PARTICLE TECHNOLOGY AND FLUIDIZATION

A Model for the Spray Zone in Early-Stage Fluidized Bed Granulation

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The formation of granules in the spray zone of a top-spray fluid-bed granulation process using a known and uniform drop-size is studied experimentally and theoretically. Experimental results indicate a multi-modal size distribution of spherically-shaped granules. A model is presented to explain this based on the formation of nuclei, and the rapid coalescence of some of these nuclei with droplets or other nuclei in the spray zone of the bed. The model is based on a Bernoulli process and predicts the number frequency of granules to which n droplets have contributed. The model predictions are validated with experimental results for granule size distribution, and the nucleus residence time in the spray zone required to bring model predictions and experimental results into line is shown to be physically plausible by comparing with PEPT tracking of an agglomerate-like tracer particle. © 2006 American Institute of Chemical Engineers *AIChE J,* 52: 2736–2741, 2006
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Introduction

Granulation is a process in which small particles are clustered into larger ones. Most often this is brought about by applying a binder in the liquid phase. Agglomerating the small primary particles of a given powder into larger granules improves the handling characteristics in a number of ways. The flow properties improve, since the cohesion between large particles is less important relative to their weight. The dustiness is reduced, and the bulk density is often increased, giving lower transport costs. The wettability is increased and the compactibility of the powder is often improved.

In fluid-bed granulation, droplets are sprayed onto a fluidized powder to form granules. The spray nozzle is often hung above the bed to spray on the bed surface, and the fluidized-bed vessel is often conical of shape to bring about good circulation and mixing of the bed material.

In granulation a narrow-size distribution is often preferable, since a wide one may cause segregation in the powder in subsequent handling, possibly leading to nonhomogeneity also in chemical composition or concentration of active ingredients.

A significant literature is devoted to the study of fluid-bed granulation and control of the product, that is, the granule size and quality. The factors influencing the product quality include equipment related factors, process related factors and product and formulation related factors. Often the spray is in the form of a fine mist, and the granule properties are sought controlled by influencing the agglomeration and breakup processes in the fluidized bed, and by subsequent classification and recycling of granules.

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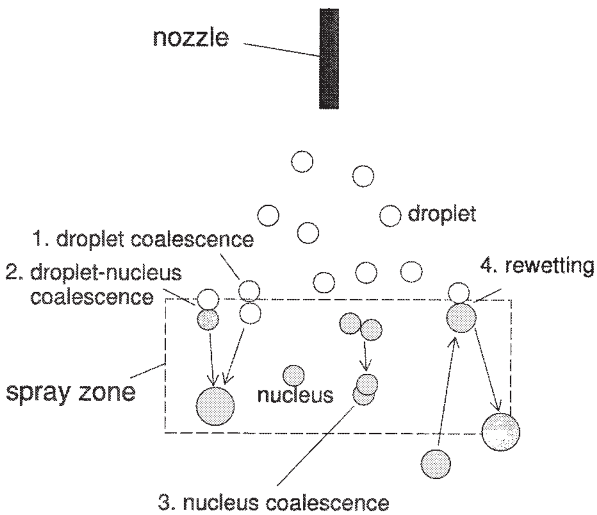

Figure 1. Droplet and nucleus coalescence and rewetting of recycled granules.

However, close and direct control of the granule size upon formation is desirable, "right first time" avoids the need for recycling granules outside the acceptable size range. In this article we are specifically interested in spraying larger droplets onto the bed, and controlling the granule size by the droplet size. Relevant literature for this is works discussing the production of one primary granule from one drop of binder, and relations between spray droplet size and the size of the produced granules. Knowledge in this field is, however, limited.

Waldie[1] formed closely sized granules in a fluid-bed granulator by introducing droplets of known size. He found a relationship between droplet size and primary granule size. He concluded that rupture of granules is not significant if the binder added to the spraying liquid results in enough bond strength between the particles. This result was to be expected, because a fluidized bed is a low-shear device.

Iveson et al.[2] have published a recent, comprehensive review of wet granulation and models predicting the granule size and quality.

Nucleation of granules was recently described by Schaafsma et al.[3] In that article it was suggested that it may be feasible to produce granules by nucleation only (that is, one drop from the spray nozzle forms one granule), thereby, achieving well defined granules. Secondary granule growth in principle leads to a granule size distribution, which is broad and difficult to control.

