ASIAN JOURNAL OF PHARMACEUTICAL SCIENCES ■■ (2018) ■■–■■

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/ajps

Original Research Paper

DEM modeling of high shear wet granulation of a simple system

Saurabh Sarkar [a], *Bodhisattwa Chaudhuri* [a,b,*]

[a] *Department of Pharmaceutical Sciences, University of Connecticut, Storrs, CT 06269, USA*
[b] *Institute of Material Sciences, University of Connecticut, Storrs, CT 06269, USA*

ARTICLE INFO

Article history:
Received 30 January 2017
Accepted 4 January 2018
Available online

Keywords:
High shear wet granulation
Discrete element method
Capillary bridge model

ABSTRACT

High shear wet granulation (HSWG) is one of the most poorly understood processes with known difficulties in optimization and scale up. The purpose of the current study is to develop a DEM model which can be applied under dynamic process conditions with high predictive capacity to improve process insight. The DEM model is used to predict agglomeration as a function of impeller speed and liquid addition rate in a high shear wet granulator. The DEM model tracks dynamic formation and breakage of liquid bridges between particles as liquid binder in the system is added, and corrects for the change in material properties as a function of the binder content.

1. Introduction

Granulation, a widely used process in pharmaceutical, agriculture, food and paper industries, is the technique of agglomerating particles together into semi-permanent granules (aggregates) made up of easily distinguishable original particles [1]. This size enlargement process is achieved by various means such as (i) compression techniques: bracketing and extrusion (ii) heat bonding: sintering (iii) drop formation: prilling and spray drying and lastly by (iv) process agitation in the presence of a binder during "wet granulation". In wet granulation, the binder liquid is sprayed onto the surface of a mixed granular bed, resulting in the formation of aggregates as the particles are held together by capillary bridge forces. The granules as formed offer significant improvement over the ungranulated powder in terms of material properties and behavior such as flow, appearance, handling, strength, rate of dissolution while reducing dustiness and segregation. Within the pharmaceutical industry, wet granulation – despite stability concerns with liquid addition, is often resorted to when the formulation displays poor compressibility and flow [2]. However, despite the long history and widespread use of HSWG; the interplay of material, geometric and process variables at different length scales is rather poorly understood which contributes in large parts toward operation on an empirical basis in most manufacturing units [3], especially with regards to end point determination and scale up. Industrial practitioners often use

* *Corresponding author.* University of Connecticut, 69 N Eagleville Rd, School of Pharmacy, Rm 502, Storrs, CT 06269, USA. Tel.: +1 860 4864861.
E-mail address: bodhi.chaudhuri@uconn.edu (B. Chaudhuri).

Peer review under responsibility of Shenyang Pharmaceutical University.
https://doi.org/10.1016/j.ajps.2018.01.001

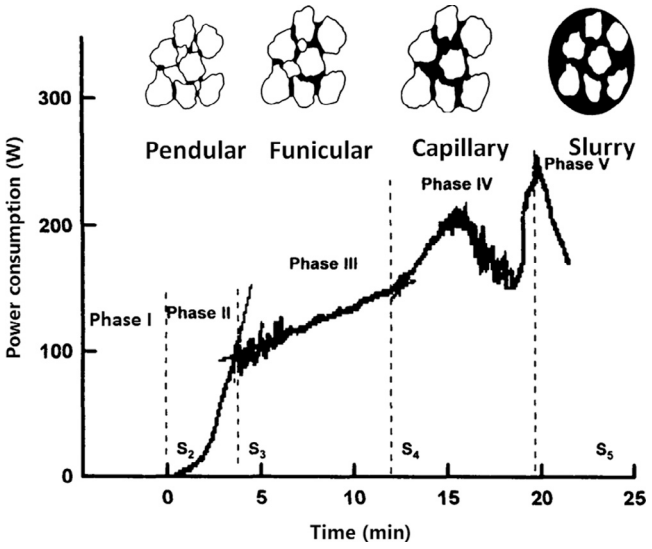

Fig. 1 – Parametric division of a power consumption profile during wet granulation (5,6): (A) Phase I – Powders are moistened, (B) Phase II – Pendular stage: liquid bridges are formed, (c) Phase III – Funicular stage: interparticulate void fills up, (d) Phase IV – Capillary stage: interparticle voids are saturated with capillary bridges, and (e) Phase V – Particles are submerged in bulk liquid.

prior experience for process optimization in a manner akin to an art form, as opposed to relying on strict scientific principles. While user experience is often critical and cannot be undermined in practical situations, hit and trial optimization incurs huge costs from expensive experimental designs. In a fast paced and dynamically changing industrial landscape, process understanding should be improved to comply with Quality by Design initiatives, and enable streamlined and robust process development.

