Available online at www.sciencedirect.com

SCIENCE DIRECT®

European Journal of Pharmaceutics and Biopharmaceutics 63 (2006) 270–277

European Journal of Pharmaceutics and Biopharmaceutics

www.elsevier.com/locate/ejpb

Research paper

Quantification of the compactibility of pharmaceutical powders

Jørn M. Sonnergaard *

Department of Pharmaceutics and Analytical Chemistry, The Danish University of Pharmaceutical Sciences, Copenhagen, Denmark

Received 21 June 2005; accepted in revised form 15 October 2005
Available online 6 May 2006

Abstract

The purpose of this study is to investigate and to quantify the compactibility of pharmaceutical powders by a simple linear relationship between the diametral compressive strength of tablets and the applied compaction pressure. The mechanical strength of the tablets is characterized as the crushing force normalized with the dimension of the tablet and termed the specific crushing strength, SCS. The proposed model: $\mathrm{SCS} = \mathrm{Cp} * P + b$ estimates the slope of the regression line Cp as a dimensionless compactibility parameter and is reported with the corresponding standard deviation S_{Cp}. The linear region of the compactibility profile is selected using the 95% predictability limits bordering the regression line. Eleven different materials were tested and acceptable fits to the linear model were observed in all cases. The ability of the model to discriminate between the investigated materials is excellent, in cases where the difference may be difficult to show a simple *t*-test is used as an inference tool. No difference was found between lactose tablets of different masses (500 and 1000 mg). A relationship between the compactibility parameter and the compressibility characterized by the Walker coefficient is demonstrated.

Keywords: Compactibility; Methodology; Mathematical models; Specific crushing strength; Walker equation; Compressibility

1. Introduction

The compaction properties of pharmaceutical powders are for clarity separated in two distinct terms, i.e. the compressibility as the ability of the powder to deform under pressure and the compactibility as the ability of a powder to form coherent compacts. While the former property has been subject to numerous investigations including development of mathematical descriptive models the latter is seldom in focus although this characteristic should be more relevant and interesting from a practical pharmaceutical point of view. With the growing interest in the functionality of excipients and the related test methods, there is obviously a need for a simple and standardized measure of the compactibilty. A tool is needed where decision-making on differences or similarities between powders in relation to the compactibility is achievable on an objective and statistically established basis.

The mechanical strength of a single compact is easily determined as the force needed to crush the tablet diametrically. As this crushing or breaking force is expected to be dependent on the tablet dimensions it is reasonable to normalize the force to a specific strength by division with the dimensions of the tablet, i.e. the cross-sectional area [1]. To avoid the general disorder in the terminology where force, strength and hardness are mixed up and to emphasize that the strength is normalized the term specific crushing strength (SCS) will be used. The specific crushing strength in units of pressure (Pa) is for flat-faced cylindrical tablets defined as

$$\mathrm{SCS} = \frac{F}{Dh}, \tag{1}$$

where F is the crushing force and D and h are the diameter and height of the cylindrical tablet. The tensile strength (TS) is defined as [2]

$$\mathrm{TS} = \frac{2F}{\pi Dh}. \tag{2}$$

* Department of Pharmaceutics, The Danish University of Pharmaceutical Sciences, Universitetsparken 2, DK-2100 Copenhagen, Denmark. Tel.: +45 35 306 271; fax: +45 35 306 031.
E-mail address: jms@dfuni.dk.

0939-6411/$ - see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejpb.2005.10.012

The specific crushing strength deviates mathematically from the well-known indirect tensile strength only by the factor $2/\pi$ and has therefore the same power in discriminative analysis. Furthermore, the specific crushing strength is without restrictions regarding the mode of failure as different crack patterns may be observed. The utilization of tensile strength may cause confusion in cases where some tablets fail under tension and some under shear forces [3]. Difficulties may arise in a precise and objective definition of ideal fracture [4] and Eq. (2) is shown to be erroneous since the stress distribution in anisotropic media like tablets is different from isotropic bodies [5]. In a critical review on the subject Darvell [6] concluded that "it is extremely doubtful if the supposed indirect tensile tests actually cause failure in tension and that they therefore measure the tensile strength".