In this article, we will discuss these issues, looking at the formation of granules formed from the primary powder (nuclei), and at the mechanisms for secondary granule growth in fluidized-bed granulation processes. This secondary growth is by coalescence of droplets and/or nuclei before they leave the spray zone, and is a quick process, which should not be confused with rewetting (a granule which reappears in the spray zone from the bulk bed, where it is wetted again by a droplet) (Figure 1).

The formation of nuclei and coalescence of the just formed nuclei before they leave the spray zone takes place throughout the process, but occurs most prominently in the early stage of the agglomeration process, when there are fewer granules reappearing in the spray zone.[3] A model to describe the dynamics of this coalescence in the spray zone is introduced in this article.

Different types of coalescence may take place in the spray zone:

(1) coalescence of two or more droplets
(2) coalescence of droplet(s) with nuclei
(3) coalescence of nuclei

Objective of this work

We wish, in the light of experimental observations, to formulate a model for the agglomerate-size distribution arising from early-stage fluid-bed granulation, spraying with a precisely known droplet size. In this way we will shed light upon the formation of granules in the spray zone.

Equipment and experimental method

Particular for this project is that the droplets are of a known and precisely controlled size. A special actuator-driven nozzle was, therefore, developed, capable of generating droplets of uniform size. This nozzle and the other equipment is described in detail in Schaafsma et al.[3]

Details of the experimental procedure for producing the granules are given in Schaafsma et al.[3] For completeness, the experimental setup is sketched in Figure 2.

In this article, we concentrate on three of the four types of experiments discussed in Schaafsma et al.[3] They are listed in Table 1.

In all the experiments the fluidized beds of primary particles (α-lactose mono-hydrate 200 mesh powder (the mean size was measured to be 23 μm) from DMV Veghel, Holland) were sprayed for 3–4 min, whereafter, the beds with granules were removed for analysis.

The trend in the pharmaceutical industry is for more potent

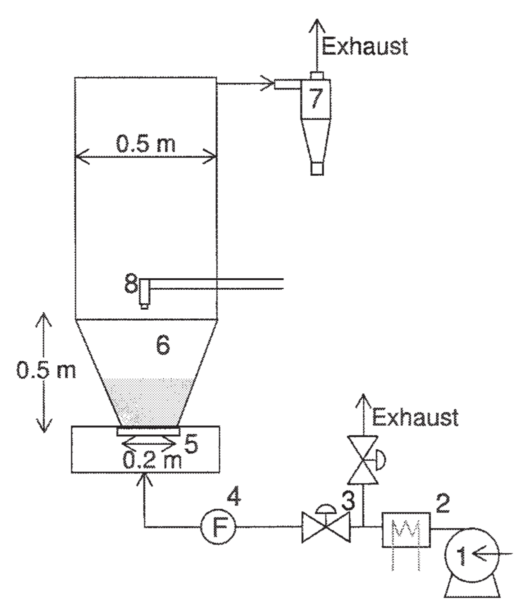

Figure 2. Sketch of the experimental setup.

1. Roots blower; 2. heater; 3. control valves; 4. mass-flow meter; 5. wind box; 6. product chamber; 7. cyclone; 8. actuator-driven nozzle.

Table 1. Droplet Sizes and Liquid Flows

Experiment Identifier	Binder Conc. (w/w)	Liquid Flow (g/min)	Droplet Size (μm)	Density (kg/m^3)
A	13%PVP	4.60	195	1022
B	20%PVP	6.10	226	1028
C	20%PVP	11.57	337	1028

drugs, resulting in tablets—and their precursor granules—consisting mainly of excipients, such as starch, lactose, microcrystalline cellulose or salts, and only a small fraction of the active drug component. Many such excipients have similar physical properties, and lactose was chosen as the bed material to make the experiments representative for a broad range of industrial granulation processes.

We stress at this point that the experiments and the model described in this article focus on the early part of the granulation process, namely the first 3–4 min, where the volume of granules is small compared to the volume of primary powder. An industrial fluidized-bed granulation process will normally be carried out for much longer, about 30 min. A one-drop-one-granule process, as is discussed in the Introduction, would have to be carried out, such that the granule concentration in the bed is low.

