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The influence of particle interfacial energies and mixing energy on the mixture quality of the dry-coating process

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ABSTRACT

We investigate the effect of particle interface energies and mixing energy input on the macroscopic behavior of the dry-coating process by using the discrete element method (DEM). It is observed that the quality of the coating process is governed by two dimensionless numbers: the Stokes number *St* (mixing energy/strength of agglomerates) and the reduced intermixing coefficient Λ (cohesion /adhesion strength). Three unfavorable and one favorable process regimes were identified, and represented in a regime map as a function of *St* and Λ. For low *St* and Λ, carriers are lumped and random mixing is fairly poor. For low *St* and high Λ, the agglomerates are merged together and remain intact. At high St, the fine-carrier adhesion breaks and creates abundance of debris. Between these regions process conditions are favorable as is supported by experimental evidences. Results of this study can be used to establish guidelines for efficient operation of the dry-coating process in a high-shear mixer.

1. Introduction

The synthesis of particles with tailored properties has become increasingly important for a variety of industrial and technological applications [45,55,59]. Methods have been developed to create particles with desired features and functionalities, including the modification of particle surface by means of coating with finer particles. Conventionally, particles have been coated using various techniques, such as spray coating, fluidization, coacervation, and interfacial polymerization [55]. These techniques, broadly categorized as wet-coating processes, result in the formation of a rather permanent thin film around a core particle, with the consequent alteration of its physical and/or chemical properties [43]. In the search for alternative coating techniques with less environmental impact and higher efficiency than wet coating, the solventless process of dry-coating has been introduced [72]. In this process, micron-sized particles (fines) are loosely dispersed onto relatively larger particles (carriers) in order to create value-added composite particulate materials [2]. An exclusive application of this process is the formulation of the dry powder inhaler (DPI), wherein fine active pharmaceutical ingredient (API) particles are blended with larger carriers to enhance the flow, reduce the aggregation, and aid the dispersion of APIs [61,65]. The dry-coating process can be described with the following essential steps (Fig. 1a-c) [3]:

a. The mixing starts when the agglomerates of fine particles attach to their adjacent coarse particles and are carried around; i.e. creation of first coated carriers.
b. When the agglomerate collide with or are compressed by coarse particles, they break apart; i.e. fragmentation of agglomerates.
c. The continuous collision and friction of carriers deteriorate the remaining agglomerates and disperse fine particles onto the carriers' surface, i.e. increase in coated area.

Interparticle forces play a key role in the formation and breakage of agglomerates and in controlling the adhesion of fines to a carrier's surface [7]. The adhesion in carrier-basedDPI systems may be attributed to multiple factors, including surface energy, relative humidity, the morphology of the API, the presence of ternary components, and themorphology of the carrier. Clearly, any change in the force of API-carrier interaction will have a direct effect on the aerosolisation efficiency of the API when inhaled since the force required to liberate the drug from the carrier will be altered. In manufacturing dry coated carriers, both the agglomerates, formed by the fine particles, and the carriers undergo shear and collision forces until the product achieves specific standards, usually related to surface coverage and homogeneity of the coating.

Previous studies on dry-coating have examined the mixing mechanism of adhesive particles with disparate sizes (i.e. ordered mixing) [28]. It was discovered that, due to the dispersion of fines onto a carrier's surface, such a mixture may show a higher degree of homogeneity than

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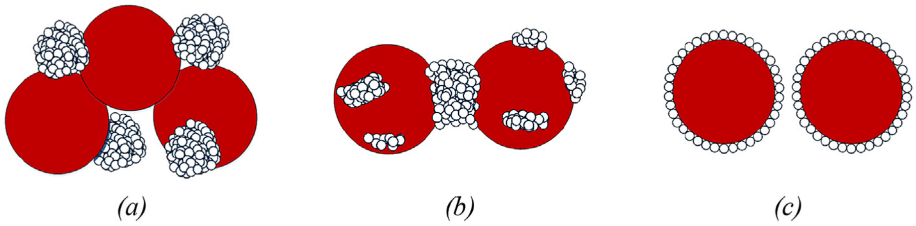

Fig. 1. Mechanisms of dry-coating. (a)Random mixing of agglomerates and coarse particles; (b)Partial breakage of agglomerates; (c)Gradual dispersion of fines over carriers.

a randomized mixture of non-interacting particles [75]. Hitherto, numerous experimental attempts have been made to improve the basic understanding of the dry-coating process and expand its applicability. Coating efficiency in various mixers, including mechanofusion, hybridizer, and magnetically assisted impaction-coating (MAIC) [55,76] has been studied and the effect of operating parameters and particle properties on the ultimate tailored mixture has been explored. However, despite all the available studies on the dry-coating process, there remain some fundamental questions that cannot be addressed accurately with experimentation alone, such as the relative importance and interplay of the mechanisms governing dry-coating. This information is important for understanding and optimizing the process. Another challenging aspect of the dry-coating process is that it is influenced by several variables, including particles size and shape, interparticle forces, mixing time and power, and addition of a third component [59]. This gap of theoretical knowledge on the dry-coating process can be filled by means of mathematical/numerical modelling. A few preliminary, quantitative models have been proposed to link the macroscopic features of the dry-coating process and particle interaction in the system [4,5,12,30,66]. For instance, a correlation between the number of fines in the monolayer and the fine/carrier size ratio has been proposed by Alonso et al. [5] yet no other parameters have been taken into account in model's development. Chen et al. [12] have established a macroscopic model to describe the effect of angular speed on the force imposed on the particles in the action zone of mechanofusion.

