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Review Article

To Study the Mechanisms of Granule Formation in the Wet Granulation Process

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ABSTRACT

Traditionally wet agglomeration processes have been considered an empirical art, with great difficulties in predicting and explaining observed behavior. Industry has faced a range of problems including poor product quality control, large recycle ratios, surging and even the total failure of scale up from laboratory to full scale production. However, in recent years there has been a rapid advancement in our understanding of the fundamental processes that control product properties and granulation behavior. This review critically assesses the current understanding of the of wet granulation processes. This review focuses on wetting and nucleation followed by binder delivery and binder dispersion. It also focus on the challenge that now faces us is to transfer these theoretical developments into industrial practice. Standard, reliable methods need to be developed to measure the formulation properties that control granulation behavior. There also needs to be a better understanding of the mixing behavior, flow patterns and impact velocities in different types of granulation equipment.

Keywords: Granulation, nucleation, wetting, granule formation, traditional methods

Introduction

Granulation, also known as agglomeration, balling or palletization, is the process of agglomerating particles together into larger, semi-permanent aggregates (granules) inwhich the original particles can still be distinguished[1]. The wet granulation processes, this is performed by spraying aliquid binder onto the particles as they are agitated in atumbling drum, high shear mixer, fluidized bed or similardevice[2]. The liquid binds the particles together by a combination of capillary and viscous forces until more permanent bonds are formed by subsequent drying or sintering[1].

Granulation is an illustration of particle design. The desired attributes of the product granules are controlled bya combination of formulation design i.e. choosing the feed powder and liquid properties and process design i.e. choosing the type of granulator and the operating parameters. Some of the desired properties of granulated products include: improved flow [3]and handling; reduced dustiness which minimizes losses, inhalation and explosion risks; which facilitates controlled metering; increased bulk density; reduced pressure loss for fluid flow through a packed bed, which is useful in blast furnaces and leach heaps; controlled dissolution rates; and the co-mixing of particles which would otherwise segregate during handling. Granulated products often maintain a high proportion of the surface area of the original particles, which is useful in applications involving catalysts or requiring rapid dissolution[4].

Granulation finds application in a wide range of industries including mineral processing, agricultural products, detergents, pharmaceuticals, foodstuffs and specialty chemicals. In the chemical industry alone it has been estimated that 60% of products are manufactured as particulates and a further 20% use powders as ingredients. The annual value of these products is estimated at US$1 trillionin the US alone[5]. Granulation is a key step in many of these industries. Improper granulation causes problems in down-stream processes such as caking, segregation and poor tableting performance. Granulation has been a subject of research for almost 50years. Some of the earliest pioneering work was performed by Newitt and Conway-Jones [6] and Capes and Danckwerts[7] using sand in drum granulators.

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Since then, a large volume of work has been published studying materials ranging from minerals to pharmaceuticals, granulated in equipment ranging from fluidized beds to high shear mixers. However, in spite of its widespread use, economic importance and almost 50 years of research, granulation has in practice remained more of an art than a science[8].Existing continuous industrial plants frequently operate with recycle ratios as high as 5:1 and suffer from cyclic behavior, surging, erratic product quality and unplanned shutdowns[9]. There is no formal methodology for the design or operation of granulation circuits [10]. Engineers do not predict the granulation behavior of new formulations from their fundamental properties. Neither has it been known how to vary a formulation in order to obtain a desired change in product properties. Expensive and extensive laboratory and pilot scale testing of all new materials is still undertaken. This is a particular problem in industries where there are many and frequently changing formulations with widely varying properties e.g. food, pharmaceuticals and agricultural chemicals. Regulations often require these new formulations to be registered before there is sufficient material available for laboratory and pilot scale granulation tests. Even when pilot scale testing does occur, there is still a significant failure rate during scale up to industrial production. However, we are now close to being able to change this poor state of affairs. In the last decade, there have been significant advancements in our understanding of granulation. We now have a qualitative understanding of the effects of different variables on granulation behavior; and our knowledge is advancing rapidly enough such that we should soon be able to make quantitative predictions based on a sound scientific understanding of the underlying phenomena. In particular, following the pioneering work of Ennis et al.[11], binder viscosity has been recognized as an important parameter in controlling granulation behavior. There has also been a growing awareness of the importance of powder wetting and liquid distribution in controlling granule nucleation and subsequent growth behavior[3]. These recent advances in understanding, together with the fact that there have been no major reviews of this topic in the last 5 years, make it appropriate as we begin a new century to review the extent of our current knowledge and highlight the areas requiring further research[12].