Sizing of the primary particles and the granules was done using two techniques: sieve analysis using a series of Retsch sieves, and image analysis using software from Quantimet 520+, Cambridge instruments.

Experimental Observations

Distribution of the spray over the bed surface

The droplet distribution in the spray zone was determined independently by spraying into small cups at a well-chosen level similar to the bed height in fluidized state (Figure 3). The results were similar for all the sprays, and are given in Table 2 as the outer radii of concentric annuli on the surface under the nozzle, and the spray density in these annuli divided by the mean spray density over the entire area. The piezoelectric nozzle, which is able to produce uniformly sized droplets, was operated as described in Schaafsma et al.[3]

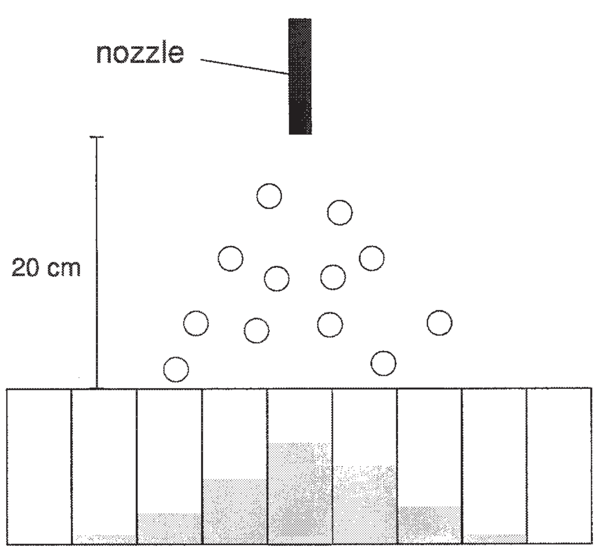

Figure 3. Determination of the radial liquid distribution on the spray surface.

Table 2. Relative Spray Density in Concentric Annuli on the Surface Under the Nozzle

Outer radius (cm)	0.625	1.875	3.125	4.375	5.625
Rel. spray density, ϕ_V (−)	6.61	3.96	1.65	0.549	0.099

Character of the granules

Figure 4 shows the size distribution of granules after experiment A. The distribution is clearly multimodal, as were those resulting from the other experiments. The first mode represents granules formed from one droplet, and each successive mode granules formed from one additional droplet.

Measuring the successive sizes, and setting the volumes out against the number of droplets contributing to the granule, results in a straight line,[4] the slope of which gives the so-called "nucleation ratio," K from

$$\frac{\pi}{6} d_g^3 = K \frac{\pi}{6} d_d^3 n \tag{1}$$

where d_g is the granule diameter at a peak, d_d is the droplet diameter, and n is the number of droplets contributing to the granule. K in general depends on the physical characteristics of the binder liquid and the powder. It was the same, 5.87, in all the present experiments.

It is relatively easy to distinguish a granule formed by quick coalescence in the spray zone, which is what we are studying here, from one formed by agglomeration of granules. The left picture in Figure 5 shows three granules, two formed from one droplet and one—of twice the volume—formed from two droplets by coalescence in the spray zone, all are spherical. To the right an agglomerate formed by later coalescence of two already formed granules is shown, it is clearly nonspherical.

Extensive microscope inspection showed that the latter type of nonspherical agglomerate was a very rare occurrence in the experiments discussed in this article.

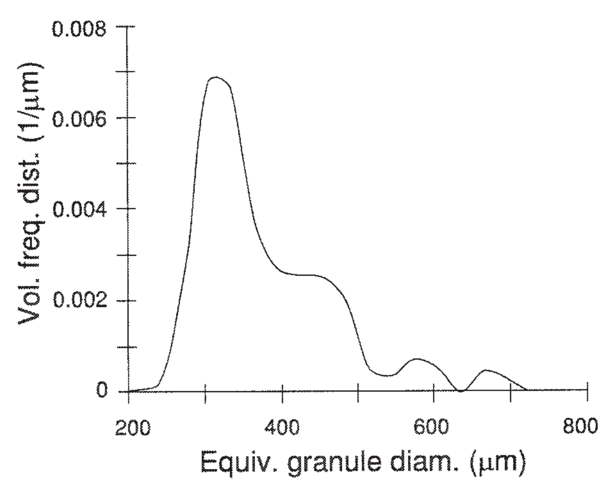

Figure 4. Size distribution of granules after the experiment using 13% PVP binder.

