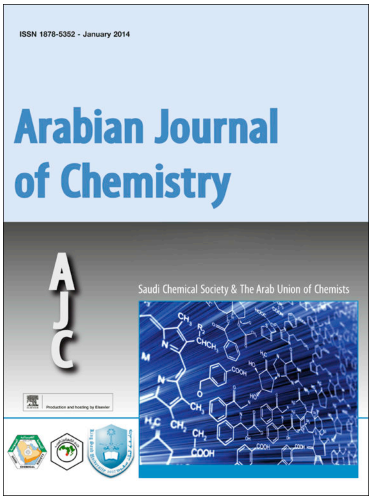

Review article

A review on key aspects of wet granulation process for continuous pharmaceutical manufacturing of solid dosage oral formulations

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A review on key aspects of wet granulation process for continuous pharmaceutical manufacturing of solid dosage oral formulations

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Abstract

Wet granulation process is a major unit operation in production of pharmaceuticals as solid dosage oral formulation. Indeed, granulation is used to improve the formulation properties such as flowability, compressibility, and so on for pharmaceutical manufacturing. Different types of granulations can be used in pharmaceutical manufacturing in which the selection of proper process depends on the operational conditions as well as formulation properties. In current decades, twin-screw wet granulation has been of paramount interest owing to its superior properties. Pharmaceutical manufacturing industry are trying to move towards continuous mode by which the efficiency can be improved compared to the batch mode. Therefore, development of continuous granulation process is of great importance. In this review article, various processing units applicable for wet granulation of pharmaceutical formulations for solid dosage forms are reviewed and discussed. The advantages and disadvantages of the processes are discussed and listed along with modeling approaches for simulation of process. The governing models and numerical schemes applicable for design of wet granulation are also critically discussed. The main focus is on wet granulation as this method has attracted much attention in pharmaceutical processing.

Keywords: Granulation process; Modelling; Pharmaceutical processing; Particle technology

1. Introduction

Preparation and manufacturing of solid dosage oral formulations constitutes main portion of pharmaceutical manufacturing due to the main application of solid dosage drugs which can be orally administered for different remediation and treatments [1-5]. Manufacturing lines include various processing steps so that each unit plays its role in preparation of drug products. Compared to preparation of biopharmaceuticals, small molecules pharmaceutical production can be run in continuous mode. In the manufacturing line, granulation plays crucial role which deals with particle flow and solid-state processing [6-10]. Granulation is identified as the enlargement process of small particles into granules. This process is extensively applied in disparate industrial-based applications like pharmaceutics, food and chemical [11-15]. Engineering control of granulation is of critical importance for manufacturing drugs with enhanced efficacy [16-18]. Granulation is usually done to enhance the powders flowability and avoid the co-mixing of substances [19]. Important granule characteristics including granule size distribution (GSD) and porosity can be driven using the rate of disparate macroscopic mechanisms such as nucleation, aggregation and consolidation [20-22]. Despite the emergence of different challenges, continuous processing has been recently of great interest for all important industries owing to its great potential of application with various advantages for the process. Table 1 aims to present the advantages and challenges towards the use of continuous processing for different types of industries.

Table 1. Positive points and challenges towards the use of continuous processing for different types of industries [21, 23-27].

Advantages	**Challenges**
Improved level of throughput	Modulating flow and level control
Reduction of inventory and related storage	Real-time in-process quality
Enhanced process safety	Real-time quality control
Reduced amount of air, water and power application	The need for personnel training
Decrease in the clean-up time	Superfluous controls and instrumentation
Reduced operator involvement	Fast corrections in various operating conditions
Reduced process footprint	Advanced process control

One of the prominent positive points of continuous processes is the non-existence of scale-up between clinical production and commercial manufacturing. Hence, continuous processes may prevent time wasting and expensive bio-equivalence investigations [28-31]. Additionally, continuous manufacturing processes are appropriate for the implementation of process analytical technology (PAT) tools, which guarantee permanent product quality and therefore, permitting a real time release strategy [11, 32-34]. PAT is an important tool in development of continuous manufacturing and plays crucial role in the regard for pharmaceutical manufacturing.

Various granulation processes have been developed and employed for solid particles such as high shear granulation, roller compaction, fluidized bed, twin-screw granulator, etc. Application of granulation process depends on the formulation and material properties. Twin-screw granulation (TSG) is an outstanding continuous process, which possesses great potential of application and excellent efficacy in granulating powders. This technique has brilliant advantages such as negligible residence time, superior management of granule properties, and great combination of active pharmaceutical ingredients (APIs) [35-39]. Due to the abovementioned characteristics, twin-screw granulation has been recently of paramount attention in continuous granulation of pharmaceutical powders for oral dosage formulations. With the aim of effective implementation of the twin-screw granulator, promising mechanistic modeling can be developed for the continuous granulation in twin-screw granulation process. Development of promising models are important to facilitate the continuous granulation of APIs and implementing the Quality-by-Design (QbD) paradigm. Figures 1 and 2 illustrate the developed experimental setup and screw configuration applied for twin-screw wet granulation for pharmaceutical formulations. As seen the twin-screw granulator consists of different elements such as extruder, screws, liquid injection pump, and feeder.

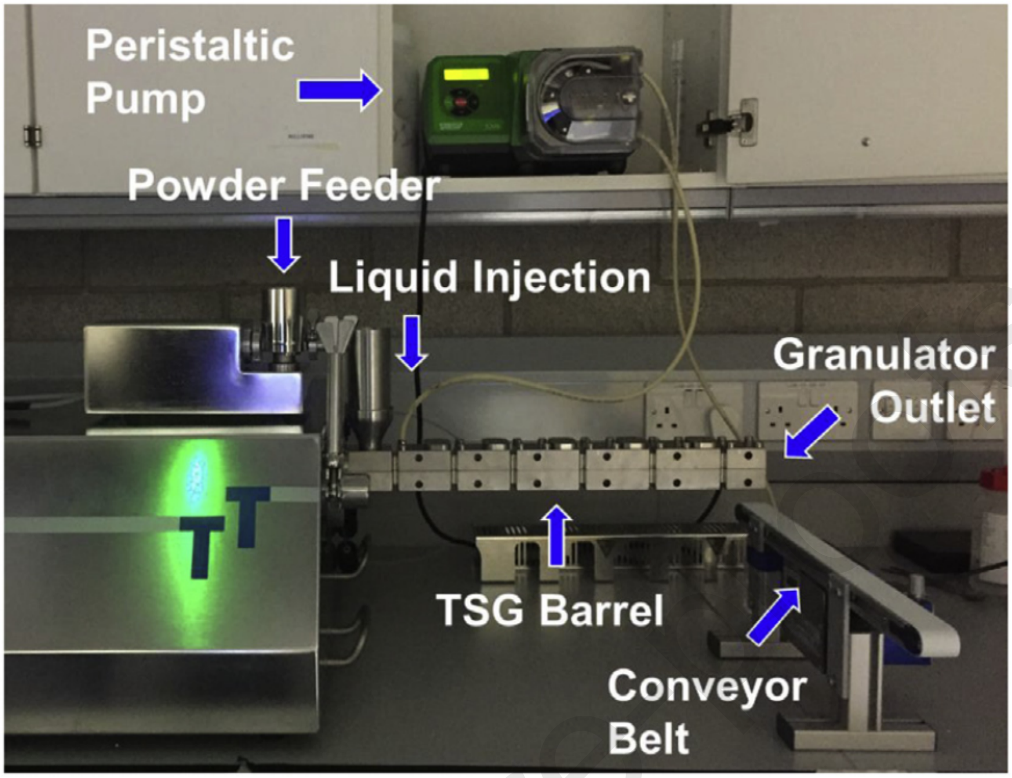

Figure 1. Experimental set up for twin-screw wet granulation. Reprinted from [40] with permission from Elsevier.

