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Compositional distributions in multicomponent aggregation

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Abstract

We consider the granulation of two components, a "solute" (the component of interest) and an excipient. We specifically focus on cases such that the aggregation kernel is independent of the composition of the aggregating granules. In this case, theory predicts that the distribution of components is a Gaussian function such that the mean concentration of solute in granules of a given size is equal to the overall mass fraction of solute in the system, and the variance is inversely proportional to the granule size. To study these effects, we perform numerical simulations of the bicomponent population balance equation using a constant aggregation kernel as well as a kernel based on the kinetic theory of granular flow (KTGF). If the solute and excipient are initially present in the same size (monodisperse initial conditions), both kernels produce identical distributions of components. With different initial conditions, the KTGF kernel leads to better mixing of components, manifested in the form of narrower compositional distributions. These behaviors are in agreement with the predictions of the theory of aggregative mixing. We further demonstrate that the overall mixedness of the system is controlled by the initial degree of segregation in the feed and show that the size distribution in the feed can be optimized to produce the narrowest possible distribution of components during granulation.

Keywords: Granulation; Multicomponent; Population balance; Monte Carlo

1. Introduction

Wet granulation is a size enlargement process in which a multicomponent mixture that contains an active compound, an excipient, and a binder, is led to produce an agglomerated powder until desired properties are met with respect to mechanical strength of granules, flow characteristics and composition. Granulation is performed by spraying the liquid binder onto a solid powder in a fluidized bed or other mixing device (tumbling drums, high-shear mixers). Agglomeration is initiated by the wetting action of the binder, which acts as the bonding agent and leads to size enlargement. Depending on the cohesive strength of the coalescing granules, disintegration is also possible, either via breakage of wet granules, or by fracture of dried granules in which the binder has solidified. In the past 15 years there has been considerable activity in the development of simulation tools for granulation (Darelius et al., 2005, 2006; Rajniak et al., 2006; Wang et al., 2006; Blandin et al., 2005; Cameron et al., 2005; Gantt and Gatzke, 2005; Immanuel and Doyle, 2005; Rajniak and Chern, 2004; Tan et al., 2004; van den Dries and Vromans, 2003; Heinrich et al., 2002, 2003; Iveson, 2002; Liu and Litster, 2002; Wang and Cameron, 2002; Adetayo and Ennis, 2000; Pottmann et al., 2000; Talu et al., 2000; Zhang et al., 2000; Cryer, 1999; Masteau and Thomas, 1999; Annapragada and Neily, 1996; Adetayo et al., 1995) and this progress has been summarized in some recent review articles (Cameron et al., 2005; Wang and Cameron, 2002; Iveson et al., 2001). These approaches use increasingly sophisticated models to describe the physics of granule interaction which are then coupled to the population balance equation (PBE) and solved for the size distribution. Virtually all of these studies consider granulation of a single component (univariate PBE), although some work has been done with multivariate systems in which other granule properties such as porosity or surface area has been included in the model.

Multicomponent granulation has received less attention in the literature, in part due to the fundamental questions in one-component systems that remain unresolved but also due to

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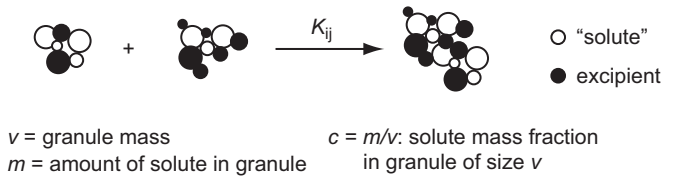

Fig. 1. Schematic of bicomponent aggregation.

