European Journal of Pharmaceutics and Biopharmaceutics 80 (2012) 209–216

Contents lists available at SciVerse ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

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

Research paper

A protocol for the classification of powder compression characteristics

Josefina Nordström [a,*], Ingvild Klevan [b], Göran Alderborn [a]

[a] Department of Pharmacy, Uppsala University, Uppsala, Sweden
[b] Department of Pharmacy, University of Tromsø, Tromsø, Norway

ARTICLE INFO

Article history:
Received 23 May 2011
Accepted in revised form 12 September 2011
Available online 17 September 2011

Keywords:
Classification system
Compression parameters
Heckel
Kawakita
Particle mechanical properties
Powder compression

ABSTRACT

In this paper, a structured protocol for powder compression analysis as a test to assess the mechanical properties of particles in a formulation development programme is presented. First, the sequence of classification steps of the protocol is described, and secondly, the protocol is illustrated using compression data of six powders of two model substances, sodium chloride and mannitol. From powder compression data, a set of compression variables are derived, and by using critical values of these variables, the stages expressed during the compression of the powders are identified and the powders are classified into groups with respect to the expression of particle rearrangement, particle fragmentation and particle plastic deformation during compression. It is concluded that the proposed protocol could, in a satisfactorily way, describe and distinguish between the powders regarding their compression behaviour. Hence, the protocol could be a valuable tool for the formulation scientist to comprehensively assess important functionality-related characteristics of drugs and excipients.

1. Introduction

In order to effectively and rationally develop pharmaceutical dosage forms, an understanding of the properties of pharmaceutical materials, and how material properties can be changed or modulated to improve their functionality during manufacturing and use, is critical. As a consequence, the development scientist needs access to several methods of analysis during the formulation work to comprehensively assess important functionality-related characteristics of drugs and excipients [1,2].

The mechanics of a solid is a physical characteristic of relevance for the behaviour of particles during processing and for the quality and properties of formulated products [3]. Methods or procedures by which mechanical properties of particles can be characterized have, compared to the characterization of other functional properties, hitherto attended more limited interest in pharmaceutical science. In the literature, three approaches are reported by which mechanical properties of particulate matter are characterized: Uniaxial confined compression of a powder, testing of compacts (e.g. indentation and bending tests) and testing of single particles (e.g. compression loading and nanoindentation). An example is the use of nanoindentation as a means to characterize single-particle properties, which was suggested to be a valuable method in the early development phase [4]. One of the few comprehensive procedures to characterize and classify mechanical properties has been suggested by Roberts and Rowe [5], a procedure in which two of the approaches were combined, i.e. compact testing and powder compression. Another pertinent example of a comprehensive procedure has been developed by Hiestand and Smith [6], using compact testing as a means to derive a series of indices of tableting performance.

Powder compression is an attractive method of analysis from both a statistical and a material consumption perspective, i.e. a large number of particles are used in the test but the total amount of material required is low compared to mechanical characterization by compact testing. Furthermore, by powder compression, great variations in properties of the particles with respect to their size, shape and ability to form compacts can easily be handled. It is, however, important to recognize that variations in loading condition during compression [7–10] as well as in the data handling procedure, e.g. the importance of setting a valid starting point for the compression [11], may affect the value of the derived compression parameters. Thus, the standardization of experimental variables and data handling procedure is critical for the reproducibility of powder compression data. In addition, using compression equations based on tablet porosity data represents a special problem when analysing the compression properties of granulated particles [12].

In some earlier papers [13–15], a classification system for describing compression properties of powders, based on the use of some common compression parameters, was suggested. In this study, we bring together conclusions and considerations from these studies into a structured protocol which may enable the use of powder compression as a test to identify the

* Corresponding author. Department of Pharmacy, Uppsala University, Box 580, SE-751 23 Uppsala, Sweden. Tel.: +46 18 4714550; fax: +46 18 4714377.
E-mail address: josefina.nordstrom@farmaci.uu.se (J. Nordström).

0939-6411/$ - see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejpb.2011.09.006

functionality-related characteristics of particles in a formulation development programme. The intention with this paper was thus firstly to present such a protocol and, secondly, to illustrate the sequence of classification steps of the protocol using compression data of six powders of two model substances, sodium chloride and mannitol.

2. Theoretical considerations and overview of protocol

2.1. Stage models of powder compression

The possibility to rationally use compression data as a means to characterize material properties must be based on a mechanistic conception of the compression process. It is commonly assumed in the literature that powder compression, i.e. the compression of a powder up to maximum applied pressure ignoring densification and elastic recovery with reduced pressure (unloading), involves processes that occur in distinct stages [16,17]. This conception is based on the hypothesis that within a certain range of compression pressure, one specific physical process is controlling the rate of compression (i.e. the rate of change in compact density or porosity with pressure). Powder compression is thus viewed as a process occurring in a sequence of consecutive stages, each stage representing a certain part of the total pressure range used. The physical processes involved in the different stages are normally described on the particulate scale with the underlying objective that the analysis of the compression process gives an opportunity to extract information about the mechanical properties of the material (i.e. the particle). However, several interpretations of this sequence model exist in the literature in terms of the number of regions involved in the compression process as well as the sequence of physical processes. The variation in number of regions is probably the result of, firstly, the great variation in materials used in different industrial branches and, secondly, different opinions regarding to what extent a mechanistic model can be refined in terms of the number of identifiable stages.