The diametral crushing strength method was criticized by Leuenberger and Jetzer [7] as the authors did not find it to be a scientifically well-based variable for characterizing the compactibility, because complicated fracture patterns may occur instead of ideal failure. However, by analysing the repeatability of the crushing force in 12 samples of 100 tablets the coefficient of variation was within 2–5% for tablets produced on a laboratory scale and 5–12% for industrially produced commercial available tablets [8]. This observed small variability together with the demonstrated normal distribution of the data indicates that the crushing strength is a reliable method in describing the mechanical properties. Recently more than 3000 tablets were tested for an inter-laboratory comparison of 16 commercial crushing force testers [9]. This investigation demonstrated that the diametral crushing test is a stable and uncomplicated method in expressing the mechanical quality of compacts.

Expressing the mechanical strength as the work of failure – the total amount of work needed to break or crush the tablet – is technically more complicated than measurement of the crushing force. The work of failure is calculated by numerical integration of the applied force with respect to the distance travelled by the jaws. Rees and Rue [10] concluded that the work of failure is a better quantitative assessment of the mechanical properties than tensile strength. The three- or four-point bending of a square compact in the flexure test as an alternative to the diametral compression test does not seem to add further important information to this field of study [11]. The mechanical strength determined as indentation hardness might, according to Leuenberger and Jetzer [7], be preferable to the crushing strength method in cases where the material has capping tendencies, which will severely spoil the crushing strength measurement.

The mechanical strength measured by any of the mentioned methods is anticipated to be associated with the number of contact points generated in the compact. It is therefore necessary to illustrate or to compute the relationship between the mechanical strength and the principal generating factor: the compaction pressure. The compactibility of a specific substance is most often expressed graphically in a XY-plot as a relationship between compaction pressure and mechanical strength. If the mechanical strength is reported as the crushing force, it is necessary to attach information on either the dimensions of the compact or the tablet weight [12,13].

There are several examples in the literature indicating that the compactibility profile in its full extension has an essential sigmoid shape [10,14]. At relatively low pressures, it was shown by Kuentz and Leuenberger [4] that the mechanical strength increases by a power function with increasing pressure. At high pressures, it is often observed and expected that the crushing strength levels off and even sometimes decreases to a lower level due to capping or lamination tendencies. It might thus be recognized that the strength/pressure relation is fundamentally s-shaped, but that a linear segment is distinctively apparent and describes the most relevant and informative part of the increase in strength related to the compaction pressure.

A practical approach and the simplest way to quantify the compactibility is the one-point estimate, where for instance the minimum pressure needed to make a compact of a given strength is reported [15]. Alternatively a tensile strength at a given pressure is defined [16] or a strength at a fixed porosity [17]. The advantage of these simple one-point estimates is that they are without any assumptions about the overall mathematical relation between the strength and the pressure. The only calculation required is a point-to-point linear interpolation.

A simple linear relationship between tensile strength and pressure up to 310 MPa was found for lactose monohydrate tablets ranging in mass from 0.4 to 1 g [18]. Earlier Higuchi et al. [19] postulated a logarithmic relationship where the strength measured in Strong Cobb units was linearly dependent on the logarithmic transformed compaction force. Newton and Grant [20] observed a better fit of data derived from lactose and dextrose tablets to a double logarithmic equation than to a straight linear relationship.

A power function Eq. (3) valid only at low pressures was suggested by Kuentz and Leuenberger [4]

$$\mathrm{TS} = k \cdot P^{T/2}, \tag{3}$$

where P is the maximum compaction pressure and k and the exponent T are constants. The Weibull equation which is well known in many other pharmaceutical disciplines was used in an attempt to quantify the tablet strength relationship with compaction pressure [21].

An interesting model-independent method for the determination of the compactibility was proposed by Amidon et al. [22]. A plot with the average breaking force versus three levels of logarithmic transformed compaction pressures is constructed and the area under the curve determined by use of the trapezoid rule. The numerical value of the integral expressing the compactibility is termed $F1x$, where the subscript x represents the midpoint pressure value. As the compaction pressures are increased