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Prediction of solid fraction from powder mixtures based on single component compression analysis

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ABSTRACT

The aim of this study was to provide a systematic evaluation of various compression models (Percolation, Kawakita, Exponential model) in respect to predict tablet's solid fraction for direct compression mixtures, based on single component compression analysis. Four mixtures were compressed over a wide pressure range at various fractions of microcrystalline cellulose (MCC) and pre-agglomerated lactose monohydrate (LAC) to compare an adjusted Percolation, Kawakita and a simple Exponential model. Based on single compression analysis of the pure excipients and application of these models, it was possible to predict the solid fraction of all mixtures. The Kawakita model showed overall superior prediction accuracy, whereas the Percolation model resulted in the best fit for mixtures containing microcrystalline cellulose in a range of 72%–48%. Both models were in good agreement at residuals below 3%.

1. Introduction

The solid fraction of tablets is commonly understood as an important aspect of formulation design as it directly influences tablet tensile strength, disintegration, dissolution time, drug product stability (Rajkumar et al., 2016; Quodbach and Kleinebudde, 2016; Mishra and Rohera, 2016; Ajit Narang and Sai Boddu, 2015) and also serves as scale up characteristic (Tye et al., 2005). Thereby, it can be considered as critical quality attribute of tablets (Yu et al., 2014).

Hence, prediction of the tablet solid fraction based on single compression analysis of commonly used excipients for direct compression would be highly beneficial for development purposes. It could serve as a systematic guidance for the formulator to select appropriate excipients depending on the active pharmaceutical ingredient to build quality into the drug product according to the Quality by Design approach.

Compression analysis of pharmaceutical powders has been reported by many different authors (Sonnergaard, 1999; Sun and Grant, 2001; Ilkka and Paronen, 1993; Nicklasson and Alderborn, 2000; Frenning et al., 2009; Nordström et al., 2008; Patel et al., 2006). The most frequently used compression equations are (Heckel (1961) and Kawakita and Lüdde (1971), which provide a physical interpretation of the volume reduction process of powders 1dependent on the applied compaction pressure. The Heckel equation for pharmaceutical powders is derived from compression experiments of metal powders and assumes that the consolidation (plastic deformation) follows first-order kinetics, which results in the Heckel equation $-\ln(\varepsilon) = kP + A$, where ε is the porosity of the compact and k the

Abbreviations: LAC, lactose monohydrate (Tablettose 80®); MCC, microcrystalline cellulose (Avicel® PH102); CARB, carboxymethylcellulose sodium (AcDiSol®); MGST, magnesium stearate (LIGAMED®); V_p, volume of tablet at applied pressure [cm^3]; D, diamter [cm]; h, height [cm]; m, mass [g]; μ, pi; ρ_{App}, apparent density [g/cm^3]; ρ_{TRUE}, density [g/cm^3]; $\bar{x}_i$, solid fraction mean of six tablets; x_i, solid fraction predicted; $x_{Excipient}$, weight fraction of excipient in mixture [% w/w]; χ, system property; S, proportionally constant; *p*, site occupation or bond proability; x, $_{pp}$compression pressure [MPa]; q, critical exponent or compressibility exponent; σ_t, tensile strength [N^2/mm^2]; σ_{tmax}, maximal tensile strength [N^2/mm^2]; SF, solid fraction; SF_{max}, maximal solid fraction; C, degree of volume reduction; P, pressure [MPa]; V_0, initial volume [cm^3]; a, Kawakita constant; b, Kawakita constant; V_{min}, minimal achievable volume [cm^3]; d,f,g, exponential constants.

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reciprocate of the yield pressure. A linear course of the Heckel equation at increasing pressure indicates plastic deformation. However, in contrast to metal powders pharmaceutical powders display additionally to plastic particle rearrangement and/or elastic deformation, which leads to deviations from the linear course of plastic deformation behaviour. In this context the Heckel plot shows a curvature in the lower pressure region (Sonnergaard, 1999). Duberg and Nyström (1986) decided to divide the Heckel plot into 3 phases for pharmaceutical powders to reach a better applicability of the Heckel equation: particle rearrangement or fracturing, elastic or plastic deformation and decompression. Consequently, not a single Heckel equation will describe the compressibility of pharmaceutical powders appropriately for the entire range of the compression pressure, As for implementing a prediction model for solid fraction for the widest possible range of compaction pressure requires a model, which parameters describe the compression behaviour of the respective pressure range, the Heckel equation was excluded for this study. In contrast to the Heckel model, the Kawakita equation assumes that particles under compression pressure are in an equilibrium and the product of the pressure term and volume term is constant (Nicklasson and Alderborn, 2000). Consequently, a linear course is obtained when plotting P/C vs. compression pressure, where C is the degree of volume reduction. The Kawakita parameters a and b^{-1} are determined by linear regression and likely to deliver appropriate results over the whole compression pressure. Promising results were found using the Kawakita equation (Frenning et al., 2009; Mazel et al., 2011; Busignies et al., 2012), to predict the compressibility of a tablet successfully.