A deeper understanding of the mechanisms governing dry particle coating can be achieved with numerical simulation of particle motion using the discrete element method (DEM). Existing studies focus on the primary steps in the dry-coating process, including the adhesive mixture of similar particles [1,32,33,41,42], detailed analyses of a single agglomerate breakage while impacting a wall [19,25,51,68,70], and investigation of the effect of air-flow force and particle-wall impact on the detachment mechanism of API particles in carrier based DPI formulations [73,74]. Apart from conducting simulation in scale of an individual agglomerate, there are several studies where the entire mixing process is simulated. Mixing of particles with different sizes, but without cohesion, has been simulated by Sato et al. [60], and the collisional force and frequency have been calculated. A comprehensive DEM based model has been developed by Deng et al. [20] to study adhesive mixing in a MAIC. The effects of particle properties and mixing conditions on the homogeneity of mixing have been investigated, but the particles are all of the same size (i.e. no coating). Due to the difficulties of simulating a large number of cohesive particles with disparate sizes, no DEM study has been performed on the dry-coating process holistically and the interplay of variables have not been studied thoroughly [18].

Therefore, a fundamental understanding of a real dry-coating process is still partly missing. Not only is it necessary to have a model that encompasses all the stages of dry-coating, but it is at the same time crucial to determine the effect of influential parameters on the process behavior. Lately, our research group have tried to cope with the challenges in simulation of the dry coting process by breaking down the problem. The initial attempts were made by Nguyen et al. [46,47], as they explored the dry-coating process on the single agglomerate scale where an agglomerate of fine particles collide with a single carrier. The collision velocity and impact angle were found to have a significant effect on agglomerate breakage and subsequent adhesion. The same authors expanded their studies by considering the effect of the surface energy of particles on the carrier's capturing pattern, and they successfully built a regime map for the breakage and adhesion of a fine agglomerate impacting a spherical target [47].

The aim of the present work is to extend our understanding of dry-coating mechanisms by using the DEM framework developed in our group for this purpose [63]. Our simulations address the dry-coating process in a holistic manner, in the sense that we examine the interplay and relative importance between three of the main phenomena that occur in the process; namely, (i)mixing of fines and carriers, (ii) agglomerate breakage/re-formation and (iii) fine-carrier adhesion and redistribution of fines between carriers. To limit the scope, we focused on the effect of the surface energy of particles and impeller speed on the dynamic behavior of the dry-coating process. The simulation results are summarized in a regime map that shows the mechanisms that dominate the coating as a function of two dimensionless parameters, the Stokes number, and the reduced intermixing coefficient. This map can be used, for instance, to identify the conditions that will lead to desired or undesired mixing.

2. Computational model and set-up

Simulation of the dry-coating process was carried out in a Couette shear cell due to its well-known rheology and its ability to impose constant and effective shear to particles [31,39]. The latter feature helps to decrease the computational cost drastically by reducing the required process time. To increase the intensity of shear insertion in the annular gap, the inner cylinder was equipped with four equidistant square baffles. The simulation domain is schematically shown in Fig. 2. The cell was first filled randomly with 200 mono-sized carrier particles with material properties that corresponded to D-Mannitol (a common carrier particle in the dry-coating process), which formed a layer. Then, 10 agglomerates of 1000 μm-sized fine particles each,

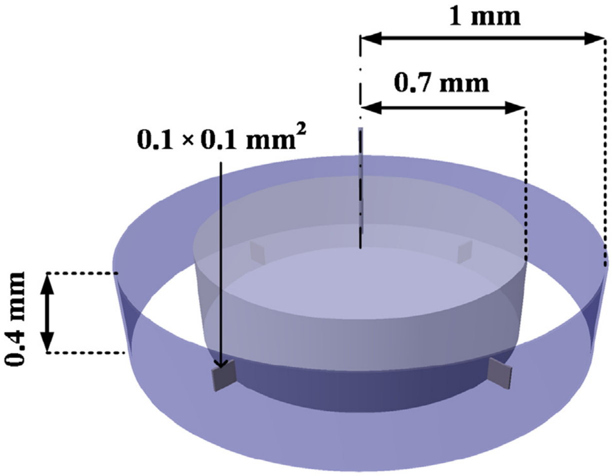

Fig. 2. Schematic of the simulated Couette cell and dimensions.