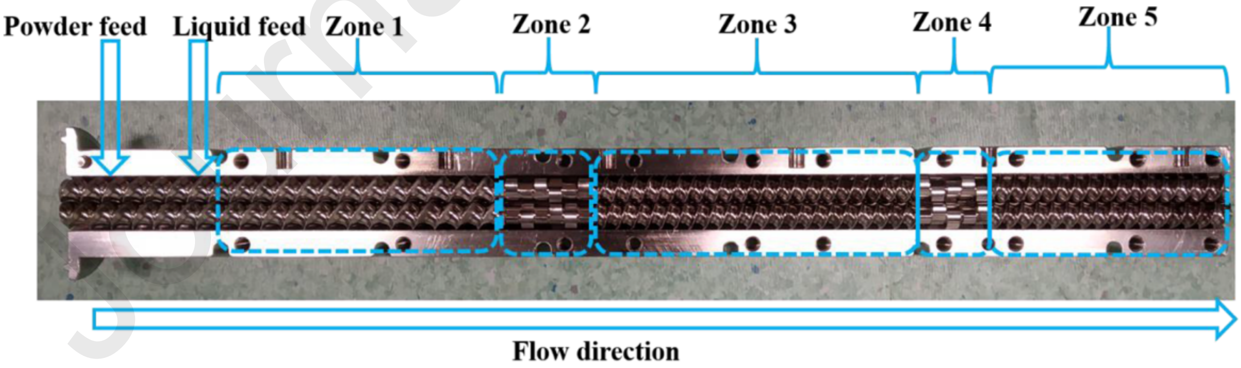

Figure 2. Screw configuration applied for twin-screw wet granulation. Reprinted from [37] with permission from Elsevier.

The prominent aim of this manuscript is to provide a comprehensive overview on the state-of-the-art of modeling approaches such as PBM, DEM and ANN towards granulation process. As the future outlook, a number of questions have been recognized and responded to fill the existed knowledge gap towards the development of the granulation process in pharmaceutical applications.

2. Current modeling approaches for different granulation techniques

It has been recently identified that the existence of promising mathematical models may considerably eventuate in the creation of functional knowledge-based control of process [37, 41-43]. Unfortunately, the majority of applied parameters in high shear wet granulation models are hard to measure. The majority of analyses on the basis of disparate types of granulation models are usually perceived to be implemented under default parameter values. This is prominently because of significant difficulties in the achievement of experimental data or paucity of appropriate measurement equipment to validate the developed model. Hence, it would be of great importance to describe appropriate mathematical models for granulation process. This section aims to review the state-of-the-art advancements in modeling approaches for different granulation techniques, which results in the perception of functional/operational gaps and thus, finding possible ways to face with the challenges. It has been reported that there are three main methods for modeling granulation: 1) population balance model (PBM), 2) Discrete Element Method (DEM), and 3) Machine Learning (ML) methods [21, 44, 45].

2.1. Population balance modeling

The population balance modeling (PBM) is identified as an efficient model to statistically interpret a system of particles that undergoes size increment and/or reduction. Indeed, PBM delas with particulate processes to track the evolution of particles properties. Apart from granulation, PBM technique possess great potential of use in disparate engineering sciences such as crystallization, aerosols coagulation and polymerization [46]. In the high-shear wet granulation process, the population balance equation for a well-mixed system can be derived as follows [47]:

$$\frac{\partial n}{\partial x}(x,t)+\frac{\partial}{\partial x}\left[n\frac{dx}{dt}\right](x,t)=R_{birth}(x,t)-R_{death}(x,t) \tag{1}$$

In this equation, $\frac{\partial}{\partial x}\left[n\frac{dx}{dt}\right](x,t)$, $R_{birth}(x,t)$ and $R_{death}(x,t)$ are described as the continuous growth along the internal direction of the particle diameter, the net formation and depletion rates of particles, respectively. Contribution of the aggregation impacts and breakage eventuates in modifying the Eq.1 to the following equation [48]:

$$\frac{\partial n}{\partial x}(x,t)+\frac{\partial}{\partial x}\left[n\frac{dx}{dt}\right](x,t)=\frac{1}{2}\int_0^x\beta(x-y,y)n(x-y,t)n(y,t)dy-n(x,t)\int_0^\infty\beta(x,y)n(y,t) \\ +\int_0^x K_{break}(y)\xi_{break}(y,x-y)n(y,t)dy-K_{break}(x)n(x,t) \tag{2}$$

In the pharmaceutical industry, granulation is often implemented as batch processes and thus, the majority of modeling investigations regarding to pharmaceutical granulation have concentrated on batch processes. In batch process, there is no spatial coordinate involved in the model owing to the assumption of a well-mixed system, but the model of a continuous system consists of both internal and external coordinates, which is presented by the following equation [49]:

$$\frac{\partial n}{\partial x}(x,z,t)+\frac{\partial}{\partial x}\left[n\frac{dx}{dt}\right](x,z,t)$$
$$=\frac{1}{2}\int_0^x \beta(x-y,y)n(x-y,z,t)n(y,z,t)dy-n(x,z,t)\int_0^\infty \beta(x,y)n(y,z,t)n(y,z,$$
$$+\int_0^x K_{break}(y)\xi_{break}(y,x-y)n(y,z,t)dy-K_{break}(x)n(x,z,t)-\frac{\partial}{\partial z}[\dot{Z}n(x,z,t$$

(3
)

In the abovementioned equation, $\dot{Z}=\frac{dz}{dt}$ is explained as the spatial velocity in the external coordinate. Simultaneous application of computational fluid dynamics (CFD) and discrete element method (DEM) has shown brilliant potential for numerical definition of particle flow regime and their visit frequency through a special granulator zone [50-52]. Moreover, the DEM may be combined with the PBM by considering a dense flow of particles [53-55]. For high-shear wet granulation, the combination of PBM and DEM approaches has shown appropriate performance. Figure 3 represents the knowledge development framework (KDF) applying modeling and measurement equipment.

