Prediction of Tablet Characteristics from Residual Stress Distribution Estimated by the Finite Element Method

YOSHIHIRO HAYASHI,[1] TAKAHIRO MIURA,[2] TAKUYA SHIMADA,[3] YOSHINORI ONUKI,[1] YASUKO OBATA,[1] KOZO TAKAYAMA[1]

[1]Department of Pharmaceutics, Hoshi University, Tokyo, 142–8501, Japan
[2]Mechanical CAE Division, Cybernet Systems Company, Ltd., Tokyo, 101–0022, Japan
[3]Nano Seeds Corporation, Gifu, 504–0839, Japan

Received 9 April 2013; revised 17 June 2013; accepted 2 July 2013

Published online 29 July 2013 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.23675

ABSTRACT: Tablet characteristics of tensile strength and disintegration time were predicted using residual stress distribution, simulated by the finite element method (FEM). The Drucker–Prager Cap (DPC) model was selected as the method for modeling the mechanical behavior of pharmaceutical powders composed of lactose (LAC), cornstarch (CS), and microcrystalline cellulose (MCC). The DPC model was calibrated using a direct shear test and analysis of the hardening law of the powder. The constructed DPC model was fed into the analysis using the FEM, and the mechanical behavior of pharmaceutical powders during compaction was analyzed using the FEM. The results revealed that the residual stress distribution of the tablets was uniform when the compression force increased. In particular, the residual stress distribution of tablets composed of equal amounts of LAC, CS, and MCC was more uniform than the tablets composed of 67% LAC and 33% CS, with no MCC. The tensile strength and disintegration time were predicted accurately from the residual stress distribution of tablets using multiple linear regression analysis and partial least squares regression analysis. This suggests that the residual stress distribution of tablets is related closely to the tensile strength and disintegration time. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 102:3678–3686, 2013

Keywords: tableting; excipients; mathematical model; powder technology; processing

INTRODUCTION

The International Conference on Harmonization (ICH) Q8(R2) guidelines recently announced that pharmaceutical design and development should be based on science, rather than being based on empirical knowledge only.[1] The concept of "quality by design" (QbD) is described in the ICH Q8 recommendations, which propose that the design and development of pharmaceutical formulations and manufacturing processes should ensure the prescribed quality by understanding how these factors affect the quality of pharmaceutical products. A key goal of QbD is to identify the most important critical quality attributes (CQAs) and to understand their relationships with the product performance.[2] According to the ICH Q8(R2), a CQA is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. CQAs are generally associated with the drug substance, excipients, intermediates (in-process materials), or the drug product.

Tablets are a very commonly and widely used dosage form for the oral administration of drugs.[3] Tablets have advantages over other dosage forms of drug delivery, such as physicochemical stability, accurate dosages, and the ease of drug-release control. Moreover, tablets are convenient for patients because they are portable and easy to administer. When a tablet is chosen as the final product, the tableting process is a critical step in the manufacture, because pharmaceutical responses, such as hardness, dissolution property, friability, accurate mass, and content uniformity, are strongly affected by this process. Therefore, understanding the mechanical behavior of powders during the tableting process is very important.

Numerical investigation of the tableting process can assist in providing an understanding of the influence of tooling properties, lubrication, and compaction kinematics (e.g., compaction speed and compaction sequences), and provide guidance for the optimization of tooling design and the improvement of powder formulation. One numerical analysis method is the finite element method (FEM), which is well established for the modeling of deformation of powders in various industries, such as compaction in ceramic industries, and analyzing pharmaceutical powder compaction.[4,5] In the FEM, powders are modeled as continuum media and the compaction behavior is analyzed by solving boundary-value problems.

The Drucker–Prager Cap (DPC) model is one of the continuum mechanical models in which the powder is considered a porous medium. The DPC model can represent the densification and hardening of the powder, as well as the interparticle friction.[6,7] The DPC model is therefore frequently used to analyze the strain, relative density changes, and stress distribution of tablets during the tableting process.[8–10] The DPC model is characterized by parameters such as cohesion, internal friction angle, Young's modulus, Poisson ratio, parameters related to volume change and hardening mechanisms, and so on. In general, full calibration of the DPC model requires triaxial and hydrostatic compressions, and proportional loading tests. These tests are commonly used for metallurgical powders.[11,12] Because pharmaceutical powders are very soft and loosely packed, the application of triaxial cells in pharmaceutical materials is difficult. A shear cell test, which is based on the Mohr–Coulomb failure criterion, supplies data on the powder's cohesion and the friction angle at different pressures.[13,14] A direct shear test

Correspondence to: Yoshihiro Hayashi (Telephone: +81-3-5498-5783; Fax: +81-3-5498-5783; E-mail: d105@hoshi.ac.jp)

Journal of Pharmaceutical Sciences, Vol. 102, 3678–3686 (2013)

could also supply data on the cohesion and friction angle based on the Mohr–Coulomb failure criterion.