Model

We assume one droplet falling on the particles in the spray zone leads to the formation of a nucleus, which then normally leaves the spray zone and travels through the bed incorporating particles until the fully sized agglomerate is formed. However, in some cases coalescence of a nucleus takes place by n additional droplets impacting on or near it before it leaves the spraying zone. This leads to a larger nucleus and finally to an agglomerate about $n + 1$ times larger by volume or mass than normal granules.

In the following we consider that a nucleus has formed, and calculate the probability of coalescence of this with n, $n = 0$, 1, 2 . . . additional droplets or nuclei while still in the spray zone.

We require an estimate of the size of a nucleus. The formation of a granule and the associated flow of the liquid binder through the pores between the particles has been studied closely both experimentally, and theoretically in the course of this project.[5] It was, among other things, established that the initial liquid flow through a small nucleus/granule is very fast, taking less than 1/10 of a second. Obviously, a nucleus formed in the spray zone will contain some particles, and be larger than the droplet from which it was formed. On the other hand, it is likely to be smaller than the final granule, since the percolation of liquid during the latter stages of granule formation is much slower. In this work, we assumed the nucleus to be formed instantaneously, and we made two alternative assumptions about the nucleus size:

1. The nucleus diameter was assumed to be equal to the droplet diameter, as a minimum possible value, and
2. The nucleus volume was assumed to be double the droplet volume, taking the nucleus to consist of an assembly of particles with the interstitial space (of volume fraction about 0.5) saturated with liquid.[4]

Once a nucleus with diameter d_a is formed, a droplet will impact on it, or form a second nucleus to coalesce with it, if the droplet's centroid hits within a radius d_a of the nucleus. The new nucleus will have twice the volume, and therefore a diameter d_{a2} of

$$\frac{1}{6}\pi d_{a2}^3 = 2\,\frac{1}{6}\pi d_a^3 \Rightarrow d_{a2} = \sqrt[3]{2}\,d_a \qquad (2)$$

Mathematically, the event of a droplet falling so close to a nucleus that it coalesces with it constitutes "success" in a Bernoulli trial. The probability of success is, thus, $\pi d_a^2/A_s$, where A_s is the total area of the spray zone.

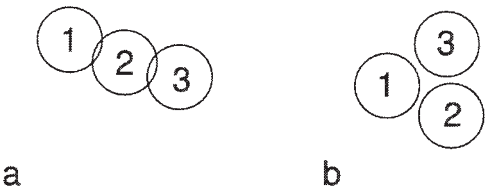

Figure 6. An illustration of how coalescence depends on impact configuration, in case b, droplet 3 (or the nucleus formed by it) does not coalesce with nucleus 1, although it falls closer to it than in case a, where it does coalesce with it.

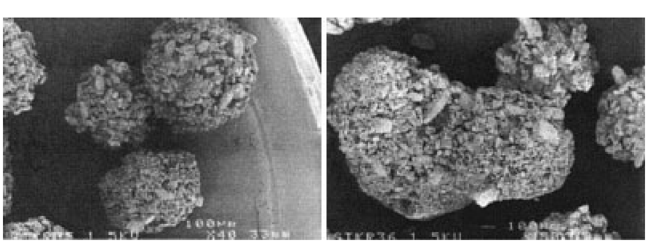

Figure 5. Left: three granules, two formed by one droplet and one from two droplets by coalescence in the spray zone, all are spherical. Right: an agglomerate formed by coalescence of two granules, it is nonspherical.

Similar considerations about the coalescence probability and the resulting nucleus growth can be made for coalescence with additional droplets.