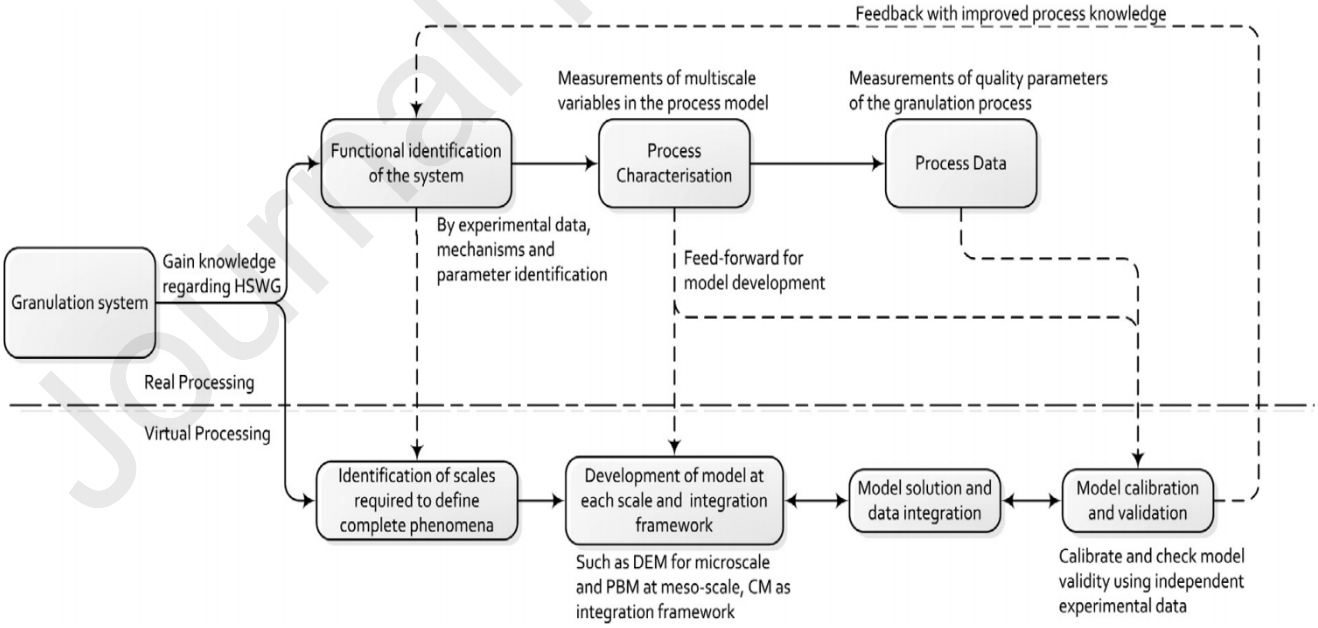

Figure 3. Schematic demonstration of the KDF applying modeling and measurement equipment. Reprinted from [21] with permission from Elsevier.

2.2. Discrete element method

In recent years, discrete element method (DEM) is identified as a bridge to overcome the disadvantages of the PBM approach in micro- and meso-scales [14, 56-60]. Two prominent classifications of DEM include hard-sphere (HS) and soft-sphere (SS) methods, which are of great application in granulation modeling. Table 2 aims to present comprehensive information about the advantages and disadvantages of different DEM methods. These approaches have been investigated by various researchers [7, 61-65]. The HS approach assumes the rigidity of particles. Therefore, the collision of particles is rapid and binary, which is not valid for extremely dense high-shear wet granulation system. In the SS approach, the instantaneity of contacts cannot be assumed and the simultaneous presence of more than one contact is possible. Figure 4 schematically illustrates the normal and tangential contact forces applying a spring, dashpot and slider approach.

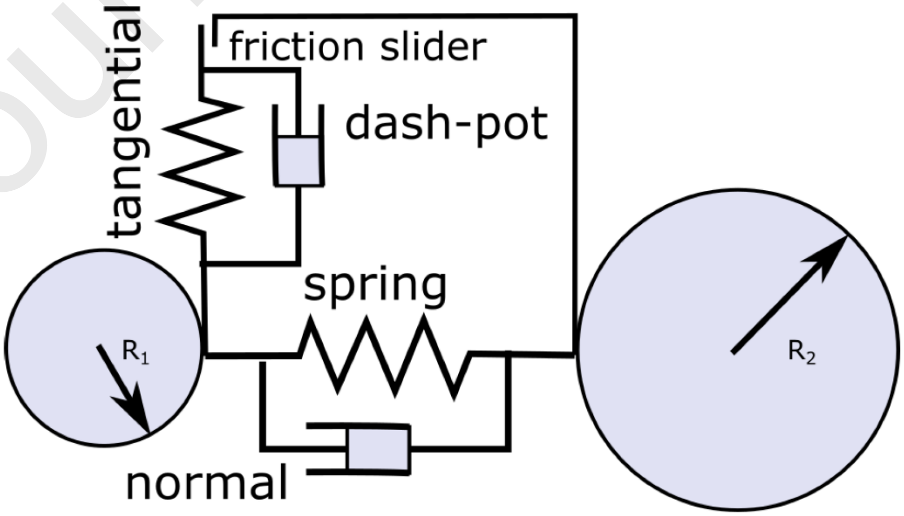

Figure 4. Schematic demonstration of the normal / tangential contact forces applying a spring, dashpot and slider approach. Reprinted from [66].

The following equations are derived to express linear / angular momentum equations for each granule in the granulator as follows [21]:

$$m_i \frac{dv_i}{dt} = m\vec{g} + \overrightarrow{F_P} + \overrightarrow{F_W} \tag{4}$$

$$I_i \frac{d\omega_i}{dt} = \overrightarrow{M_P} + \overrightarrow{M_W} \tag{5}$$

DEM possesses some privileges in comparison with PBM in cases of good capability to express complicated particle–particle interaction laws and to permit distribution of properties. Unlike DEM, PBM doesn't have the potential of application for theoretical-based process design owing to powder specifications and important hydrodynamic parameters regarding liquid–solid interaction. Additionally, DEM can be well applied to compute numerous particle-scale quantities of interest like local concentrations and particle phase stresses throughout the implementation of simulation [7, 57, 61, 67]. Despite the abovementioned advantages, significant computational cost is the main drawback of DEM, which can be taken place owing to the small integration time-step applied in this technique.

2.3. Artificial neural network model

The artificial neural network (ANN) model is a novel and promising model approach which can be used for simulation of wet and dry granulation processes. This technique is classified as Machine Learning (ML) method in simulation of processes which needs measured data for model's calibration. The technique has been successfully used for simulation of twin-screw granulation which include three input operational parameters such as liquid to solid ratio, screw speed and powder flow rate. In different circumstances, d-values of particle size distribution can be regarded as response parameters for the ML model. Fundamentally, the ANN model contains three layers including input, hidden and output layers [68-72]. The hidden layers contain various nodes for prediction of the output. Validation procedure, activation function, hidden layers and nodes number in each layer of network are identified as the principal parameters in the advancement of ANN model for prediction of granulation process. The abovementioned parameters are of great importance to perceive the optimized ANN topology for estimating the process. Discovery of the optimum ANN topology is an important challenge towards the development of ANN model due to the non-existence of straightforward method for this. Figure 5 illustrates the topology of the boosted ANN employed for a TSG process [68, 73-75].

