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Use of partial least-squares analysis and fractionated X-ray computed tomography images in the investigation of density distribution of round tablets

Yusuke Hattori, Ryota Aoki, Makoto Otsuka *

Research Institute of Pharmaceutical Sciences, Faculty of Pharmacy, Musashino University, 1-1-20 Shin-machi Nishitokyo-shi, Tokyo 202-8585, Japan

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ABSTRACT

Non-destructive and quantitative investigation of density distribution of round tablets was the objectives of this study. The density distribution of round tablets was observed using X-ray computed tomography (X-ray CT). The distribution images were visualized by fractionating the CT images into 25 unit cells and averaging the CT number for each cell. The profiles of the distribution were analyzed with respect to the compression pressure by partial least squares (PLS) method. Analysis using the PLS method resulted in regression and loading vectors depicting the contribution of the change in density due to the variation of compression pressure. The vectors were also composed of 25 positions and used to reconstruct density mapping. The reconstructed maps quantitatively indicated the regions reflecting changes in density. At the upper and lower surface of tablets, increasing the compression pressure increased density in the edge region and decreased density in the center region. The center region under the upper surface was weakly affected by the pressure change. These results well agreed with the simulation results of finite elemental method. We suggest that the effects of compression pressure visually revealed in each region of the tablet by the X-ray CT and PLS methods are generated by density imbalance resulting from high pressure compression.

1. Introduction

Powder compression is performed just prior to tablet coating, the final process in preparing tablet pharmaceuticals. Compared to the direct compression of powders, compression molding of wet granules provides tablets with stability, including qualities such as uniformity and mechanical strength [1–3]. However, the recent trend in the production of tablet pharmaceuticals is towards direct compression in order to reduce production costs. Generally, the direct compression requires higher compression pressure than the compression of granules. The high compression pressure might lead tableting failure and impose a strain on the compression machine. The technology of direct compression is improved by using functional binding additives and disintegrating agents [2,4,5].

On the other hand, with increasing use of direct compression it becomes important to understand the powder compaction process. Compaction leads to a powder density distribution in the tablet depending on the compression pressure and speed. Optimization of the tableting process is necessary to produce large amount of tablets with a stable quality. The most appropriate distribution pattern for a pharmaceutical product may be different from other products depending on the type of solid formulation or the active ingredient. For example, the desired pattern for orally disintegrating tablets is to distribute voids and condensed regions to allow disintegrative properties with mechanical strength [6,7]. In the case of bio-products such as bacteria, the activity of the bacteria must be maintained by avoiding the use of high pressure, because many bacteria are easily inactivated by pressure [8–10].

The density distribution of tablets was previously determined by compression and cutting of zebra-striped tablets and visualizing the cut plane [11]. More recently the distribution was investigated using non-destructive imaging technologies such as X-ray computed tomography (X-ray CT) [12], nuclear magnetic resonance (NMR) [13], terahertz spectroscopy [14], and chemical imaging [15]. Sinka et al. and Djemai and Sinka have made comparisons between the imaging results obtained using NMR and X-ray CT [12,13], and concluded that these methods showed agreement in the distribution results. According to the previous reports of X-ray CT, it was discussed that there were some effects on the density distribution, such as the shapes of punches and die, the physical properties of powder, friction between powder particles and die, and the sequence of punch motion. However the effect of compression pressure on the distribution was not discussed [12].

Finite element method (FEM) has also been used to investigate tablet compaction and density distribution [16–19]. FEM is a powerful technique to obtain numerical models of diffusion, deformation, and potential field in fluids, elastic solids, and other materials [20]. Hayashi

* Corresponding author.
E-mail address: motsuka@musashino-u.ac.jp (M. Otsuka).

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et al. reported the nondestructive prediction of tablet characteristics by means of FEM [19]. However, there are still discrepancies between imaging results by X-ray CT and calculated results by FEM. In the previous reports of X-ray CT, high resolution images were obtained and the density distribution was discussed. Considering the powder particle size, the size is approximately 50 μm; thus, the high resolution CT image might represent the density of each particle. In this study, it was assumed that the powder compression led density distribution in macro-scale. Thus, the CT images were analyzed by fractionated into 25 unit cells.

Additionally, as an alternative analytical method, we used the partial least squares (PLS) method, which is based on principle component analysis of experimental results, and is widely used to calibrate large spectral data sets. Moreover, it is possible to extract effective variables from the explanatory data set contributing to changes in the chemical and physical properties of the sample.

In this study, we focused on the understanding of the relation between compression pressure and density distribution in tablets of standard shape and standard pharmaceutical formulation. The density distribution of round tablets was experimentally obtained using fractionated X-ray CT images. The PLS method was used to analyze the correlation between the distribution pattern and compression pressure.

