European Journal of Pharmaceutics and Biopharmaceutics 72 (2009) 148–155

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

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

Research paper

Application of multivariate methods to compression behavior evaluation of directly compressible materials

Rahul V. Haware, Ingunn Tho, Annette Bauer-Brandl *

Department of Pharmacy, Section of Pharamaceutics and Biopharamaceutics, University of Tromsø, Tromsø, Norway

ARTICLE INFO

Article history:
Received 16 July 2008
Accepted in revised form 7 November 2008
Available online 28 November 2008

Keywords:
Compression
Heckel equation
Multivariate methods
Directly compressible excipients
Formulation development tools

ABSTRACT

The present study is an approach to describe and predict compaction and tablet properties by a combination of a set of commonly used mathematical descriptors and multivariate methods based on continuous compression profiles. Effects of formulation and process parameters (e.g. composition, powder properties, compression speed) of well-known direct compression excipients of widely plastic, elastic, and fragmentary properties, and binary mixtures thereof were characterized. 2^3-Full factorial designs with three centre points were applied for Avicel® PH 102, Starch 1500® and Spherolac® 100. Tablets (11 mm diameter) were compressed from hand-weighed powder (of constant true volume) at 104.1 ± 0.2 MPa using a compaction simulator, yielding highly repeatable data. Heckel equation and work-related parameters were derived. Data were evaluated by multivariate analysis (principal component analysis (PCA) and partial least squares (PLS-2, PLS-1) models). The PCA indicated that Hausner ratio, work of compression (WoC), and tensile strength (TS) are negatively correlated to yield pressure of plastic (YPpl) and elastic deformation (YPel), Emcompress® fraction, helium-, bulk-, and tapped density, and particle size. PLS-2 model correlated all design variables, their interaction and square effects with all response variables. These correlations were further quantified for the most important responses (e.g. WoC, TS, YPpl, and YPel) by optimizing separate PLS-1 models. The results were found in accordance with expectations and show the ability of this approach to quantify compression behavior, as a step towards a 'formulation development tool' for tablets.

1. Introduction

Still the development of new tablet formulations is empirical, requires numerous experiments, and does not necessarily lead to the optimum formulation. The ultimate goal, therefore, is a formulation development tool that would allow the formulation scientist to predict compression behavior on industrial scale as well as on tablet properties based on a limited number of simple experiments and quick evaluation methods.

There is no single and simple function or equation that may serve as a general compaction equation capable to explain all the mechanisms of an entire compression process. It is yet not even likely to be achieved in the near future, if possible at all. An alternative approach is to use a set of frequently used functions and descriptors that only cover some of the aspects (such as Heckel, Kawakita, Cooper-Eaton, and work-related parameters) and establish a 'compression database' with the most important parameters derived for the wide range of tableting excipients. The parameters from such database may then serve as 'fingerprints' for the prediction and optimization of the tableting properties of new tablet formulations. It is a prerequisite that the compression parameters derived are accurate, and both the experiments and the evaluation should be quick and simple to carry out.

In order to develop such a tool, it should be an advantage to start with accurate time-resolved force and displacement data (compression profiles) obtained from a compaction simulator, and apply commonly used and accepted mathematical models on a set of well-known pharmaceutical excipients of widely different deformation nature. Evaluation of the deformation behavior by multivariate methods is a useful way of mapping common trends, describe and quantify the behavior of variables and responses and to develop models suitable for the prediction of behavior within a predefined design space. The aim of the present work was therefore to study the compression behavior of four commercially available direct compression materials of mainly plastic, elastic and fragmentary properties and their respective binary blends, to cover a wide range of properties. A compaction simulator was used to produce highly accurate and reproducible data [1]. The objective was to evaluate continuous compaction profiles in response to process and formulation parameters from force–displacement curves, work related descriptors and from the Heckel equation, and to

* Corresponding author. Department of Pharmacy, Section of Pharmaceutics and Biopharmaceutics, University of Tromsø, N-9037 Tromsø, Norway. Tel.: +47 77 646160; fax: +47 77 646151.
E-mail address: annetteb@farmasi.uit.no (A. Bauer-Brandl).

0939-6411/$ - see front matter © 2009 Published by Elsevier B.V.
doi:10.1016/j.ejpb.2008.11.008

quantify relationships by multivariate methods. In order to keep the procedure quick and simple, "in-die" methods were preferred instead of more time consuming "out of die" methods.

2. Materials

Microcrystalline cellulose, Avicel® PH 102 (Batch K.W. 907014), was a free sample from FMC biopolymer, Belgium. Dibasic calcium phosphate dihydrate, Emcompress® (Batch A740 57A) was donated by JRS Pharma, Germany. A partially pregelatinized starch, Starch 1500® (Batch IN 509959), was a free sample from Colorcon, England, and Spherolac® 100 (Batch L.9909 A4132), which is α-lactose monohydrate, was donated by Meggle Pharma, Germany. Magnesium sterate (Batch MF19/70089) was purchased from NMD, Norway.