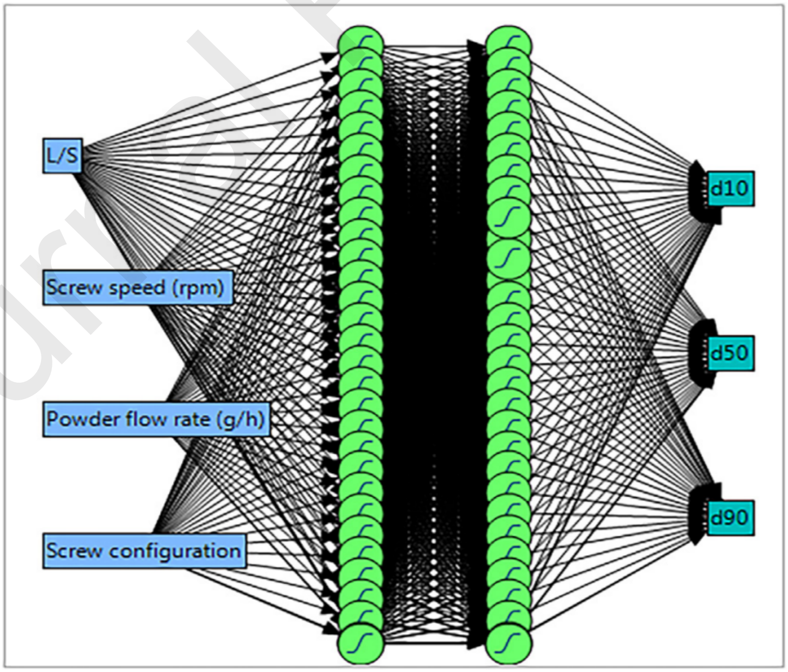

Figure 5. Schematic demonstration of the boosted ANN topology for estimation of granules d-values. Reprinted from [76] with permission from Elsevier.

To solve the PBM, solution time is of great need to achieve great results in terms of stability and accuracy as well. In recent years, ANN has been developed to prognosticate the particles mean residence time (MRT), needed for the simulation of particle size distribution in a twin-screw wet granulation. Hence, the hybrid ANN-PBM model is of great interest to consider process parameters and materials properties as inputs [37]. Figure 6 schematically demonstrates the optimized ANN topology achieved by trial and error for prediction of MRT.

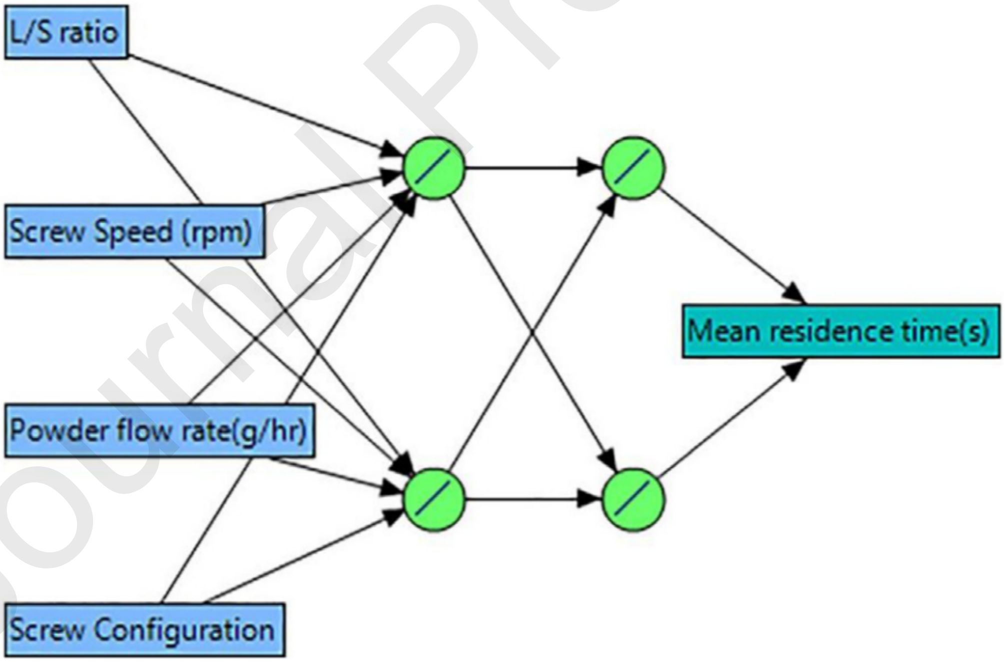

Figure 6. Schematic demonstration of the boosted ANN topology for prediction of MRT. Reprinted from [77] with permission from Elsevier.

2.4. *Mass conserving finite volume scheme (FVS)*

Apart from the modeling approaches applicable for granulation process, the numerical schemes also play crucial role, particularly for the solution of PBM. The numerical schemes have been currently of paramount interest to discretize the PBM such as finite volume scheme (FVS). This procedure is on the basis of total mass conservation in the system via the addition of two simple weights to the discrete formulation. In order to obtain the mathematical formulation of the FVS, the assumption of particle properties concentration on the mean of the cells must be taken into account. With the aim of developing the formulation of the FVS, the discrete computational domain is built from a continuous domain with upper limit. The mean of each cell of the domain can be derived as follows [78, 79]:

$$u_{\frac{1}{2}} = 0, \;\; u_i = \frac{u_{i+\frac{1}{2}} - u_{i-\frac{1}{2}}}{2} \qquad for \;\; i = 1,2,3,\ldots\ldots I. \tag{6}$$

$\Delta u_i = \frac{u_{i+\frac{1}{2}} - u_{i-\frac{1}{2}}}{2}$ is known as the step size of the ith cell. N_i is defined as the number of particles in ith cell and can be predicted using the following equation [78, 79]:

$$N_i = \int_{u_{i-\frac{1}{2}}}^{u_{i+\frac{1}{2}}} n(t,u)du \tag{7}$$

The FVS is on the basis of modifying the PBM equation into a series of ordinary differential equations via integrating the boundaries of the ith cell as follows [78, 79]:

$$\frac{\partial N_i}{\partial x} = \frac{1}{2}\int_{u_{i-\frac{1}{2}}}^{u_{i+\frac{1}{2}}} du \int_0^{\vartheta} \beta(t,u-\varepsilon,\varepsilon) n(t,u-\varepsilon) n(t,\varepsilon) d\varepsilon - \int_{u_{i-\frac{1}{2}}}^{u_{i+\frac{1}{2}}} du n(t,u) \int_0^{\infty} \beta(t,u,\varepsilon) n(t,\varepsilon) + \int_{u_{i-\frac{1}{2}}}^{u_{i+\frac{1}{2}}} du \int_u^{\infty} b(u,\varepsilon) S(\varepsilon) n(t,\varepsilon) d\varepsilon - \int_{u_{i-\frac{1}{2}}}^{u_{i+\frac{1}{2}}} du S(u) n(t,u) \quad (8)$$

Owing to the assumption of concentrated particle properties on the cells, the number density function may be rendered by a set of delta functions as follows [78, 79]:

$$n(t,u) = \sum_{i=1}^{I} N_i \delta(u - u_i) \quad (9)$$

Combination of two abovementioned equations results in achieving the following equation [78, 79]:

$$\frac{\partial N_i}{\partial x} = B_i - D_i \quad (10)$$

In this equation, B_i and D_i relate to simultaneous aggregation-breakage mechanisms in the ith cell. Table 2 aims to comprehensively review disparate physical modeling approaches in granulation investigations.