This paper is based on three fundamental sets of rate processes which are important in determining wet granulation behavior. These are: wetting and nucleation; consolidation and growth; and breakage and attrition [13-15]. Once these processes are sufficiently understood, then it will be possible to theoretically predict the effect of formulation properties, equipment type and operating conditions on granulation behavior, provided that these can be adequately characterized. We first give a brief background of the transition to this new view from the more traditional ways of describing granulation. Then the three main sections of this paper discuss in turn the wetting and nucleation, consolidation and growth, and attrition and breakage processes. The current state of understanding in each of these areas is critically reviewed. Deficiencies in understanding are highlighted with suggestions made for future research. The conclusions summarize the findings and major recommendations. This review does not cover equipment design and selection issues or population balance modeling of granulation systems. The interested reader should consult there views referred to above for further information on these topics.

The changing description of granulation processes

Granulation behavior has traditionally been described in terms of a number of different mechanisms, some of which are shown in Fig. 1[7]. However, such a picture of many competing mechanisms is daunting. Quantitative prediction of granule attributes is difficult. In addition, the demarcation between these mechanisms arbitrarily depends on the cut off size between granule and non-granular material, which depends on the measurer’s interests and ability to count small particles. These mechanisms could all be considered as cases of coalescence and/or breakage. It is simply the size of the coalescing particles and the availability of surface liquid which varies from case to case. Hence, it is becoming more common to view granulations a combination of only three sets of rate processes Fig. 2.[15]

a. Wetting and nucleation- In this step the liquid binder is brought into contact with a dry powder bed, and is distributed through the bed to give a distribution of nuclei granules;

b. Consolidation and growth, where collisions between two granules, granules and feed powder, or a granule and the equipment lead to granule compaction and growth; and

c. Attrition and breakage, where wet or dried granules break due to impact, wear or compaction in the granulator or during subsequent product handling.