2. Theoretical background of PLS

The details of PLS is described in many other papers [21,22]; hence, here the fundamental theorem is introduced. The regression analysis of PLS was performed with based on the orthogonal decomposition of data set matrixes X and Y as following equations;

$$X = tp^T = t_1p_1^T + t_2p_2^T + \cdots + t_mp_m^T \quad (1)$$

$$Y = uq^T = u_1q_1^T + u_2q_2^T + \cdots + u_mq_m^T \quad (2)$$

where t and u are the score matrixes, and p and q are the loading vector matrixes. In the PLS, X and Y matrixes are called explanatory and objective variables, respectively. The regression vector b is obtained with the loading vectors as following equation;

$$b = W\left(p^TW\right)^{-1}q \quad (3)$$

where W is the weight defined by X^Tu/X^Tu. Therefore, loading vector p means the decomposed vector component, and the first vector p_1 indicates the highest rate of contribution to the X matrix. On the other hand, regression vector is composed of p and q vectors; thus, regression vector represents the contributing component of the X matrix for the Y matrix.

3. Materials and methods

3.1. Powder compression

Round tablets were prepared with anhydrous lactose (SuperTab 21AN, DFE pharma, Goch, Germany), potato starch (manufacturing dedicated, Kozakai Pharmaceutical, Tokyo, Japan), theophylline (Shizuoka Coffein, Shizuoka), and magnesium stearate (Wako Pure Chemical Industries, Osaka). The content of each tablet was 62%, 27%, 10%, and 1% of these materials, respectively. All powders were sieved using an 850 μm mesh before blending, and were blended for 20 min at 35 rpm using a V-blender (2 L) (excluding magnesium stearate). Following the pre-blending, magnesium stearate was added into the blend and blended for 5 min at 35 rpm.

Tablets were compressed using an 8 mm diameter die and concave upper and lower punches with 9 mm curvature radius. The compression was carried out by stressing with the upper punch, where the lower punch was stationary. The pressure was controlled at 100, 159, and 219 MPa with a compression testing machine (TG-50 kN, Minebea, Nagano). The moving speed of the upper punch was 10 mm/min. Three tablets were prepared at each compression pressure.

3.2. X-ray CT measurements

The two-dimensional X-ray CT slice image was obtained for each tablet using a Latheta LCT-200 CT scanner (Hitachi Aloka Medical, Tokyo). The slicing was performed under the conditions of 24 mm in diameter as the field of view, 48 μm scan thickness, and 48 μm spatial resolutions. The scan thickness means thickness of one slice; thus, the absorbance of X-ray due to the object increases with increasing the thickness. In the X-ray CT measurements, the absorbance due to the object μ was converted to the relative value to the absorbance due to water μ_{water} and air μ_{air} as following equation:

$$\text{CT number(HU)} = 1000\frac{\mu-\mu_{water}}{\mu_{water}-\mu_{air}} \quad (4)$$

where the converted value is called CT number with Hounsfield unit (HU). The X-ray tube voltage and current were 50 kV and 0.5 mA, respectively. As shown in Fig. 1, the center of the round tablet was observed, and half of the section was fractionated into 25 unit cells in a lattice pattern, where the average CT number was calculated for each cell. Since the cells at the convex lower and upper surface of the tablet include empty space (outside of tablet), the average number was calculated excluding the outside of the tablet.

3.3. PLS regression analysis

PLS regression was performed for density profiles of 25 variables and compression pressure as explanatory and objective variables,

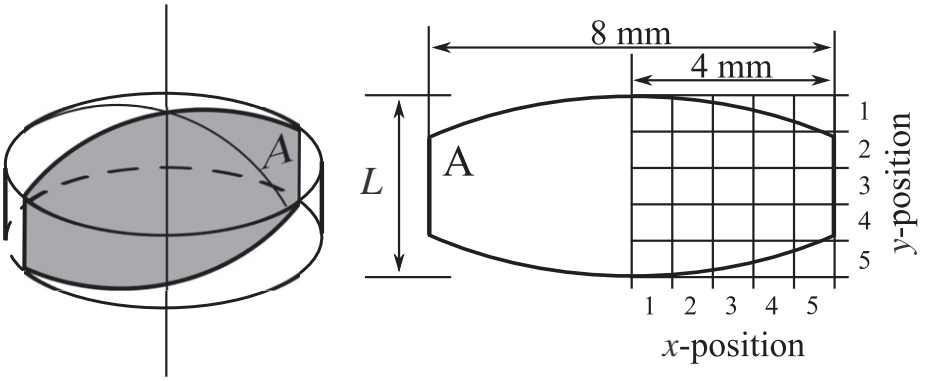

Fig. 1. Schematic illustrations of the sliced area of the tablet by X-ray CT (A) and the fractionated lattice pattern of the cross-section.