Table 2. Advantages of physical modeling approaches and their associated challenges.

Model	Advantages	Challenges	Ref.
PBM	Simulation of a great number of particles	Semi-mechanistic approach because of the paucity of process knowledge	[80, 81]
DEM	Mechanistic attitude	Computational restrictions	[57]

Hybrid PBM-DEM	Ability of modeling complicated dynamic mechanisms by interconnection of micro-scale to meso-scale	Difficulty of implementation Owing to challenges like wet granule yield strength, asperity height and so on.	[82, 83]
PBM with volume of fluid VoF procedures	Mechanistic attitude spatial distribution of binder in wet granule	Difficulty of implementation Requirement of considerable simplification	[84]
Hybrid PBM-CFD	Mechanistic approach Ability of application for developing simplified model	Lack of suitability for dense particle system Neglection of particle–particle interaction	[75, 85]
Hybrid PBM-CM-DEM	Enhanced precision of the PBM	Low number of particles	[86, 87]

3. Conclusion and future perspectives

Granulation has been recently perceived as an indisputably important processes in the pharmaceutical industry for the efficient manufacturing of various types of drugs in commercial scale. The prominent purpose of this technique is to fabricate granules applied directly as drugs or perform as an intermediate product in tablets / capsules. This paper aims to provide a short overview on the state-of-the-art of modeling approaches such as PBM, DEM and ANN towards granulation process. Paradigm alteration from batch to continuous granulation process has been an important turning point for the pharmaceutical industry and manufacturing of solid dosage forms. First-principles modeling approaches have recently attracted paramount attentions due to playing an indisputable role in optimization and control of important quality parameters in pharmaceutical granulation. Despite their importance, they must possess an acceptable level of reliability to obtain the purpose of simulation for granulation. By increasing the model dimensions, the existed modeling approaches have demonstrated performance constraints. Therefore, this important limitation has encouraged the investigators to develop more computationally-efficient mathematical procedures to facilitate the numerical modeling of pharmaceutical processes such as granulation.

References

[1] M. Raissy, H. Ghafarifarsani, S. H. Hoseinifar, E. R. El-Haroun, S. Shahbazi Naserabad, and H. Van Doan, "The effect of dietary combined herbs extracts (oak acorn, coriander, and common mallow) on growth, digestive enzymes, antioxidant and immune response, and resistance against Aeromonas hydrophila infection in common carp, Cyprinus carpio," *Aquaculture,* vol. 546, p. 737287, 2022.

[2] A. Davoodnia, " A Highly Efficient and Fast Method for the Synthesis of Biscoumarins Using Tetrabutylammonium Hexatungstate [TBA]2[W6O19] as Green and Reusable Heterogeneous Catalyst," *Bulletin of the Korean Chemical Society,* vol. 32, pp. 4286-4290, 12/20 2011.

[3] S. Halim, N. Mohamad, R. Pm, N. H. Zakaria, and N. A. Muhammad, "In-vitro Study: Camp Overshoot Caused by Chronic Morphine Alleviated by the Synergistic Combination of Zamzam Water and Methadone in Human Primary Glioblastoma Cell Line (U-87 MG)," *IIUM Medical Journal Malaysia,* vol. 18, 2019.

[4] R. Suliman, F. Asmani, M. Suliman, M. Hussain, J. Khan, M. Kaleemullah*, et al.*, "A New Approach for Predicting Antioxidant Property of Herbal Extracts," *International Journal of Pharmacognosy and Phytochemical Research,* vol. 7, pp. 166-174, 2015.

[5] S. Fattepur, K. Nilugal, T. Darshan, M. F. Bacayo, F. Asmani, I. Abdullah*, et al.*, "Toxicological and pharmacological activity of ethanolic extracts of Catharanthus roseus in expermental animals," *International Journal of Medical Toxicology & Legal Medicine,* vol. 21, p. 141, 01/01 2018.

[6] A. Emrani, A. Davoodnia, and N. Tavakoli-Hoseini, " Alumina supported ammonium dihydrogenphosphate (NH4 H2PO4/Al2O3): Preparation, characterization and its application as catalyst in the synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles," Bulletin of the Korean Chemical Society, vol. 32, pp. 2385-2390, 07/20 2011.

[7] S. S. Ang, A. B. Salleh, L. T. Chor, Y. M. Normi, B. A. Tejo, M. B. A. Rahman*, et al.*, "Biochemical Characterization of the Cytochrome P450 CYP107CB2 from Bacillus lehensis G1," *The protein journal,* vol. 37, pp. 180-193, 2018.

[8] C. Fu, A. Rahmani, W. Suksatan, S. M. Alizadeh, M. Zarringhalam, S. Chupradit*, et al.*, "Comprehensive investigations of mixed convection of Fe–ethylene-glycol nanofluid inside an enclosure with different obstacles using lattice Boltzmann method," *Scientific Reports,* vol. 11, p. 20710, 2021/10/20 2021.

[9] M. Bibi, S. Khan, A.-U.-R. Kakar, N. Khan, A. H. Tareen, S. Bibi*, et al.*, "Determination of essential and non-essential elements in Xylanthemum macropodum of Balochistan, Pakistan," *Baghdad Journal of Biochemistry and Applied Biological Sciences,* vol. 2, pp. 95-105, 06/30 2021.

[10] A. U. Itodo, S. Ande, and M. O. Audu, "Detoxification of acetaminophen overdose using formulated carbo tablets," *Journal of Medicinal and Chemical Sciences,* vol. 3, pp. 183-198, 2020.

[11] C. Portier, K. Pandelaere, U. Delaet, T. Vigh, A. Kumar, G. Di Pretoro*, et al.*, "Continuous twin screw granulation: Influence of process and formulation variables on granule quality attributes of model formulations," *International journal of pharmaceutics,* vol. 576, p. 118981, 2020.

[12] H. Ghafarifarsani, S. H. Hoseinifar, T. J. Adorian, F. R. Goulart Ferrigolo, M. Raissy, and H. Van Doan, "The effects of combined inclusion of Malvae sylvestris, Origanum vulgare, and Allium hirtifolium boiss for common carp (Cyprinus carpio) diet: Growth performance, antioxidant defense, and immunological parameters," *Fish & Shellfish Immunology,* vol. 119, pp. 670-677, 2021/12/01/ 2021.

