach was based on the classical dimensionless Power number/Reynolds number relationship.¹⁰ However, the universality of the concept of using dimensionless numbers to predict scale-up parameters for all types and designs of mixers used in pharmaceutical granulation could not be completely established, it being necessary to introduce corrections in the equation to account for geometric differences between mixers (e.g., shape factors) or operating conditions (e.g., batch size in proportion to the overall shape of the mixer). This fact pointed to the existence of extremely complex non-linear interactions between the parameters studied, and made it difficult to obtain a general model for the granulation process.

Soft computing methods offer novel solutions to improve modeling and control in pharmaceuticals.¹¹ Among the available artificial intelligence tools, artificial neural networks have been widely used for modeling several pharmaceutical process.^{12,13} Despite its unquestionable utility to facilitate understanding of the processes and predict results without any mechanistic assumption, artificial neural networks have the disadvantage of generating black-box models. Gene expression programming (GEP) introduced by Ferreira^{14,15} has been proposed as a technology to overcome this limitation and to solve problems within the pharmaceutical field, as it is able to provide high predictive experimental equations relating the variables, and hence to generate transparent models. A complete explanation about this methodology and its application for modeling formulations can be found in Colbourn et al.¹⁶

The author declares no conflicts of interest.

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To our knowledge, there is no example in the literature of the application of artificial intelligence tools in the scale-up of high shear granulation process. The hypothesis of the present work was that it is possible to apply those technologies, particularly GEP, to develop a unique and useful model for describing the impeller power of high shear mixer granulators of different scales from 25 to 600L as a function of process variables and formulation properties. The model should allow defining optimal endpoint of different scales on mixer granulators, and hence help in the scaling up process.

Experimental

Database

In this study, results from experiments carried out in 4 fixed size bowl mixer granulators (Fielder PMA; Aeromatic-Fielder Ltd.) of nominal volumes 25, 65, 100, and 600L were used. PMAs 25L, 100L, and 600 L are geometrically similar in all dimensions, but PMA 65L is not. PMAs 65L, 100L, and 600L have variable speed motors on both impeller and chopper, and PMA 25L has 2 speeds. In all cases, chopper speed was kept constant at 1500 rpm. Impeller diameters (D , m) were noted.

Weight/weight composition of the model formulation was as follows: 80% lactose (450 mesh; DMV International), 18% maize starch, and 2% pregelated starch (both from National Starch and Chemical Company Ltd.). Batch sizes were selected in order to maintain the proportion of the volume of mixer (0.3 kg/L). They were 7.5, 16.25, 30, and 180 kg.

The raw materials were introduced into the bowl and dry mixed for 2 min at a specific impeller speed (N , rps). The impeller power was noted and water was then sprayed on at a constant rate. Samples of wet mass were taken at pre-set times equivalent to different endpoints as given by the load on the impeller motor. The amount of liquid added was estimated (%liq) and the height of the wet bed in the mixer was measured (h , m). The differential power for each sample was calculated (ΔP , W). Due to the size of the bowl of PMA 25L machine, it was not possible to take multiple samples from a single mix, and hence it was necessary to perform individual experiments for each endpoint.

The bulk density of the collected samples (ρ , kg/m³) was determined by weighing a glass vessel of known volume, empty and filled with wet mass flush with the rim as previously described by Cliff and Parker.⁹

The consistency of wet masses (η , Nm) was measured using a mixer torque rheometer (Caleva MTR; Sturminster Newton) as described previously by Hancock et al.¹⁷ Briefly, to generate a baseline torque value, the machine was run empty at 52 rpm for 20 s. Then 30 g of wet mass sample was added and the instrument was allowed to run for 30 s before initiating the data capture process (30 s). Each measurement was conducted in duplicate.

All results are shown in Table 1.

Endpoint Predictions Based on Dimensionless Numbers

Following the methodology previously suggested by several authors^{5,6} for predicting the behavior of plant scale equipment from information generated at laboratory scale machines, 3 dimensionless numbers were calculated. The Power number (N_p) is defined as $\Delta P g / \rho N^3 D^5$, the Reynolds number (N_{Re}) is defined as $D^2 N \rho / \eta$, and the Froude number (N_{Fr}) is defined as $N^2 D / g$, where ΔP is the differential impeller power (W), N the impeller speed (rps), D the impeller diameter (m), g the gravity (9.8 m/s²), ρ the wet mass bulk density (kg/m³), and η (Nm) the wet mass consistency obtained by mixer torque rheometry.

