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

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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 programing 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 programing 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. Scale-up methodologies can be classified into 2 main categories: (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 authors have followed the method proposed by Cliff and Parker 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. 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 pharmaceutics. Among the available artificial intelligence tools, artificial neural networks have been widely used for modeling several pharmaceutical process. 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 programing (GEP) introduced by Ferreira 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.

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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; Aromatic-Fielder Ltd.) of nominal volumes 25, 65, 100, and 600L were used. PMAs 25L, 100L, and 600L 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% pregelled 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 30 s. Each measurement was conducted in duplicate.

**Endpoint Predictions Based on Dimensionless Numbers**

Following the methodology previously suggested by several authors, the regression analysis of Ln/Ln plot for the 3 equipments together allowed Equation 1 to be obtained:

\[ \frac{N_{p}}{N_{R}} = \frac{N_{F}}{N_{Re}} \times \frac{D_{p}}{D_{Re}} \]

Where:
- \( N_{p} \) is the impeller power (W),
- \( N_{Re} \) is the Reynolds number (Nrs),
- \( N_{F} \) is the Froude number (Nf),
- \( D_{p} \) is the impeller diameter (m),
- \( g \) is the gravity (9.8 m/s²),
- \( \rho \) is the wet mass bulk density (kg/m³), and
- \( h \) is the wet mass consistency obtained by mixer torque rheometry.

\( N_{p} = \frac{fn(N_{Rs}, N_{Fr}, h, D)} \)

The regression analysis of Ln/Ln plot for the 3 equipments together allowed Equation 1 to be obtained:

\[ N_{p} = 273.96 \times N_{Re} \times N_{Fr} \times h/D \]

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.

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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