[13] H. Ghafarifarsani, S. H. Hoseinifar, M. Aftabgard, and H. Van Doan, "The improving role of savory (Satureja hortensis) essential oil for Caspian roach (Rutilus caspicus) fry: Growth, haematological, immunological, and antioxidant parameters and resistance to salinity stress," *Aquaculture,* vol. 548, p. 737653, 2022/02/15/ 2022.

[14] Z. Deng, C. Liu, and Z. Zhu, "Inter-hours rolling scheduling of behind-the-meter storage operating systems using electricity price forecasting based on deep convolutional neural network," *International Journal of Electrical Power & Energy Systems,* vol. 125, p. 106499, 2021/02/01/ 2021.

[15] J. Guo, C. Zhu, Y. Zhao, H. Wang, X. He, and D. Cai, *LAMP: Label Augmented Multimodal Pretraining*, 2020.

[16] O. Zulhabri, K. Hamimi Rasyiqah Hassan, A. Azrina Zainal, H. Halijah, and F. Santosh, "The Anti-Angiogenic Properties of Morinda citrifolia. L (Mengkudu) Leaves Using Chicken Chorioallantoic Membrane (CAM) Assay," *Pharmacognosy Journal,* vol. 11, 2019.

[17] Q. Abdul, K. Attiq-Ur-Rehman, K. Naqeebullah, Samiullah, H. Abdul, K. Rehana*, et al.*, "The antioxidant, antimicrobial, and clinical effects with elemental contents of pomegranate (Punica granatum) peel extracts: A review," *Baghdad Journal of Biochemistry and Applied Biological Sciences,* vol. 2, pp. 21-28, 03/08 2021.

[18] J. Khan, S. Norfarhani, R. Sahu, S. Ruhi, M. Kaleemullah, S. Al-Dhalli*, et al.*, "Development and evaluation of topical emulgel of aspirin using different polymeric bases," *RESEARCH JOURNAL OF PHARMACY AND TECHNOLOGY,* vol. 13, pp. 6300-6304, 01/01 2020.

[19] B. J. Ennis, "Theory of granulation: An engineering perspective," in *Handbook of Pharmaceutical Granulation Technology*, ed: CRC Press, 2016, pp. 22-74.

[20] R. M. Dhenge, J. J. Cartwright, M. J. Hounslow, and A. D. Salman, "Twin screw granulation: Steps in granule growth," *International journal of pharmaceutics,* vol. 438, pp. 20-32, 2012.

[21] A. Kumar, K. V. Gernaey, T. De Beer, and I. Nopens, "Model-based analysis of high shear wet granulation from batch to continuous processes in pharmaceutical production–a critical review," *European Journal of Pharmaceutics and Biopharmaceutics,* vol. 85, pp. 814-832, 2013.

[22] A. Emrani, A. Davoodnia, and N. Tavakoli-Hoseini, "Alumina supported ammonium dihydrogenphosphate (NH 4 H 2 PO 4/Al 2 O 3): Preparation, characterization and its application as catalyst in the synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles," *Bulletin of the Korean Chemical Society,* vol. 32, pp. 2385-2390, 2011.

[23] A. S. Rathore, S. Nikita, G. Thakur, and N. Deore, "Challenges in process control for continuous processing for production of monoclonal antibody products," *Current Opinion in Chemical Engineering,* vol. 31, p. 100671, 2021.

[24] M. Mollan and M. Lodaya, "Continuous processing in pharmaceutical manufacturing," *Pharmaceutical Manufacturing Magazine,* pp. 1-9, 2004.

[25] A. Davoodnia, "A highly efficient and fast method for the synthesis of biscoumarins using tetrabutylammonium hexatungstate [TBA] 2 [W 6 O 19] as green and reusable heterogeneous catalyst," *Bulletin of the Korean Chemical Society,* vol. 32, pp. 4286-4290, 2011.

[26] Q. Nguyen, M. Babanezhad, A. Taghvaie Nakhjiri, M. Rezakazemi, and S. Shirazian, "Prediction of thermal distribution and fluid flow in the domain with multi-solid structures using Cubic-Interpolated Pseudo-Particle model," *PLoS One,* vol. 15, p. e0233850, 2020.

[27] S. Yang, S. A. Jasim, D. Bokov, S. Chupradit, A. T. Nakhjiri, and A. El-Shafay, "Membrane distillation technology for molecular separation: a review on the fouling, wetting and transport phenomena," *Journal of Molecular Liquids,* p. 118115, 2021.

[28] M. Teżyk, B. Milanowski, A. Ernst, and J. Lulek, "Recent progress in continuous and semi-continuous processing of solid oral dosage forms: a review," *Drug development and industrial pharmacy,* vol. 42, pp. 1195-1214, 2016.

[29] J. Vercruysse, E. Peeters, M. Fonteyne, P. Cappuyns, U. Delaet, I. Van Assche*, et al.*, "Use of a continuous twin screw granulation and drying system during formulation development and process optimization," *European Journal of Pharmaceutics and Biopharmaceutics,* vol. 89, pp. 239-247, 2015.

[30] M. Bibi, S. Khan, N. Khan, A. H. Tareen, S. Bibi, and H. Taj, "Determination of essential and non-essential elements in Xylanthemum macropodum of Balochistan, Pakistan," *Baghdad Journal of Biochemistry and Applied Biological Sciences,* vol. 2, pp. 94-103, 2021.

[31] M. Babanezhad, I. Behroyan, A. T. Nakhjiri, M. Rezakazemi, A. Marjani, and S. Shirazian, "Prediction of turbulence eddy dissipation of water flow in a heated metal foam tube," *Scientific reports,* vol. 10, pp. 1-12, 2020.

[32] S. Byrn, M. Futran, H. Thomas, E. Jayjock, N. Maron, R. F. Meyer*, et al.*, "Achieving continuous manufacturing for final dosage formation: challenges and how to meet them. May 20–21, 2014 continuous manufacturing symposium," *Journal of pharmaceutical sciences,* vol. 104, pp. 792-802, 2015.

[33] A. Qahir, N. Khan, A. Hakeem, and R. Kamal, "The antioxidant, antimicrobial, and clinical effects with elemental contents of Pomegranate (Punica Granatum) Peel Extraction: A Review," *Baghdad Journal of Biochemistry and Applied Biological Sciences,* vol. 2, pp. 21-28, 2021.

[34] M. Pishnamazi, A. T. Nakhjiri, M. Ghadiri, A. Marjani, A. Heydarinasab, and S. Shirazian, "Computational fluid dynamics simulation of NO2 molecular sequestration from a gaseous stream using NaOH liquid absorbent through porous membrane contactors," *Journal of Molecular Liquids,* vol. 313, p. 113584, 2020.

[35] T. C. Seem, N. A. Rowson, A. Ingram, Z. Huang, S. Yu, M. de Matas*, et al.*, "Twin screw granulation — A literature review," *Powder Technology,* vol. 276, pp. 89-102, 2015/05/01/ 2015.

[36] R. M. Dhenge, R. S. Fyles, J. J. Cartwright, D. G. Doughty, M. J. Hounslow, and A. D. Salman, "Twin screw wet granulation: Granule properties," *Chemical Engineering Journal,* vol. 164, pp. 322-329, 2010.