A complete survey of the literature is not given here but important examples of formulations of the sequence model follow. Heckel [18] identified two stages, i.e. particle rearrangement followed by particle deformation, and he concluded that they corresponded to the stages suggested earlier by Seelig and Wulff [19], who were the first to suggest that the compression process comprises distinct stages with associated mechanisms [20]. James [16], also using metal powders, suggested three stages, i.e. interparticle movement, particle elastic and plastic deformation and finally compact contraction due to elastic deformation. Sun and Grant [21] suggested principally the same three regions for pharmaceutical powders, i.e. particle rearrangement (low-pressure region), particle plastic deformation (medium pressure region) and tablet elastic deformation (high-pressure region), while Duberg and Nyström [22] suggested two regions in sequence in the powder densification process, i.e. particle fragmentation followed by particle elastic and plastic deformation. Johansson and Alderborn [12] presented a sequence of three stages during the compression of granulated particles, i.e. granule repositioning, local granule deformation and finally bulk granule deformation and densification. This sequence of regions was later modified by Nordström et al. [23] by adding granule cracking as a rate-controlling mechanism in the low-pressure region, giving the following sequence of stages: granule rearrangement, granule cracking and finally, granule plastic deformation and densification.

Alternative views to a sequence model are also presented in the literature. It has been suggested that the compression process cannot be resolved into a sequence of distinct stages, each controlled by a single mechanism, but should be conceptually understood as a process where different mechanisms are active simultaneously and the sum effect of the mechanisms controls the rate of compression [24]. Sonnergaard described two mechanisms operating simultaneously, particle fragmentation and particle plastic deformation. Morris and Schwartz [25] discussed also a single compression region from punch-to-powder contact to maximum pressure in which several mechanisms could be expressed. Another alternative view was presented by Holman [26], who discussed regions of the compression process in terms of the structure of the formed compact rather than the mechanism of response of the powder that caused densification. Based on this percolation approach, Holman divided the compression process in up to four stages denoted as powder, flexible coherent particulate compact, rigid coherent particulate compact and continuum solid body.

It is concluded here that the sequence model is a dominant conception in the literature and the following is an attempt to summarize the literature: The powder compression process starts with a particle rearrangement process and ends with a stiff body. Particle plastic deformation is a dominant mechanism over a wide range of compression pressures, and this mechanism has also been in focus of modelling ambitions, e.g. Frenning et al. [27]. For granular solids, densification may occur in parallel with the granule plastic deformation. Finally, particles may crack and fragment into smaller particles, a process that often occurs initially in the compression process and precedes plastic deformation. This summary represents thus an up to four-stage model, which is consistent with the summary proposed earlier by Denny [28]: Particle rearrangement, particle fragmentation, particle plastic deformation and finally, elastic deformation of a stiff compact. Important to add is that the number of mechanisms and thus stages that in practice is expressed by a given powder varies between powders and depends on particulate and mechanical properties of particles and the pressure range (i.e. the degree of powder densification) used [23]. The four-stage model is from a system perspective characterized by two transition points. The first is the transition from a flowing (rearranging) into a cohesive powder with locked particles, i.e. the powder jamming transition [29,30]. The second is the transition from a plastically deforming compact into an elastically deforming compact.

2.2. Selection of compression parameters

In order to use powder compression as a test method, a procedure must be used that enables firstly the identification of the number of stages that is expressed during loading and, secondly, the derivation of measures of to what extent the underlying mechanisms of compression are expressed. An important aspect of such measures is that they should provide information about the fundamental mechanical characteristics of particles, i.e. to what extent the particles are prone to fracture and deform plastically while loaded. In a series of papers [13–15], a strategy for such a procedure has been outlined that can potentially satisfy these requirements. This strategy is based on the use of compression parameters as indicators of compression mechanisms followed by the identification of stages of compression in terms of their relative importance for the overall appearance of a compression profile.

The protocol suggested in this paper is based on, albeit not restricted to, three compression equations. These three equations have been selected since it has been reported that they include parameters that are considered to be defined in terms of physical significance, i.e. the equations often denoted the Kawakita and Lüdde [31], the Heckel [18,32] and the Shapiro general compression equation [33]. Regarding the Heckel equation, it seems to be a widespread opinion that the Heckel parameter (often denoted the yield stress or yield pressure) is an indication of the plasticity or hardness of the particles. This assumption originates from the