If we for the moment neglect the effect of the nucleus growth due to coalescence, the probability of n hits on a formed agglomerate in N trials is simply given by the binomial distribution

$$P[n] = \binom{N}{n}\left(\frac{\pi d_a^2}{A_s}\right)^n\left(1 - \frac{\pi d_a^2}{A_s}\right)^{(N-n)} \qquad n = 0, N \qquad (3)$$

Call the residence time in the spraying zone of a formed nucleus τ, and the number of droplets per second from the sprayer N_t, then the number of "trials" is: τN_t, and the probability of a nucleus consisting of $n + 1$ droplets becomes

$$P[n+1] = \binom{\tau N_t}{n}\left(\frac{\pi d_a^2}{A_s}\right)^n\left(1 - \frac{\pi d_a^2}{A_s}\right)^{(\tau N_t - n)}, \quad n = 0, \tau N_t \qquad (4)$$

We need, however, to take into account that the nucleus grows as coalescence takes place. As mentioned earlier, a nucleus grows to $d_{a2} = \sqrt[3]{2}\,d_a$ when coalescing with one droplet or nucleus, and in general to $d_{an} = \sqrt[3]{n}\,d_a$ if coalescing with $n - 1$ droplets or nuclei. Whether, for instance, three droplet impacts will form one nucleus or not depends on the geometrical arrangement of their impact as seen in Figure 6.

To take growth into account, at least approximately, we assume that droplet impacts are consecutive, so that for two coalescence events for a nucleus "success" means that the centroids of two droplets fall within an area $\pi[(d_{a2} + d_a)/2]^2 = (\pi/4)(d_{a2} + d_a)^2$ of the nucleus' centroid. The probability of this is approximately given by the binomial distribution

$$P[3] = \binom{\tau N_t}{2}\left(\frac{\frac{\pi}{4}(d_{a2} + d_a)^2}{A_s}\right)^2\left(1 - \frac{\frac{\pi}{4}(d_{a2} + d_a)^2}{A_s}\right)^{(\tau N_t - 2)} \qquad (5)$$

and in general for n coalescence events

$$P[n+1] = \binom{\tau N_t}{n}\left(\frac{\frac{\pi}{4}(d_{an}+d_a)^2}{A_s}\right)^n \times \left(1-\frac{\frac{\pi}{4}(d_{an}+d_a)^2}{A_s}\right)^{(\tau N_t - n)} \qquad n = 0, \tau N_t \quad (6)$$

We note that this is only an approximation, and that there are mathematical difficulties with this. While the probabilities in the binomial distribution, Eq. 4 sum to unity, those in Eq. 6 are each taken from a separate binomial distribution, and do not. In our case they sum to about 1.2. We could normalize, but normalizing at this stage will not bring about any improvement in practice, since normalization is carried out below.

As mentioned, the spray density, and therefore N_t, is not uniform over the cross-section of the spray zone. We, therefore, now consider the five annular areas given in Table 2 separately.

The probabilities in Eq. 6 are approximately equal to the number fractions $x_{N,n}$, of each type of granule obtained, so that $P[n] \approx x_{N,n}$. If the granules are spherical, the volume fractions $x_{V,n}$ of fully grown granules formed from the nuclei in each of the annular areas can be calculated from

$$x_{V,n} = \frac{x_{N,n}\frac{\pi}{6}d_a^3 nK}{\sum_n x_{N,n}\frac{\pi}{6}d_a^3 nK} \quad (7)$$

where K relates the nucleus size to the final granule volume, equalling 5.87, as mentioned, if d_a is assumed to equal d_d. The mass fractions will equal the volume fractions if the densities of all the granules are the same.

Denoting the annular area by subscript i, we thus obtain for the overall mass fraction of n-granules

$$\frac{\sum_i x_{V,n}A_{s,i}\phi_{V,i}}{\sum_n \sum_i x_{V,n}A_{s,i}\phi_{V,i}} \quad (8)$$

Results of the model and comparison with experiments

We know N_t for each annular area in the spray zone from the droplet size, the volumetric flow rate from the nozzle and the relative spray density. The unknown parameter is therefore the nucleus residence time in the spraying zone τ. We can use this as a fit-parameter, and verify if the model gives us the same ratios of n-nuclei as we measure, and whether the absolute value of τ is reasonably consistent with experiment. Moreover, since the flowpattern in the bed during the three experiments is similar, we might expect the optimal values of τ to be somewhat similar between the experiments, and if they are, this supports the validity of the model.

In Figure 7 the measured volume fractions of granules with n droplets contributing for the three experiments labelled A, B and C in Table 1 have been set out as points. The calculated volume fractions according to Eqs. 6 and 7 and expression (Eq. 8) are also shown with lines connecting the calculated points. Clearly, the agreement between model and experiment is very good, and the volume fractions exhibit the qualitative trends predicted by the model.