[37] H. Y. Ismail, S. Shirazian, M. Singh, D. Whitaker, A. B. Albadarin, and G. M. Walker, "Compartmental approach for modelling twin-screw granulation using population balances," *International journal of pharmaceutics,* vol. 576, p. 118737, 2020.

[38] A. Itodo, S. Ande, and M. Audu, "Detoxification of acetaminophen overdose using formulated carbo tablets," *Journal of Medicinal and Chemical Sciences,* vol. 3, pp. 183-198, 2020.

[39] Y. Cao, Z. U. Rehman, N. Ghasem, M. Al-Marzouqi, N. Abdullatif, A. T. Nakhjiri*, et al.*, "Intensification of CO 2 absorption using MDEA-based nanofluid in a hollow fibre membrane contactor," *Scientific Reports,* vol. 11, pp. 1-12, 2021.

[40] S. Shirazian, J. Zeglinski, S. Darwish, M. Kuhs, A. B. Albadarin, D. M. Croker*, et al.*, "Continuous twin screw wet granulation: The combined effect of process parameters on residence time, particle size, and granule morphology," *Journal of Drug Delivery Science and Technology,* vol. 48, pp. 319-327, 2018.

[41] C. Fu, A. Rahmani, W. Suksatan, S. Alizadeh, M. Zarringhalam, S. Chupradit*, et al.*, "Comprehensive investigations of mixed convection of Fe–ethylene-glycol nanofluid inside an enclosure with different obstacles using lattice Boltzmann method," *Scientific Reports,* vol. 11, pp. 1-16, 2021.

[42] Y. Cao, A. Khan, A. T. Nakhjiri, A. B. Albadarin, T. A. Kurniawan, and M. Rezakazemi, "Recent advancements in molecular separation of gases using microporous membrane systems: A comprehensive review on the applied liquid absorbents," *Journal of Molecular Liquids,* p. 116439, 2021.

[43] M. Pishnamazi, A. T. Nakhjiri, A. S. Taleghani, A. Marjani, A. Heydarinasab, and S. Shirazian, "Computational investigation on the effect of [Bmim][BF_4] ionic liquid addition to MEA alkanolamine absorbent for enhancing CO_2 mass transfer inside membranes," *Journal of Molecular Liquids,* vol. 314, p. 113635, 2020.

[44] H. Ghafarifarsani, S. H. Hoseinifar, T. J. Adorian, F. R. G. Ferrigolo, M. Raissy, and H. Van Doan, "The effects of combined inclusion of Malvae sylvestris, Origanum vulgare, and Allium hirtifolium boiss for common carp (Cyprinus carpio) diet: Growth performance, antioxidant defense, and immunological parameters," *Fish & Shellfish Immunology,* 2021.

[45] M. Elveny, A. Khan, A. T. Nakhjiri, and A. B. Albadarin, "A state-of-the-art review on the application of various pharmaceutical nanoparticles as a promising technology in cancer treatment," 2021.

[46] A. A. Barrera Jiménez, D. Van Hauwermeiren, M. Peeters, T. De Beer, and I. Nopens, "Improvement of a 1D Population Balance Model for Twin-Screw Wet Granulation by Using Identifiability Analysis," *Pharmaceutics,* vol. 13, p. 692, 2021.

[47] D. Ramkrishna, *Population balances: Theory and applications to particulate systems in engineering*: Elsevier, 2000.

[48] M. A. Pinto, C. D. Immanuel, and F. J. Doyle III, "A feasible solution technique for higher-dimensional population balance models," *Computers & Chemical Engineering,* vol. 31, pp. 1242-1256, 2007.

[49] I. Cameron, F. Wang, C. Immanuel, and F. Stepanek, "Process systems modelling and applications in granulation: A review," *Chemical Engineering Science,* vol. 60, pp. 3723-3750, 2005.

[50] C. Drumm, M. M. Attarakih, and H.-J. Bart, "Coupling of CFD with DPBM for an RDC extractor," *Chemical engineering science,* vol. 64, pp. 721-732, 2009.

[51] C. Garth, A. Middel, and H. Hagen, "CFD Simulation of Liquid-Liquid Extraction Columns and Visualization of Eulerian Datasets," *Visualization of Large and Unstructured Data Sets: Applications in Geospatial Planning, Modeling and Engineering-Proceedings of IRTG,* vol. 1131, pp. 59-70, 2011.

[52] M. Babanezhad, A. T. Nakhjiri, A. Marjani, and S. Shirazian, "Pattern recognition of the fluid flow in a 3D domain by combination of Lattice Boltzmann and ANFIS methods," *Scientific Reports,* vol. 10, pp. 1-13, 2020.

[53] M. Raissy, H. Ghafarifarsani, S. H. Hoseinifar, E. R. El-Haroun, S. S. Naserabad, and H. Van Doan, "The effect of dietary combined herbs extracts (oak acorn, coriander, and common mallow) on growth, digestive enzymes, antioxidant and immune response, and resistance against Aeromonas hydrophila infection in common carp, Cyprinus carpio," *Aquaculture,* vol. 546, p. 737287, 2022.

[54] B. Freireich, J. Li, J. Litster, and C. Wassgren, "Incorporating particle flow information from discrete element simulations in population balance models of mixer-coaters," *Chemical Engineering Science,* vol. 66, pp. 3592-3604, 2011.

[55] J. Li, B. Freireich, C. Wassgren, and J. D. Litster, "A general compartment-based population balance model for particle coating and layered granulation," *AIChE Journal,* vol. 58, pp. 1397-1408, 2012.

[56] J. A. Gantt, I. T. Cameron, J. D. Litster, and E. P. Gatzke, "Determination of coalescence kernels for high-shear granulation using DEM simulations," *Powder Technology,* vol. 170, pp. 53-63, 2006.

[57] H. Nakamura, H. Fujii, and S. Watano, "Scale-up of high shear mixer-granulator based on discrete element analysis," *Powder Technology,* vol. 236, pp. 149-156, 2013.

[58] W. R. Ketterhagen, M. T. am Ende, and B. C. Hancock, "Process modeling in the pharmaceutical industry using the discrete element method," *Journal of pharmaceutical sciences,* vol. 98, pp. 442-470, 2009.

[59] A. Marjani, A. T. Nakhjiri, M. Pishnamazi, and S. Shirazian, "Evaluation of potassium glycinate, potassium lysinate, potassium sarcosinate and potassium threonate solutions in CO2 capture using membranes," *Arabian Journal of Chemistry,* vol. 14, p. 102979, 2021.

[60] H. Ghafarifarsani, S. H. Hoseinifar, M. Aftabgard, and H. Van Doan, "The improving role of savory (Satureja hortensis) essential oil for Caspian Roach (Rutilus caspicus) fry: Growth, haematological, immunological, and antioxidant parameters and resistance to salinity stress," *Aquaculture,* p. 737653, 2021.

[61] J. A. Gantt and E. P. Gatzke, "High-shear granulation modeling using a discrete element simulation approach," *Powder Technology,* vol. 156, pp. 195-212, 2005.