Table 1

Database Including Results From Experiments in 25L, 65L, 100L, and 600L Mixer Granulators

Equipment	D (m)	N (rps)	%Liquid	h (m)	ρ (kg/m ³)	η (Nm)	ΔP (W)
PMA 25L	0.404	4.78	7.56	0.12	425	0.051	55
PMA 25L	0.404	4.78	11.72	0.12	452	0.117	451
PMA 25L	0.404	4.78	17.00	0.10	536	0.147	534
PMA 25L	0.404	4.78	22.30	0.08	642	0.169	1051
PMA 25L	0.404	4.78	25.45	0.07	776	0.241	1282
PMA 25L	0.404	4.78	18.06	0.11	518	0.165	528
PMA 25L	0.404	9.53	9.45	0.11	448	0.101	995
PMA 25L	0.404	9.53	13.60	0.10	525	0.107	2100
PMA 25L	0.404	9.53	7.46	0.12	434	0.070	187
PMA 25L	0.404	9.53	17.38	0.08	649	0.156	2350
PMA 100L	0.647	2.63	5.57	0.20	450	0.100	182
PMA 100L	0.647	2.63	11.13	0.21	440	0.134	661
PMA 100L	0.647	2.63	16.70	0.20	490	0.214	775
PMA 100L	0.647	2.63	22.27	0.17	587	0.213	1186
PMA 100L	0.647	2.63	27.50	0.13	800	0.350	2326
PMA 100L	0.647	3.75	5.00	0.18	490	0.077	224
PMA 100L	0.647	3.75	10.00	0.21	430	0.154	960
PMA 100L	0.647	3.75	15.00	0.21	460	0.194	1184
PMA 100L	0.647	3.75	20.00	0.17	586	0.190	1600
PMA 100L	0.647	3.75	25.00	0.13	770	0.259	3136
PMA 100L	0.647	5.16	4.03	0.18	480	0.087	175
PMA 100L	0.647	5.16	8.06	0.21	430	0.112	1051
PMA 100L	0.647	5.16	12.09	0.21	440	0.143	1357
PMA 100L	0.647	5.16	16.13	0.20	480	0.165	2014
PMA 100L	0.647	5.16	20.16	0.16	610	0.113	3765
PMA 100L	0.647	5.16	21.50	0.14	700	0.165	4422
PMA 600L	1.18	2.87	4.31	0.31	536	0.055	700
PMA 600L	1.18	2.87	8.62	0.35	497	0.095	2500
PMA 600L	1.18	2.87	12.93	0.38	476	0.131	5600
PMA 600L	1.18	2.87	17.25	0.34	549	0.145	6700
PMA 600L	1.18	2.87	21.57	0.31	614	0.154	8700
PMA 600L	1.18	2.87	24.44	0.28	698	0.179	16,700
PMA 600L	1.18	2.87	26.60	0.28	713	0.220	19,600
PMA 600L	1.18	1.23	4.96	0.31	544	0.066	500
PMA 600L	1.18	1.23	9.92	0.38	460	0.103	2100
PMA 600L	1.18	1.23	14.88	0.38	478	0.136	2400
PMA 600L	1.18	1.23	19.83	0.35	546	0.152	3400
PMA 600L	1.18	1.23	24.79	0.29	670	0.161	4800
PMA 600L	1.18	1.23	27.69	0.27	747	0.261	6500
PMA 65L	0.503	4.33	5.07	0.16	473	0.069	0
PMA 65L	0.503	4.33	10.15	0.20	411	0.091	470
PMA 65L	0.503	4.33	15.23	0.19	437	0.095	740
PMA 65L	0.503	4.33	20.30	0.17	510	0.155	1070
PMA 65L	0.503	4.33	25.38	0.12	724	0.221	2030
PMA 65L	0.503	6.93	4.87	0.17	457	0.057	10
PMA 65L	0.503	6.93	9.89	0.20	411	0.097	1270
PMA 65L	0.503	6.93	14.84	0.20	433	0.119	1870
PMA 65L	0.503	6.93	19.79	0.14	603	0.145	3770
PMA 65L	0.503	6.93	24.33	0.13	706	0.224	4570

$N_p = \text{fn}\{N_{Re}, N_{Fr}, h, D\}$ functions were established for each high shear mixer.^{5,6} The regression analysis of Ln/Ln plot for the 3 equipments together allowed Equation 1 to be obtained:

$$N_p = 273.96[N_{Re} \times N_{Fr} \times h/D]^{-0.712} \quad (1)$$

Using Equation 1, impeller power values were predicted for each condition of the mixer operation and wet granule properties measured.

Artificial Intelligence Tools: Neurofuzzy Logic and Gene Expression Programming

Two commercial software packages FormRules[®] v4.03 and INForm[®] v5.01 (Intelligensys Ltd., North Yorkshire, UK) which implement neurofuzzy logic and GEP technologies, respectively, were used in this study.^{11,16}

The FormRules model was obtained using results from the PMA 25L, 100L, and 600 L experiments (41 records). The mixer volume,

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