3. Methods

3.1. Basic powder characterization of excipients as received

3.1.1. Particle size distribution

Analytical sieving was performed according to Ph.Eur. 2008 [2], using a mechanical sieve shaker (Retsch VE 1000, Retsch GmbH and Co. Kg, Hann, Germany).

3.1.2. Particle shape

Samples were mounted on an aluminum base with adhesive carbon tape and sputtered with gold under vacuum for 120 s prior to SEM examination (JSM-6300 SEM, Japan Electron Optics Laboratory, Ltd., Tokyo, Japan).

3.1.3. Flowability

Flowability of the powders was determined by indirect method using Hausner factor (HF), which is a ratio of tapped to bulk density of powder [3]. Bulk and tapped densities were determined according to Ph.Eur.2008 [4] with three repetitions (Erweka® Tapped Volumeter, Typ Svm, Heusenstamm, Germany).

3.1.4. Helium density

The helium density of the powder particles was determined by using gas pycnometer in a Micromeritics AccuPyc™1330 Pycnometer (Micromeritics GmbH, Neuss, Germany). Ten repetitive purge cycles were performed before recording results in three repetitions.

3.2. Preparation and characterization of physical blends

Binary blends were prepared in 200 g lots in a Turbula mixer (Turbula® System Schatz, Basel, Switzerland) for 3 min at 23 rpm. Lubrication of plain excipients and their binary blends with 1% magnesium sterate was performed under the same conditions.

3.3. Experimental design for the evaluation of compression behavior

The effect of punch velocity (saw tooth profile, 10.0 and 50.0 mm/s), lubricant level (0% and 1.0%), and added material Emcompress® (0% and 50.0%) as process and formulation parameters was investigated with respect to compression responses, namely yield pressure value of plastic deformation (YPpl), YP of elastic recovery (YPel), work of compression (WoC), work of elastic recovery (WoE) and tablet tensile strength (TS). The independent variables and their levels are presented in Table 1.

Three excipients (Avicel® PH 102, Starch 1500®, and Spherolac® 100 (Table 2)) were tested in a 2^3-full factorial design with three centre points each, resulting in 11 experiments per excipient. A total of 37 experiments were performed; 33 experiments from 3 excipients and 4 additional control experiments containing Emcompress® as main excipient.

Table 1
Design variable levels in the 2^3-full factorial design with three centre points.

Design variables	Experimental levels		
	Low	Intermediate	High
Punch velocity (mm/s)	10.0	30.0	50.0
Lubricant fraction (%)	0.0	0.5	1.0
Emcompress® fraction (%)	0.0	25.0	50.0

3.4. Tablet preparation

In order to compare the compression properties of different materials and different blends of materials, constant true volume (calculated from the helium density) should be used instead of constant weight since the response to punch movement (i.e. punch force) is a function of volume of solid in the die and not its weight [5]. Cylindrical 11 mm tablets of theoretically constant volume were prepared on a calibrated and validated compaction simulator (ServoPress 450, Schmidt Technology, St. Georgen, Germany; IRB, Waldkirch, Germany) [1]. Helium density value was used to calculate the mass of powder required for each tablet to be 0.2552 ± 0.01 cm^3. Prior to each compression, the punch tips and the die wall were lubricated with a 0.5% suspension of magnesium sterate in acetone. The weighed amount of powder mass was poured manually into the die and compacted at pressure 104.1 ± 1.7 MPa at constant punch velocities (as given in Table 1). Tablet mass was measured immediately after production (CP225D, Sartorius AG, Göttingen, Germany) while its dimensions (diameter and thickness) were measured 24 h after production (0.01 mm micrometer IP54, Wilson Wolpert, Netherlands). The tablets were stored for at least 24 h in desiccators at 24.6 ± 1.5 °C and a relative humidity of 22.5 ± 5.5%.

Crushing force of the tablets was determined (Erweka® GmbH, model TBH20, Heusenstamm, Germany) and tensile strengths (TS) were calculated according to the following (1) [6]:

$$TS = \frac{2F}{\pi D t} \quad (1)$$

where F is the crushing force in N, D diameter, and t is the thickness of tablet in mm.

3.5. Determination of compression parameters

Compression behavior was studied using the *in-die* method for Heckel Eq. (2) [7]:

$$\ln\left[\frac{1}{1-D}\right] = kP + A \quad (2)$$

where D is the relative density of the compact at pressure P.

The reciprocal of the slope (k) of the linear portion of the compression phase and the decompression phase, respectively (i.e. mean YP of plastic deformation (YPpl) and elastic recovery (YPel), respectively) was calculated by linear regression between 20 and 80 MPa for the compression phase, and between 20 and 90 MPa for the decompression phase.

Also, the apparent work of compression (WoC) and elastic recovery (WoE) values was determined from the force–displacement data recorded during the compression-cycle [8].

3.6. Statistical analysis

Principal component analysis (PCA) followed by partial least square regression (PLS-1 and PLS-2) was performed to identify