[62] P. Liu, R. Yang, and A. Yu, "DEM study of the transverse mixing of wet particles in rotating drums," *Chemical Engineering Science,* vol. 86, pp. 99-107, 2013.

[63] H. Herrmann and S. Luding, "Modeling granular media on the computer," *Continuum Mechanics and Thermodynamics,* vol. 10, pp. 189-231, 1998.

[64] A. T. Nakhjiri and M. H. Roudsari, "Modeling and simulation of natural convection heat transfer process in porous and non-porous media," *Appl. Res. J,* vol. 2, pp. 199-204, 2016.

[65] M. Babanezhad, I. Behroyan, A. T. Nakhjiri, A. Marjani, M. Rezakazemi, and S. Shirazian, "High-performance hybrid modeling chemical reactors using differential evolution based fuzzy inference system," *Scientific Reports,* vol. 10, pp. 1-11, 2020.

[66] A. Kumar, S. Radl, K. V. Gernaey, T. De Beer, and I. Nopens, "Particle-Scale Modeling to Understand Liquid Distribution in Twin-Screw Wet Granulation," *Pharmaceutics,* vol. 13, p. 928, 2021.

[67] A. Marjani, A. Taghvaie Nakhjiri, M. Adimi, H. Fathinejad Jirandehi, and S. Shirazian, "Modification of polyethersulfone membrane using MWCNT-NH2 nanoparticles and its application in the separation of azeotropic solutions by means of pervaporation," *PloS one,* vol. 15, p. e0236529, 2020.

[68] P. Kazemi, M. H. Khalid, J. Szlek, A. Mirtič, G. K. Reynolds, R. Jachowicz*, et al.*, "Computational intelligence modeling of granule size distribution for oscillating milling," *Powder Technology,* vol. 301, pp. 1252-1258, 2016.

[69] H. Yu, J. Fu, L. Dang, Y. Cheong, H. Tan, and H. Wei, "Prediction of the particle size distribution parameters in a high shear granulation process using a key parameter definition combined artificial neural network model," *Industrial & Engineering Chemistry Research,* vol. 54, pp. 10825-10834, 2015.

[70] J. Khan, S. Norfarhani, R. K. Sahu, S. Ruhi, M. Kaleemullah, S. Al-Dhalli*, et al.*, "Development and Evaluation of topical Emulgel of Aspirin using different Polymeric Bases," *Research Journal of Pharmacy and Technology,* vol. 13, pp. 6300-6304, 2020.

[71] M. Babanezhad, I. Behroyan, A. T. Nakhjiri, A. Marjani, and S. Shirazian, "Computational modeling of transport in porous media using an adaptive network-based fuzzy inference system," *ACS omega,* vol. 5, pp. 30826-30835, 2020.

[72] M. Babanezhad, I. Behroyan, A. T. Nakhjiri, A. Marjani, and S. Shirazian, "Performance and application analysis of ANFIS artificial intelligence for pressure prediction of nanofluid convective flow in a heated pipe," *Scientific Reports,* vol. 11, pp. 1-18, 2021.

[73] H. Gong, R. Pishgar, and J. Tay, "Artificial neural network modelling for organic and total nitrogen removal of aerobic granulation under steady-state condition," *Environmental technology,* 2018.

[74] Z. Othman, H. R. H. Khalep, A. Z. Abidin, H. Hassan, and S. Fattepur, "The Anti-Angiogenic Properties of Morinda citrifolia. L (Mengkudu) Leaves Using Chicken Chorioallantoic Membrane (CAM) Assay," *Pharmacognosy Journal,* vol. 11, 2019.

[75] M. Babanezhad, A. T. Nakhjiri, M. Rezakazemi, A. Marjani, and S. Shirazian, "Functional input and membership characteristics in the accuracy of machine learning approach for estimation of multiphase flow," *Scientific Reports,* vol. 10, pp. 1-15, 2020.

[76] S. Shirazian, M. Kuhs, S. Darwish, D. Croker, and G. M. Walker, "Artificial neural network modelling of continuous wet granulation using a twin-screw extruder," *International Journal of Pharmaceutics,* vol. 521, pp. 102-109, 2017.

[77] H. Y. Ismail, M. Singh, S. Darwish, M. Kuhs, S. Shirazian, D. M. Croker*, et al.,* "Developing ANN-Kriging hybrid model based on process parameters for prediction of mean residence time distribution in twin-screw wet granulation," *Powder Technology,* vol. 343, pp. 568-577, 2019.

[78] H. Y. Ismail, M. Singh, S. Shirazian, A. B. Albadarin, and G. M. Walker, "Development of high-performance hybrid ann-finite volume scheme (ann-fvs) for simulation of pharmaceutical continuous granulation," *Chemical Engineering Research and Design,* vol. 163, pp. 320-326, 2020.

[79] M. Singh, J. Kumar, and A. Bück, "A volume conserving discrete formulation of aggregation population balance equations on non-uniform meshes," *IFAC-PapersOnLine,* vol. 48, pp. 192-197, 2015.

[80] D. Barrasso and R. Ramachandran, "A comparison of model order reduction techniques for a four-dimensional population balance model describing multi-component wet granulation processes," *Chemical engineering science,* vol. 80, pp. 380-392, 2012.

[81] R. Ramachandran, C. D. Immanuel, F. Stepanek, J. D. Litster, and F. J. Doyle III, "A mechanistic model for breakage in population balances of granulation: Theoretical kernel development and experimental validation," *Chemical Engineering Research and Design,* vol. 87, pp. 598-614, 2009.

[82] J. A. Gantt and E. P. Gatzke, "A stochastic technique for multidimensional granulation modeling," *AIChE journal,* vol. 52, pp. 3067-3077, 2006.

[83] M. Sen, A. Dubey, R. Singh, and R. Ramachandran, "Mathematical development and comparison of a hybrid PBM-DEM description of a continuous powder mixing process," *Journal of Powder Technology,* vol. 2013, 2012.

[84] F. Štěpánek, P. Rajniak, C. Mancinelli, R. Chern, and R. Ramachandran, "Distribution and accessibility of binder in wet granules," *Powder Technology,* vol. 189, pp. 376-384, 2009.

[85] P. Rajniak, F. Stepanek, K. Dhanasekharan, R. Fan, C. Mancinelli, and R. Chern, "A combined experimental and computational study of wet granulation in a Wurster fluid bed granulator," *Powder Technology,* vol. 189, pp. 190-201, 2009.

[86] J. Bouffard, F. Bertrand, and J. Chaouki, "A multiscale model for the simulation of granulation in rotor-based equipment," *Chemical engineering science,* vol. 81, pp. 106-117, 2012.

[87] M. Babanezhad, I. Behroyan, A. T. Nakhjiri, M. Rezakazemi, A. Marjani, and S. Shirazian, "Thermal prediction of turbulent forced convection of nanofluid using computational fluid dynamics coupled genetic algorithm with fuzzy interface system," *Scientific Reports,* vol. 11, pp. 1-12, 2021.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: