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Artificial neural network modelling of continuous wet granulation using a twin-screw extruder

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ABSTRACT

Computational modelling of twin-screw granulation was conducted by using an artificial neural network (ANN) approach. Various ANN configurations were considered with changing hidden layers, nodes and activation functions to determine the optimum model for the prediction of the process. The neural networks were trained using experimental data obtained for granulation of pure microcrystalline cellulose using a 12 mm twin-screw extruder. The experimental data were obtained for various liquid binder (water) to solid ratios, screw speeds, material throughputs, and screw configurations. The granulate particle size distribution, represented by d-values (d10, d50, d90) were considered the response in the experiments and the ANN model. Linear and non-linear activation functions were taken into account in the simulations and more accurate results were obtained for non-linear function in terms of prediction. Moreover, 2 hidden layers with 2 nodes per layer and 3-Fold cross-validation method gave the most accurate simulation. The results revealed that the developed ANN model is capable of predicting granule size distribution in high-shear twin-screw granulation with a high accuracy in different conditions, and can be used for implementation of model predictive control in continuous pharmaceutical manufacturing.

1. Introduction

The development of continuous pharmaceutical manufacturing has been a subject of great interest for the pharmaceutical industry. Currently, manufacturing of solid-dosage pharmaceutical formulations are carried out in batch-wise operation. In batch-mode processing, each run that does not meet the requirements is rejected which results in time and cost deficits for the manufacturing of pharmaceutical compounds. Continuous pharmaceutical processing can overcome this drawback and therefore offer more advantages compared to batch processing. In order to develop continuous pharmaceutical manufacturing, each unit operation in the manufacturing line should be inter-connected in an appropriate way (Lee et al., 2015).

A powerful tool for development of continuous pharmaceutical manufacturing is model predictive control (MPC), which is considered as an advanced control strategy. MPC considers each unit operation and takes a holistic view of the manufacturing line. Therefore, each unit operation should be specified and its model needs to be developed to implement MPC for the manufacturing line. There are different processes in the manufacturing of solid-dosage drugs such as milling, mixing, granulation, drying, and coating. Granulation is the key step in manufacturing pharmaceutical formulations, in which granules are produced from a fine powder including an active pharmaceutical ingredient (API) and an excipient. Moreover, wet granulation is the most complex unit operation in pharmaceutical manufacturing since many mechanisms are involved in the formation of granules from fine powder (Rogers et al., 2013). Recently, twin-screw granulation has gained a lot of attention over other granulation methods due to its unique characteristics. The main advantage of twin-screw granulation is that it is an intrinsic continuous process which can promote development of continuous pharmaceutical manufacturing (Seem et al., 2015). Other advantages of twin-screw extruder in the pharmaceutical sector are its ability to mix and react the feed materials, and its short residence time.

In order to implement MPC approach for continuous manufacturing, a model of each process step is required which can be done by mathematical or computational modelling. There

Abbreviations: ANN, artificial neural network; API, active pharmaceutical ingredient; DEM, discrete element method; DoE, design of experiment; GSD, granule size distribution; MCC, microcrystalline cellulose; MPC, model predictive control; PBM, population balance model; PSD, particle size distribution; RMSE, root-mean-squared error; SSE, sum of squared error.

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Nomenclature

d D-value of particle size distribution (micron)
f Predicted value
L/S Liquid to solid ratio
K Number of experimental subsets for ANN validation
n Number of experiments
R^2 Coefficient of determination
x Linear combination of input factors
y Measured value

Subscript
i Experiment set

are different approaches for mathematical modelling of granulation process including; population balance model (PBM), discrete element method (DEM), and hybrid models. In hybrid models, both PBM and DEM models are used to benefit the advantages of both methods in modelling of granulation. For PBM, the changes of granule properties such as size distribution are calculated. However, DEM tracks the motion of each individual particle along the space, this is based on Newton's second law (Rogers et al., 2013). Given that particle size is an important product characteristic, these models primarily focus on predicting the particle size distribution in granulation. However, in wet granulation the liquid content and porosity are also very important for subsequent processes, such as tabletting.

Some theoretical and experimental work using twin-screw extruder has been carried out to simulate continuous wet granulation. Several researchers have investigated predictive modelling of wet granulation by using PBM and DEM modelling. Barrasso et al. (Barrasso et al., 2015) developed a multi-dimensional population balance model for the prediction of granule properties in a twin-screw granulation. Lumped-parameter and compartment approach were used for the numerical solution of population balance equations. This model was able to predict the granule size, liquid content, and porosity as a function of process parameters.

Subsequently, Barrasso et al. (Barrasso et al., 2015 Barrasso and Ramachandran, 2015) utilized the DEM approach for the estimation of aggregation kernel in solution of population balance model. The results showed a better prediction of particle size distribution compared to semi-empirical aggregation kernel.

The results of mechanistic models developed for twin-screw granulation revealed that these mechanistic models are quite slow for the use of MPC in the development of continuous pharmaceutical manufacturing. However, these mechanistic models can be used for the process design and optimization (Barrasso et al., 2015; Kumar et al., 2013, 2015).

The main disadvantage of aforementioned mechanistic models is that it is not fast enough to be used as a model for the development of MPC approach in continuous manufacturing. In MPC, the model of process should be able to run within a few seconds in order to predict the future behaviour of the process. Therefore, these mechanistic models fail to be applied for MPC, and in fact faster models are required for industrial applications. Recently, some researchers have tried to reduce the solution time for mechanistic model by utilizing ANN. Barrasso et al. (Barrasso et al., 2014) developed a hybrid model by coupling PBM and artificial neural network (ANN) for describing wet granulation. The main aim of a hybrid model is to make the solution time faster. The results showed that ANN is capable of simulation for wet granulation process, although it does not look at the mechanisms associated with the granulation. A list of different mechanistic and hybrids models applicable to wet granulation are reported by Kumar et al. (Kumar et al., 2013; Rogers et al., 2013).

Data-driven models have proved to be robust and efficient for the application of simulation and prediction of pharmaceutical processes. An important class of data-driven models is artificial neural network (ANN) which is powerful in process prediction (Kazemi et al., 2016; Puri et al., 2016). ANN is usually used for modelling of complex processes in which mechanistic models fail to predict the process or are computationally expensive.

ANN has been used for predication of some pharmaceutical processes such as milling. Kazemi et al. (Kazemi et al., 2016)

Table 1
Design of experiments for ANN simulation of wet granulation.

Run	L/S	Screw speed (rpm)	Powder flow rate (g/h)	Screw configuration	d10 (Micron)	d50 (Micron)	d90 (Micron)
1	0.54	64	49.75	2 kneading zones	15.07	88.535	328.8
2	0.94	200	98	2 kneading zones	151.35	417.2	1004.15
3	1.22	86	98.2	2 kneading zones	357.35	759.9	1202
4	0.54	200	69.33	2 kneading zones	23.885	130.2	360.3
5	1.22	200	61.47	2 kneading zones	307.15	689.95	1038.7
6	1.22	50	82	2 kneading zones	445.65	767	1105
7	1.21	200	49.4	1 kneading zone	385.75	1008.2	1303
8	0.78	200	49.75	1 kneading zone	65.195	271.6	653.5
9	1.21	115	49.5	1 kneading zone	455.15	1052.65	1313.5
10	0.49	185	67.55	1 kneading zone	14.605	67.46	342
11	0.65	50	97.6	1 kneading zone	10.57	76.865	342.6
12	0.52	50	97.05	1 kneading zone	8.33	35.805	300.5
13	1.22	50	82	1 kneading zone	177.5	440.55	831.8
14	0.55	200	98.6	conveying elements only	25.06	113.25	291.35
15	1.22	200	98.15	conveying elements only	332.55	860.65	1250
16	0.76	200	99.2	conveying elements only	66.91	241.2	641.45
17	0.59	85	51	conveying elements only	35.02	164.7	384.45
18	1.12	72	53.25	conveying elements only	186.775	367.975	820.125
19	0.48	50	49.8	conveying elements only	18.42	102.745	341.2
20	0.50	200	95.05	2 kneading zones with cutting elements	7.585	22.425	113.75
21	1.20	58	82	2 kneading zones with cutting elements	330.7	865.6	1273.5
22	0.66	200	49.65	2 kneading zones with cutting elements	35.605	188	490.7
23	0.54	50	61.45	2 kneading zones with cutting elements	14.875	87.55	342.7
24	1.22	200	97.38	2 kneading zones with cutting elements	325.4	763	1154