High shear wet granulation (HSWG) can be broadly considered to be interplay of three rate limiting processes: (a) wetting of particles to create nuclei, (b) consolidation and coalescence of these nuclei to give growth and agglomeration, and (c) Breakage and attrition of these nuclei under high shear [4]. The progress of wet granulation can be tracked by following the load on the impeller and generating a power consumption profile. As highlighted in Fig. 1, the general power consumption profiles obtained have been traditionally subdivided into the following phases: (1) a first slight increase in the profile, usually related to nuclei formation and moisture sorption, (2) a rapid increase in the profile slope, due to the attainment of the pendular state (when particles are held by liquid bridges at their contact points), (3) a plateau phase in the profile which indicates the transition from the pendular to the funicular state wherein the particle voids begin to fill with the binder [5,6]. These rate processes must be controlled in order to achieve granules with acceptable properties.

Pharmaceutical manufacturers often face a particular problem where there are many and frequently changing formulations with widely varying properties. Typical drugs have flow and compressibility issues, and are frequently hydrophobic particles as reflected by their large contact angles which do not lend to spreading of liquid over the surface. The energetic barrier is overcome by applying mechanical energy through an impeller in a high shear mixer/granulator. Increased energy input has to be carefully evaluated against potential for reduced physiochemical stability. There's also an issue of scale up, where the stress fields can change and a well performing batch at lab and pilot scale can fail quality testing at commercial scale. This concern is reflected in regulatory guidelines, where a new formulation is expected to demonstrate successful operation at lab, pilot and industrial scales [7].

Efforts to improve process understanding have traditionally been attempted through extensive DOE studies. While these studies have undoubtedly given a lot of insight, there are many mesoscale phenomena which cannot be readily determined. As an example, it is very difficult to attribute local distribution of capillary bridges which determines bulk behavior. It is also difficult to obtain spatially and temporally resolved stress, pressure and velocity distributions especially in a commercial scale granulator which is unique to each case as defined by geometry, process, and formulation. This leads to difficulty in comparing different experiments. It is here that simulations can lend a great advantage. A well calibrated simulation can give fundamental insight not readily obtained by experiments.

Traditionally simulation efforts in the field of HSWG have been dominated by population balance models (PBM) [8–10]. These models have several drawbacks such as development of a coalescence kernel which are often empirical in nature and need multiple fitting parameters. Quite fundamentally, they do not capture the dynamic mesoscale effects which are believed to be transmitted through formation and breakage of discrete capillary liquid between particles. This casts doubts over the ability of PBMs to model dynamic processes [11]. It is often cumbersome to develop governing equations inclusive of process parameters affecting particle size distribution. The discrete nature of capillary bridges and the ability of DEM to model dynamic processing conditions make it an attractive choice to model HSWG. However, a notable disadvantage of this approach is the huge computational cost which is further increased once a first principle capillary bridge model is included. However, it has been well demonstrated that well scaled DEM studies can give good process insight even when using particle sizes higher than those encountered in experimental studies [12]. Some DEM based efforts have thus modeled motion of wet particles, without explicit inclusion of capillary forces [13,14]. Talu et al. [15] included capillary forces to model agglomeration in a 2D system while Lian et al. [16] used a 3D box containing few particles to develop a preliminary understanding of particle agglomeration processes. These studies were done in rather small systems and much process insight cannot be gained. Simulation of larger HSWG systems remains an active area of research within the academia and industry alike. There has been a significant thrust in hybrid modeling approaches, e.g. PBM-DEM approaches are coupled with the idea of developing realistic PBM kernels from DEM simulations. However, capillary bridge forces cannot be modeled in these simulations capillary forces are largely captured by a generic cohesion term. As capillary forces are assumed to be fundamental to HSWG performance, modeling such systems remains an active area of interest and continues to gain momentum, especially with advances in computational hardware.

Please cite this article in press as: Saurabh Sarkar, Bodhisattwa Chaudhuri, DEM modeling of high shear wet granulation of a simple system, Asian Journal of Pharmaceutical Sciences (2018), doi: 10.1016/j.ajps.2018.01.001