

Book Review

Handbook of Pharmaceutical Granulation Technology

D.M. Parikh (Ed.), Marcel Dekker, Inc., New York, 1997, 536 pages, ISBN 0-8247-9882-1.

This handbook contains 16 chapters, written by 22 scientists mainly from industry, but also academia. These chapters could roughly be divided into six domains, namely (1) introduction and theoretical aspects of granulation (Chapters 1 to 4), (2) spray-drying as an alternative technique (Chapter 5), (3) different granulation techniques (Chapters 6 to 12), (4) granule size reduction (Chapter 13), (5) characterisation of granules (Chapters 14 and 15), and (6) regulatory issues. It therefore covers a wide range of topics.

In the 'Introduction', written by the editor, the author emphasises the need for such a book and tries to put granulation into perspective with other possibilities to manufacture solid dosage forms, mainly direct tableting. The author explains the need for efficient granulation procedures in the light of the current trend to reduce cost dramatically in the pharmaceutical industry. The chapter is well written, but the relevance of the recent mergers of pharmaceutical companies, which are listed, is not made clear. In the 'Theory of Granulation' (Chapter 2), the authors use a helpful approach to visualise theoretical aspects of granulation employing schematic drawings and equations when necessary. However, some of the presented facts should be looked at critically. For example, the strength of agglomerates is discussed solely on the basis of Rumpf's model, which is outdated.

Its discussion should have been undertaken in the light of modern fracture mechanics, pointing out the severe shortcomings of Rumpf's model. The units in, for example, equation (12) should have been updated into SI-units. Also, in an agglomerate of 40% porosity it is unlikely that the distance of separation between the particles is only 2.5 nm, and it is known from Deryaguin's and Kendall's work, that the distance of separation of ordinary powder particles will never be less than 20–25 nm due to surface asperities. The discussion of agglomerate strength in this chapter leads also to some repetition with respect to Chapter 14, whose objective was to discuss such issues. The information provided in Chapter 3 ('Drug Substance and Excipient Characterization') is generally very disappointing. Incorrect nomenclature, introduced by the quotation of only secondary references, dominates, for example, the section about particle shape. For example, the deficiencies of laser light scattering particle size measurements are well known, but are not mentioned by the authors, except with respect to dry powder sample measurements. The section about techniques of evaluating the specific surface area of powders will not provide any help to those readers, who have no knowledge of the subject, and cannot satisfy any reader with knowledge and experience. Disintegrants are named as excipients for granulation. However, how these perform after, for example, a wet granulation has not been mentioned. The text suggests that all disintegrants can withstand such a procedure without a loss of disintegration efficiency, but this is far from reality. In Chapter 4 ('Binders and Solvents'), the au-

thors discuss binders and solvents used for granulation comparing their advantages and disadvantages, and evaluating factors, which influence the binder efficiency critically in the view of literature reports.

In the Chapter 'Spray Drying as an Alternative Granulation Technique' (Chapter 5), the author provides a short review of the use of this technique in the pharmaceutical industry. It follows a comprehensive and well organised description of the principles of its use and the equipment for general use. The section 'Some special systems' covers only one topic, namely fluidized spray drying. At times the advantages claimed for spray drying over conventional techniques appear inflated. One should remember that this technique is not cheap, and the development of procedures and formulations is more time consuming than for conventional granulation techniques. The author eventually admits this by suggesting that such developments should be contracted out to the manufacturer of the equipment or to custom-processing companies. However, such a procedure is certainly in conflict to confidentiality criteria of several pharmaceutical companies.

In the Chapter 'Roller Compaction Technology' the author has collected a large number of references, and he provides a considerable amount of useful and important information. However, he has not arranged his account in a manner that is easy to understand. For example, in the section 'Instrumentation principles', factors influencing roller compaction are discussed, but the reader does not learn about how to instrument a roller compactor. One instrumentation possibility, the use of acoustic signal imaging, is mentioned in later sections. Other section headings appear similarly dubious. In general, the chapter makes the reader aware of the influence factors to be controlled in a roller compaction process, but questions with respect to the application of the technique remain unanswered. The sections about scale-up and validation, however, are informative. Chapter 7 ('High Shear Mixer Granulators') is, in contrast, very organised and delightfully written. The author starts by explaining the equip-