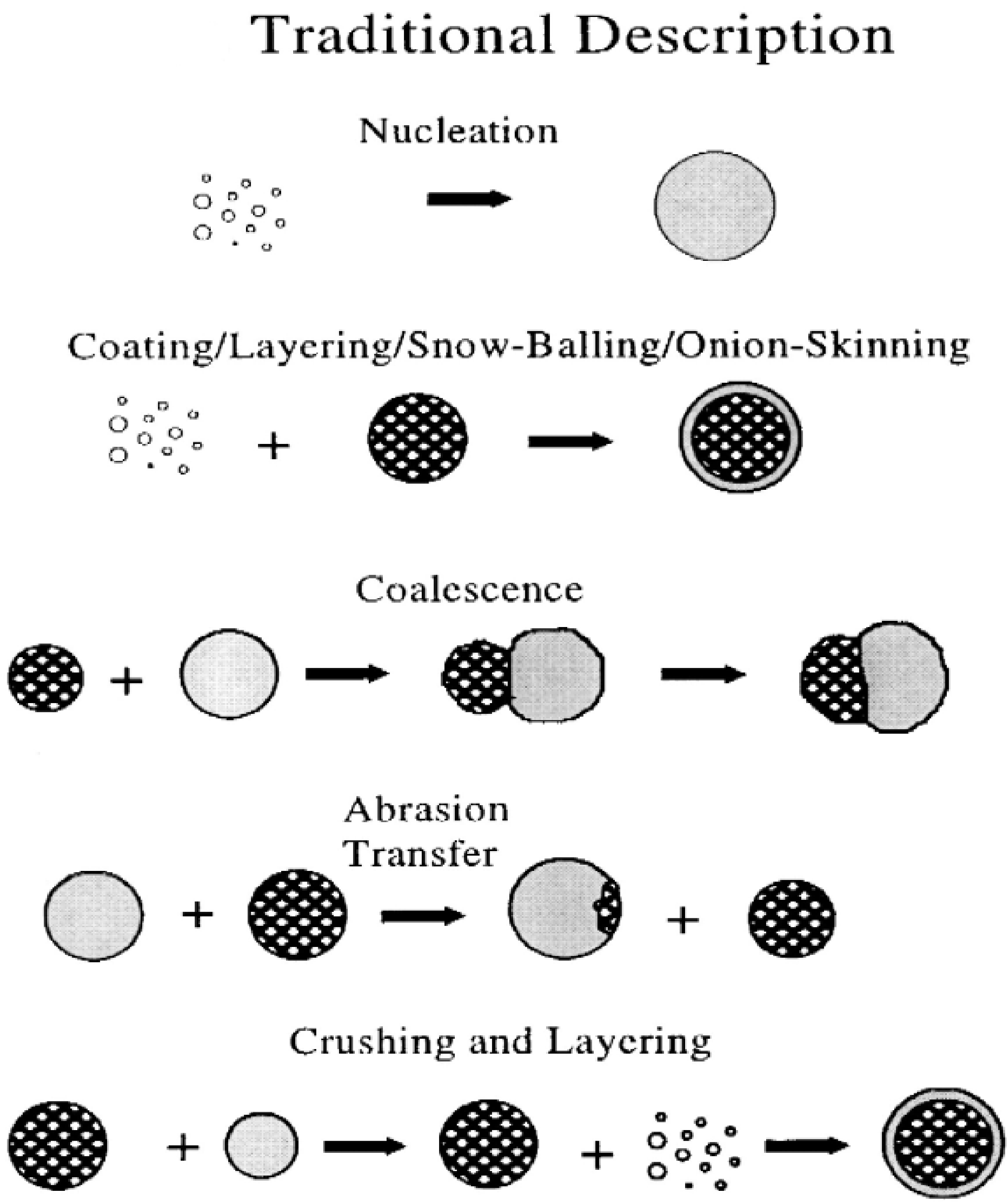

Figure 1: Schematic representation of the granulation process (taken from reference[7])