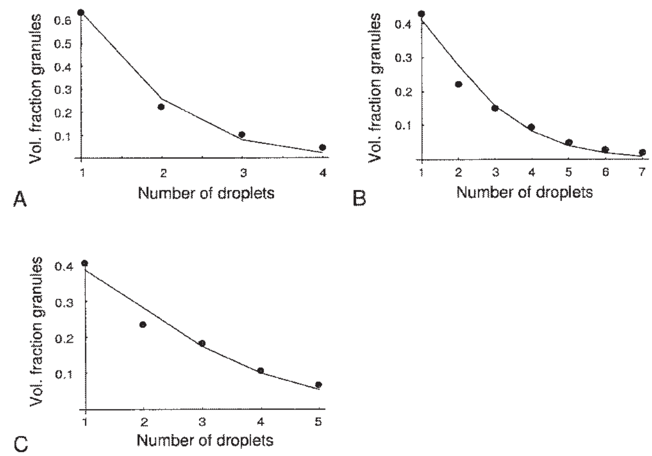

Figure 7. Experimental and calculated volume fractions of granules with *n* drops contributing.

The corresponding values of the granule residence time in the spray zone, which were fitted for minimal squared error between model and experimental data, are 0.084 s, 0.145 s and 0.157 s for experiments A, B and C, respectively.

As mentioned, the assumption that the volume of the nucleus in the spray zone is equal to that of the droplet is perhaps not entirely realistic. It is more likely that the droplet incorporates some particles instantly when impacting on the bed surface. Moreover, it is possible that the droplet may flatten somewhat upon impact. This will all increase the area on which subsequent droplets can impact to coalesce with a nucleus, it will, therefore, increase the probability of "success" in the Bernoulli trials and decrease the value of τ required to fit the data.

In fact, making the second assumption about the nucleus size mentioned in Section Model, the fits between model and experiment remained as good as those in Figure 7, while the spray-zone residence times corresponding to optimal fits were 0.0529, 0.0916 and 0.0988 experiments A, B and C, respectively.

We see in general that the values of τ are similar for the three experiments, as we had expected since the bed dynamics will be similar. In order to estimate whether the absolute values are reasonable, we can appeal to another type of measurement that we carried out in the course of this project: positron emission particle tracking (PEPT) tracking of a tracer particle in the bed. This investigation, which was carried out at the University of Birmingham, is reported separately.[6]

Figure 8 shows the height coordinate of the tracer particle, which was designed to mimick the granules in the bed, as a function of time. Clearly this confirms that a residence time in the spray zone of about 0.1 s, which is indicated in the figure by broken lines, is reasonable. In this it is, of course, difficult to estimate the depth of the spray zone. If the upper-bed surface is well-defined, a depth of the diameter of a just-formed nucleus seems a reasonable estimate, but the bed surface is likely to be somewhat ill-defined.

Conclusions

This study has introduced a conceptual model explaining the granule-size distribution in the initial stages of a top-spray,

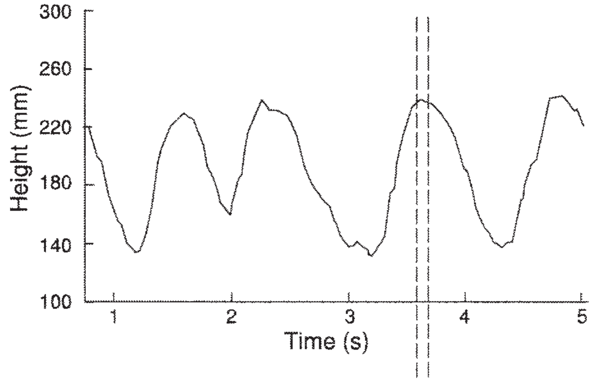

Figure 8. Height coordinate of a granule in the fluidized bed as a function of time measured by PEPT.

fluid-bed granulation process with known and uniform droplet sizes. The model predicts the fast coalescence of droplets and nuclei in the spray zone.

The model, which should be seen as an approximation, estimates the coalescence probability in the spray zone based on a modified binomial distribution, and explains the multimodal granule-size distributions observed experimentally. It reflects correctly the volumetric fractions of each granule class when assuming a nucleus residence time in the spray-zone of the order of 0.1 s, a value which is shown to be physically plausible.

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