ment, provides a comprehensive theory about the formation of granules in these systems, discusses process variables and provides the necessary information on scale-up. The enormous amount of information contained in this chapter is not only well presented, but has been used to draw conclusions valuable to the users and also provides guidance to choose equipment and how to develop the process/formulation. In Chapter 8 ('Low Shear Granulators'), the authors draw their special attention to the rotating shape granulators. A concise literature review is provided, and the influence factors on this granulation technique are discussed. However, the chapter would have benefited if the other low shear granulators had been evaluated in the same manner. The scale-up has been discussed rather from the view point 'What has been done?' than 'How could one do it?' Chapter 9 ('Batch Fluid Bed Granulation') is very well organised and contains lots of useful and important information. When describing the equipment, attention is not only drawn to 'standard variations' between equipment, but also modifications necessary with respect to the area of use, e.g. cold or tropical climate, are discussed. Guidelines are provided to choose the right equipment and the correct process parameters combining theory and practical applications in a comprehensive manner. The scale-up feasibilities are well described, both for the equipment and product-related factors. A case study helps to further enhance the procedures of a scale-up task. The reference section is, however, extremely untidy. At times, the titles of the papers are missing, and page numbers provided vary from none to both first and final page number. In Chapter 10 ('Single-Pot Processing'), the authors provide a very concise but informative text on drying technologies used in single-pot processors, linking theory and practical situations. The sections on scale-up and validation provide a practical approach to solve related problems. In Chapter 11 ('Extrusion-Spheronisation as a Granulation Technique'), the author could have emphasised the differences in the excipients, granulation liquids

and amount of liquid used during wet massing rather than the equipment, much of which had already been described in previous chapters. The description of the extruders and spheronizers is comprehensive, although little inspired by scientific depth. The references are sometimes untidy; for example, in the text it reads Lender... [45] and in the references it reads Linder..., but the real reference would read Lindner... The chapter fails to provide information on the evaluation of the product quality and its relation to dosage forms. Chapter 12 ('Continuous Granulation') provides a good introduction into the problem of how to choose between a batch granulation or a continuous granulation procedure. The description of the equipment takes the information from previous chapters into account and focuses on the main differences and important technical details of continuously operating equipment.

The heading of Chapter 13, 'Sizing of Granules', is misleading. It implies the discussion of particle size analysis techniques for granules, but it actually describes methods of size reduction of granules by means of milling. The authors have made a good attempt to introduce physical properties in relation to grinding of powders. Missing, however, are the theoretical approaches to comminution provided by Rumpf (1973) and Kendall (1978). Guidelines of how to choose the best milling technology are provided, and two types (hammer mill and Comil) of apparatus are explored in more detail with respect to process variables and related product properties. Some inconsistency arises when the oscillating and rotary granulators as well as extruders are discussed as mills.

Chapter 14 ('Granulation Characterization: Methods and Significance') overlaps greatly with Chapter 2. Particle morphology does not only comprise particle shape. Granule strength is much better explored in Chapter 1. There are methods of direct evaluation of the tensile strength of granules available (Shipway and Hutchings, 1993), but they are not mentioned in this chapter. The author recommends the replacement of tapping by vibration to assess the maximum bulk density. This is in conflict with

the presence of interparticulate adhesion and friction, which must be overcome to truly obtain the maximum bulk density of a powder. Many related models (Carr's compressibility index, Kawakita equation) are presented without appropriate interpretation or physical explanation and with reference only to secondary literature. The description of the compaction process does not take the particular properties of granules into account and how they respond to pressure, and does not reflect the current wisdom about physical processes occurring during tableting. This is also true for the characterisation of tablets. It is amazing that the author defines crushing strength and tensile strength at the beginning, but later discusses literature reports on these parameters as 'tablet hardness', a physically incorrect terminology. In general, the second half of the chapter presents a collection of literature findings without discussing them, although the aim of the chapter and book was to show how these methods can be used to develop granulation procedures and formulations. In Chapter 15 ('Bioavailability and Granule Properties'), the author provides a short introduction into the subject and objectives of bioavailability assessments, and the granulation process as an influence factor on bioavailability is comprehensively explored.

To write the last chapter ('Regulatory Issues in Granulation Processes') was certainly a difficult task in the light of still developing and changing regulations. The Scale-up and Post-Approval Changes (SUPAC) guidelines are described with balanced detail, and some other guidelines mentioned could have been explained in a similar manner. The validation of the granulation process is also described with necessary details.

The overall feeling of the book is that it was well conceived conceptually, but that at times editorial guidance was missing, leading to some overlapping and some inconsistency in style. The latter is particularly obvious in the reference sections of each chapter. Some authors provided titles, others only for some papers, and page numbers are not always given as first to last page. It appears as though all authors

agreed to use 'hardness' when describing the strength of agglomerates, although this is in conflict with physical principles. On the whole, however, most authors developed their chapter on a scientific basis. The book can be recommended for scientists working in research and development, whose work involves granulation technology and who would like to have a comprehensive review of the field.

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References

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