In this study, volume change and hardening-law parameters were estimated using a response surface method that incorporated multivariate spline interpolation (RSM-S). The basic concept of RSM-S involves the boundary element method.[15] Green's functions are used for minimum curvature interpolation of multidimensional data points. Using RSM-S, we can determine nonlinear relationships between causal factors and response variables. In addition, this method does not require any complicated methodology, such as an artificial neural network, and it has been applied to practical cases to optimize pharmaceutical formulations and process variables.[16,17]

Several studies have reported that the residual stress distribution of tablets was estimated using the FEM, in which the powder is modeled using the DPC model.[8–10] For instance, Han et al. have reported that density distributions of tablets was affected by punch geometry.[18] Tablet failure, in particular capping, is more likely to be associated with an intensive shear band formed during the decompression stage.[19,20] It has been shown that the density distribution patterns are comparable with the experimental results of others.[21–24]

The residual stress distribution of tablets might be affected by formulation and process variables. However, in the past, the influence of the residual stress distribution of tablets on characteristics of tensile strength (TS) and disintegration time (DT) has not been determined. The aim of this article was therefore to reveal differences in stress distribution between tablets composed of various formulations. Moreover, the predictive abilities of tablet characteristics of TS and DT on residual stress distribution were investigated.

Multiple linear regression analysis (MRA) and partial least squares (PLS) regressions were applied to determine the quantitative relationships between the stress distribution of tablets and the characteristics of TS and DT.

EXPERIMENTAL

Materials

Lactose (LAC; Tablettose 80, Meggle Japan Company Ltd., Tokyo, Japan), cornstarch (CS; Graflow M, Nippon Starch Chemical Company Ltd., Osaka, Japan), and microcrystalline cellulose (MCC; Ceolus PH-101, Asahi Kasei Chemicals Company Ltd., Tokyo, Japan) were purchased. Magnesium stearate (Mg-St) was purchased from Wako Pure Chemical Industries Ltd. (Osaka, Japan). LAC, CS, MCC, and Mg-St were chosen as the filling, disintegrating, binding, and lubricating agents, respectively.

Simulated Conditions of the Tableting Process

Because the compaction of cylindrical tablets is an axisymmetric case, it can be analyzed using a two-dimensional FEM. Figure 1 shows the flow of the FEM, that is, a FEM for modeling the compaction of flat-faced tablets, the model at the point of maximum compression, and the model during decompression. The powder was exhibited as a DPC model. The die wall and upper punches were modeled as rigid bodies. The interaction between the powder, die wall, and upper punch was modeled and the friction in the contacts was set to 0.195, in accordance with the reference.[19] The nodes on the symmetry axis were restricted to move only horizontally, and the nodes at the bottom boundaries were allowed to move only vertically. The upper punch could move vertically with compression.

DPC Model

The DPC model was originally developed to predict the plastic deformation of soils under compression.[6,7] The model is formulated in terms of two invariants, l_1, the first invariant of the Cauchy stress, and J_2, the second invariant of the deviator stress. In terms of principal stresses, these invariants are given as:

$$l_1 = \sigma_1 + \sigma_2 + \sigma_3 \tag{1}$$

$$J_2 = \frac{1}{6}\left\{(\sigma_1 - \sigma_3)^2 + (\sigma_2 - \sigma_3)^2 + (\sigma_3 - \sigma_1)^2\right\} \tag{2}$$

where σ_1, σ_2, and σ_3 are the maximum, intermediate, and minimum principal stresses, respectively, and compression is taken as negative.

Figure 2 shows the yield surface of the DPC model. It consists principally of three intersecting portions: a shear failure segment Y_s, a cap segment Y_c, and an expansion envelope portion Y_t, respectively. A typical geometrical shear envelope function is based on the exponential format given as:

$$Y_s(l_1, \sigma_0) = \sigma_0 - Ae^{(\beta^y l_1)} - \alpha^y l_1 \tag{3}$$

where σ_0 is the current cohesion related to a material constant and A, β^y, and α^y are shear failure parameters. In this study, A and β^y were regarded as zero and the shear failure was represented as a simple linear model.

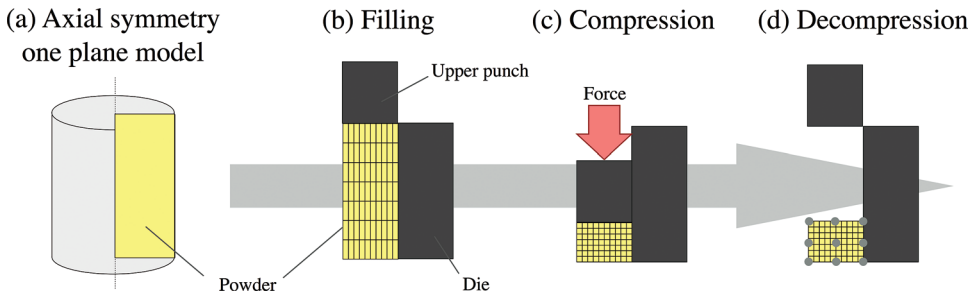

Figure 1. Flow chart of the finite element analysis: a typical finite element model for modeling the compaction of flat-faced tablets, the model at the point of maximum compression, and the model during decompression. The powder was modeled using the DPC model. An axisymmetric two-dimensional model (right half) was used.