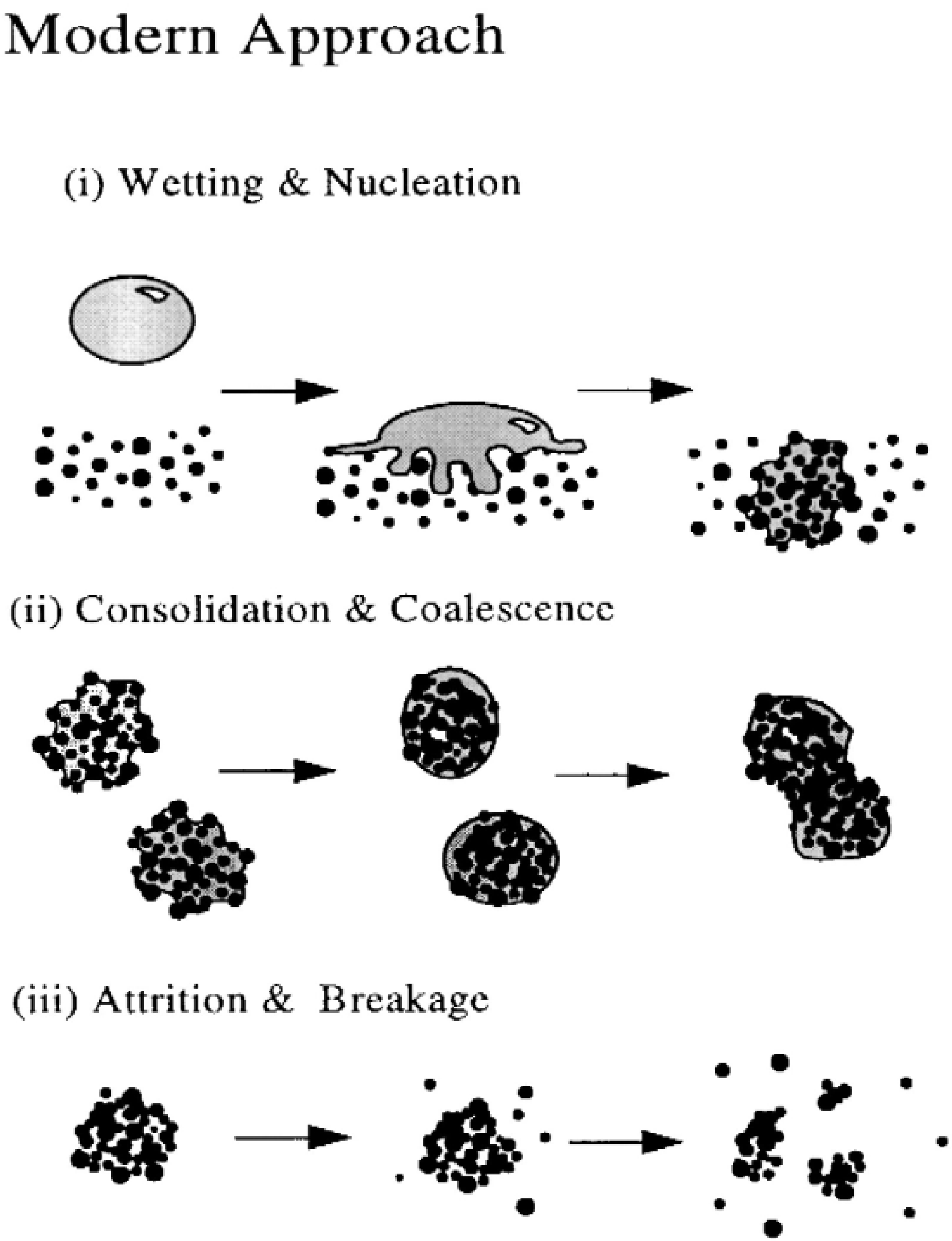

Figure 2: Schematic representation of the granulation process (taken from reference[1])

Wetting and nucleation

Wetting and nucleation is the process of bringing liquid binder into contact with dry powder and attempting to distribute this liquid evenly throughout the powder. It disregarded as an important stage in granulation processes but is rarely identified and separated from other effects such as coalescence and attrition. Many studies have focused on granule growth but have given no details of the binder addition method or the extent of binder distribution. Consequently, our knowledge of the processes controlling nucleation is limited. In this section on wet granulation nucleation and binder dispersion processes, we will focus on the *nucleation zone* also called the *wetting zone[16]*. We define this as the area where the liquid binder and powder surface first come into contact and form the initial nuclei. The size distribution of these initial nuclei depends critically on the processes happening in the nucleation zone, although other processes in the rest of the granulator, such as mechanical mixing, may subsequently alter this distribution. Two processes are important in the nucleation zone. Firstly, there is *nuclei formation*, which is a function of wetting thermodynamics and kinetics[17]. Secondly, there is *binder dispersion*, or effective mixing of the powder and binder, which is a function of process variables i.e. choosing poor combination of powder and binder for example, high contact angle or using an inefficient binder dispersion method for example, high liquid flow-rate, poor spray characteristics both produce a product that is difficult to control and reproduce[3].

Binder dispersion

The degree of binder dispersion indicates the quality of the mixing between the powder and the binder fluid, and is strongly affected by the binder delivery method. In then on-inertial regime proposed by Ennis et al. the rate of nuclei growth is totally dependent on the presence and distribution of binder. Good binder dispersion infers uniform wetting and controlled nucleation. Mort and Tardoshypothesized that the degree of dispersion of the binder is reflected in the product size distribution. If all particles contain an equal amount of binder, their physical properties should be the same and produce a narrow size distribution. If the binder is unevenly distributed, some nuclei will be more saturated than others and their growth will be preferential. This has-been confirmed by other workers [18]in experimental studies where the proportion of Alumps, defined as granules larger than 2 mm, was used as a measure of binder dispersion. All studies were performed in mixer granulators, and several different methods of adding the binder solutions were used. Atomization together with a high impeller speed produced the best binder distribution. The concentration of lumps was highest during the initial liquid addition phase i.e. the lumps were formed during nucleation, not during the growth phase[19].

Binder delivery

There are three main ways to add the binder solution in wet granulation: pouring, spraying and melting. The solution delivery method alters the final granule properties. There are three operating variables in wet binder delivery: drop size distribution, binder flow-rate and the size of the spray zone[20].

Powder mixing

Efficient powder mixing is essential to binder dispersion in all granulators. High powder flux through the spray zone allows more uniform distribution of the powder and the binder fluid by carrying local patches of high binder content out of the nucleation zone and providing a constant supply of fresh powder into the nucleation zone. However, mixing is a difficult variable to manipulate[21].