the increased complexity of multivariate population balances. Nonetheless, many practical applications involve the granulation of *multicomponent* solids. In pharmaceutical granulation, for example, an active pharmaceutical ingredient (API) is co-granulated with an inert excipient, in preparation for subsequent tablet formation. The purpose of granulation in this case is not only to increase the size of the granules, but also to improve *mixing* of components. Thus, in addition to changes in the size distribution, one needs to know the compositional distribution of components among granules of different sizes. Ideally, all granules should have the same composition, equal to the overall ratio of the bulk amounts loaded in the unit. There are, however, various reasons that lead to inhomogeneous distribution of components within granules. Imperfect mixing can arise from the fluid patterns within the agglomerator. This is more of an issue in high-shear granulation and less so in spray fluidization, which allows for better circulation and contact between the phases. Another consideration is the ability of the binder to effectively coat the granules. Thus, interfacial energy, local curvature and surface roughness of the granules can affect the process in critical ways. In granulation of a single solid, such properties affect the rate of granule growth, and possibly the size distribution, if the morphology of granules and granule/binder interactions vary with size. In granulation of two or more components such interactions have the additional effect of producing potentially severely *inhomogeneous* distribution of components, resulting in poor mixing and even segregation. While co-granulation and blending of components represents a widespread industrial unit operation, there are no general principles to guide practitioners in need of efficient and optimized performance. This paper is motivated by the need to provide such guidance, both in terms of numerical simulation tools but also in terms of theoretical predictions.

To address this problem we simplify the complexities of granulation by focusing on granule aggregation alone. Thus we consider two components, the "solute", representing the component of interest, and the "excipient". Granules of variable composition aggregate via binary events and with rate constant K_{12}, that is a function of granule properties. This mechanism leads to enlargement of granules and distributes the components, as shown schematically in Fig. 1. By focusing on agglomeration alone, we are able to study the fundamental process by which components blend. We call this *aggregative mixing*. Breakage, although present in experimental granulators, will not be considered here. In this paper we make no formal distinction between "aggregation" and "agglomeration", both of which we take to mean "binary attachment of granules". The physics of the aggregation process are included in the binary kernel, K_{12}. This is generally a complex function of granule properties that include size, porosity, wettability and degree of pore saturation by binder; of binder properties, e.g., viscosity; and process variables such as fluid patterns and energy input. The development of appropriate kernels, either empirical or based on first principles, is an area of ongoing research (Liu and Litster, 2002; Cryer, 1999; Adetayo et al., 1995; Sastry, 1975; Hounslow et al., 2001; Kapur and Fuerstenau, 1969). Here we take the approach that the kernel depends on the size (mass) of the granules, and their composition (i.e., amount of solute). With this physical picture in mind, the questions we want to answer are:

- What is the compositional distribution as a function of time and granule size?
- How should blending be quantified?
- How long does it take to reach a certain level of blending?
- Is it possible to improve blending of components in any way?

We base our study on a combination of theory and simulation. Our theoretical analysis is based on our recent formulation of bicomponent aggregation (Matsoukas et al., 2006). Here we focus on the practical aspects of this theory with respect to granulation, while leaving all derivations to the original source. We supplement theory with numerical solutions of the bivariate PBE to obtain further insights on the blending process.

2. Theory of aggregative mixing

In this section we present the mathematical formulation of the problem and outline the main conclusions of the theory whose details can be found in Matsoukas et al. (2006). The distribution in a bicomponent population of granules is described by the bivariate function $F(v,m)$ such that $F(v,m)\,\mathrm{d}v\,\mathrm{d}m$ is the number of granules with mass (excipient + solute) in the range v to $v+\mathrm{d}v$, and mass of solute in the range m to $m+\mathrm{d}m$. For $m>v$ it is understood that $F(v,m)=0$. It is convenient to define two auxiliary distributions. First, we introduce the size distribution, $f(v)$, that gives the distribution of granule sizes (mass) irrespective of granule composition. It is obtained from the bivariate distribution by integrating out the dependence on solute:

$$f(v)=\int_0^v F(v,m)\,\mathrm{d}m. \tag{1}$$

Second, we introduce the compositional distribution, $g(m|v)$, which gives the probability that a granule of size v contains solute in the amount m. This is obtained by normalizing the bivariate distribution by the number of granules with size v:

$$g(m|v)=\frac{F(v,m)}{\int_0^v F(v,m)\,\mathrm{d}m}. \tag{2}$$

It follows from these definitions that the three distributions are related in a simple manner:

$$F(v,m)=f(v)g(m|v). \tag{3}$$

That is, the bivariate distribution is the product of the (unconditional) size distribution times the (conditional) compositional