Another potential model is the percolation model. Usually employed to elucidate the governing property of a material in a mixture dependent on its volume fraction, it can also be applied to describe a property dependent on the fracture or extent of a process parameter. In our case the tablet property of interest would be the solid fraction while the process parameter would be the compaction pressure. A successful implementation of this concept has been demonstrated by various authors (Leuenberger and Leu, 1992; Martin Kuentz, 2000; Busignies et al., 2007; Kuentz et al., 1999; Ramirez et al., 2004). A sudden property change of a tablet will only be observed if the particle rearrangement is completed and an infinite cluster can be formed (Leuenberger and Leu, 1992). This sudden change (percolation threshold) is not considered by the simplification of the compressibility by the Kawakita equation. Therefore, the present work tries to apply the percolation theory for predicting the solid fraction in dependence of the compression pressure, which has the potential to enhance the predictability of the solid fraction of a ternary mixture. The predictive power of the Percolation theory, the Kawakita model, and a simple exponential model were systematically evaluated for four different direct compression formulations. The exponential model was added to elucidate whether the two parametrised models with theoretical background are superior in terms of predictability of solid fraction compared to a model without parameterised variables.

In order to show that the models can be applied practically, a typical ternary tablet composition was chosen, with different proportions of lactose monohydrate and microcrystalline cellulose. First, all models were applied to single components and thereafter an additive rule was used, for predicting the solid fraction of the mixtures, reflecting the composition of the formulation. Finally, the prediction and the observed solid fractions of the compressed mixtures were compared to evaluate the suitability of the models.

2. Material and methods

2.1. Material

Three different excipients were used: pre-agglomerated lactose monohydrate (LAC) (Tablettose 80®, Meggle Wasserburg GmbH & Co. KG), microcrystalline cellulose (MCC) (Avicel® PH102, FMC Biopolymer Co.) and carboxymethylcellulose sodium (CARB) (AcDiSol®, FMC Biopolymer Co.). Magnesium stearate (MGST) (LIGAMED®, Peter Greven GmbH & Co. KG) was used as lubricant.

2.2. Methods

2.2.1. Powder mixtures

For investigations of the single excipients, each excipient was mixed with 0.5% (w/w) magnesium stearate in a turbula mixer (Turbula type 2A, Willy A. Bachofen AG Maschinenfabrik, Switzerland) at 50 rpm for 5 min. Wherever ternary mixtures were investigated, all components were blended at 50 rpm for 3 min and afterwards lubricated with 0.5% (w/w) magnesium stearate. Four mixtures of 500 g with different proportions of microcrystalline cellulose and lactose monohydrate were used (Table 1).

2.2.2. Powder characterization

Particle size distributions of all excipients were measured in triplicate using a laser diffraction analyser (Mastersizer 2000, Malvern Instruments Ltd., United Kingdom) equipped with a dry powder feeder (Scirocco 2000) with a 50% feed rate at 0.25 bar dispersion pressure. True density was determined by 10 purges on a helium gas pycnometer (AccuPyc II, Micromeritics Instrument Corporation, USA) for MCC, LAC and CARB. For the mixtures the true density was calculated by the weight fraction of MCC, LAC and CARB divided by 99.5, as described by Gupta et al. (2005).

2.2.3. Manufacturing of tablets

Before tableting, powders and mixtures were stored in a climatic chamber over 48 h at 21 °C and 45% relative humidity. Flat-faced tablets with a weight of 200 ± 2 mg and a diameter of 10 mm were produced by a single punch press FlexiTab® (Röltgen GmbH & Co. KG, Germany). Forty-two tablets were compacted between 50 MPa–350 MPa for each excipient and mixture. Thus, six tablets each were measured at seven compression pressures. The die was filled manually. The tablets were weighed directly after ejection with an analytical balance (AT400, Mettler-Toledo GmbH, Germany). The diameter and the height of each tablet were determined by an automatic tablet tester (Erweka TBH 310 MD, Erweka GmbH, Germany), to enable calculation of the solid fraction according to Eq. (1)–(3). Tablets only consisting of LAC compressed at a compression pressure of 50 MPa were too weak for being measured in the tablet tester. Compressibility plots of the individual excipients were obtained as a prerequisite for model

Table 1
Composition of mixtures.

Formulation	MCC	LAC	CARB	MGST
Mixture #1 MCC 3:1 LAC	72.36	24.12	3.02	0.50
Mixture #2 MCC 2:1 LAC	64.32	32.16	3.01	0.50
Mixture #3 MCC 1:1 LAC	48.24	48.24	3.02	0.50
Mixture #4 MCC 1:3 LAC	24.13	72.37	3.00	0.50