Conclusions

In the last decade, substantial progress has been made in understanding and quantifying the mechanisms that control granule attributes. Controlling dimensionless groups for each of the mechanisms are established and in some cases, regime maps are becoming available. Although still developing, this research is ready to be applied in industry for the design and scale up of granulation processes and products. The first step in design and scale up is to understand which mechanisms are controlling the process.

Conflict of Interest

The author reports no conflict of interest.

Reference

1. Ennis, B. and J. Litster. Particle size enlargement. R. Perry, D. Green (editors). Perry's Chemical Engineers' Handbook, 7th edition, McGraw-Hill, New York. 1997;20-56.
2. Mote, P.B., et al. Formulation and evaluation of sustained release matrix tablets of anti-asthmatic agent using various polymers. Journal of Drug Delivery and Therapeutics. 2013;3:
3. Chaudhari, S.P. and R.H. Dave. To prepare and characterize microcrystalline cellulose granules using water and isopropyl alcohol as granulating agents and determine its end-point by thermal and rheological tools. Drug

Development and Industrial Pharmacy. 2015;41:744-752.
4. Mahida, M.V. and M. Gupta. Immediate release tablet of antihypertensive drug olmesartan medoxomile. Journal of Drug Delivery and Therapeutics. 2013;3:
5. Ennis, B. Unto dust shalt thou return. Powders and Grains. 1997;97:13-23.
6. Newitt, D. and J. Conway-Jones. A contribution to the theory and practice of granulation. Trans. Inst. Chem. Eng. 1958;36:
7. Sastry, K.V. and D. Fuerstenau. Mechanisms of agglomerate growth in green pelletization. Powder Technology. 1973;7:97-105.
8. Reddy, R. Formulation and Evaluation of Release of Trimetazidine Dihydrochloride HPMC Matrix Tablet. Journal of Drug Delivery and Therapeutics. 2012;2:
9. Marzo, L. and J. Lopez-Nino. Powdered or granular DAP. Paper read before the Fertiliser society of London. 1986;
10. Sastry, K. *Advances in the modelling and simulation of granulation circuits*. in *First international particle technology forum, Denver, USA*. 1994.
11. Ennis, B.J., J. Li, and P. Robert. The influence of viscosity on the strength of an axially strained pendular liquid bridge. Chemical Engineering Science. 1990;45:3071-3088.
12. Charumanee, S., et al. THE ROLES OF CHANNELING AGENTS ON THE DRUG RELEASE FROM WAX MATRIX TABLETS PREPARED BY MELT GRANULATION. Journal of Drug Delivery and Therapeutics. 2016;6:51-58.
13. Mort, P. and G. Tardos. Scale-up of agglomeration processes using transformations. KONA Powder and Particle Journal. 1999;17:64-75.
14. Butensky, M. and D. Hyman. Rotary drum granulation. An experimental study of the factors affecting granule size. Industrial & Engineering Chemistry Fundamentals. 1971;10:212-219.
15. Tardos, G.I., M.I. Khan, and P.R. Mort. Critical parameters and limiting conditions in binder granulation of fine powders. Powder Technology. 1997;94:245-258.
16. Schaafsma, S.H., et al. Effects and control of humidity and particle mixing in fluid-bed granulation. AIChE journal. 1999;45:1202-1210.
17. CH, S. and S. Debnath. FORMULATION & EVALUATION OF LACTIC ACID BACILLUS & ZINC SULPHATE FAST DISPERSIBLE TABLETS. Journal of Drug Delivery and Therapeutics. 2012;2:
18. Holm, P., T. Schaefer, and H. Kristensen. Granulation in high-speed mixers Part VI. Effects of process conditions on power consumption and granule growth. Powder Technology. 1985;43:225-233.
19. Mohan, L.S., K.K. Rao, and P.R. Nott. A frictional Cosserat model for the slow shearing of granular materials. arXiv preprint cond-mat/0107563. 2001;
20. Mohan, L.S., P.R. Nott, and K.K. Rao. Fully developed flow of coarse granular materials through a vertical channel. Chemical Engineering Science. 1997;52:913-933.
21. Boateng, A. Boundary layer modeling of granular flow in the transverse plane of a partially filled rotating cylinder. International Journal of Multiphase Flow. 1998;24:499-521.