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A new mathematical equation for the evaluation of the compression behavior of pharmaceutical materials

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Abstract: A new mathematical equation characterizing the compression of pharmaceutical materials is presented. This equation presumed that the rate of change of the compressible volume of powder with respect to the pressure is proportional to the compressible volume. The new model provided a good fit to several model substances employing non-linear regression techniques. The validity of the model had been verified with experimental results of various pharmaceutical powders according to the Akaikes informatics criterion (AIC) and the sum of squared deviations (SS). The parameter of the new model might reflect quantitatively the fundamental compression behaviors of the powders. It had demonstrated that the proposed model could well predict the compaction characteristics of solid particles like the Kawakita model.

Key words: compression equation; methodology; non-linear regression; Kawakita equation

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一种用于制剂学材料可压性评价的新方程研究

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摘要: 本文提出了一种新的压缩方程用于评价制剂粉体的可压性。该方程基于假设粉体可压缩体积随着压力的变化率与可压缩体积成正比。采用该模型方程将几种辅料的压缩数据进行非线性拟合, 达到了良好的拟合效果, 且方程中的参数可较好的反映粉末的压缩行为。该方程被证实对粉体压缩性的评价结果与川北方程一致。

关键词: 压缩方程; 方法学; 非线性回归; 川北方程

In the pharmaceutical field, the mathematical model equations are commonly employed to evaluate the compressing characteristics of materials[1−6]. Numerous attempts have been made to find a mathematical model to describe the compaction behavior of pharmaceutical powders. As stated in the review article[7], various equations such as Kawakita, Heckel, Walker, Balshin and Cooper and Eaton have been developed to describe the relationship between applied pressure and compacted volume. By far the most commonly used equations in the field of tablet manufacture exist itself limitations. Generally better fit is obtained with the Heckel equation in the region of middle and high pressure among low porosity materials and a better fit is also obtained with the Kawakita equation in the region of low pressure among middle and high porosity materials.

However, as the compression process consists of several stages, it may seem difficulty to look for one relatively simple formula with few parameters covering the entire compression process. The theoretical investigations of the pressure-volume relationship often lead to complicated mathematical expression, which

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is of limited practical relevance in pharmaceutical development and quality control. It has proved difficult to find one relatively simple parameter from these equations that can differentiate the compressibility among different materials and keep consistent under different experimental conditions. The reason might be that the compression process of pharmaceutical materials is very complex. It is generally accepted that several distinct stages including particle rearrangement, elastic/plastic deformation, and fragment takes place in this process. Therefore, researches which focus on the new mathematical models have been carried out in recent years[8−10].

Many of simply compression profiles are characterized by curve fitting in linear regression. It might lead to the fairly significant difference between the simulated values and the experimental values[11]. It is concluded that the traditional method in transforming variables is not always the optimal solution in mathematical handling of these data. However, the non-linear regression as the calculation technique through the iterative procedures by personal computers could be an ideal solution in mathematical handling of compression data. Non-linear regression techniques well known in pharmacokinetics have previously been used on compression data[11−14].

The purpose of this work is to develop a new compression equation for several pharmaceutical materials by non-linear regression handling method. Its parameters to characterize the compressibility of the compressed powder are evaluated. The new equation is evaluated according to Akaikes informatics criterion (AIC) and squared deviations (SS) values, in comparison with the Kawakita equation by the calculation method of non-linear regression.

Theory

Development of the new compression equation The new model presumes that the rate of change of compressible volume (V^*) with respect to pressure (P) is proportional to the compressible volume giving the differential equation:

$$\frac{dV^*}{dP} = -KV^* \tag{1}$$

Which is integrated and reformulated to:

$$\int_{V_0^*}^{V_P^*} \frac{dV^*}{V^*} = -K\int_0^P dP \tag{2}$$

$$\ln\frac{V_P^*}{V_0^*} = -KP \tag{3}$$

Eq. (3) could be transformed into an exponential equation:

$$V_P^* = V_0^* \cdot e^{-KP} \tag{4}$$

Where V_P^* and V_0^* are the compressible volume at the pressure of P and 0, respectively. The parameter K is a constant.

The relationships among the compressible volume (V^*), the volume at the infinite pressure (V_∞) and the total volume are shown as follows:

$$V_P^* = V_P - V_\infty \tag{5}$$

$$V_0^* = V_0 - V_\infty \tag{6}$$

According to Eq. (5) and Eq. (6), Eq. (4) could be transformed into the following equation:

$$V_P - V_\infty = (V_0 - V_\infty)\cdot e^{-KP} \tag{7}$$

$$V_p = V_\infty + (V_0 - V_\infty)\cdot e^{-KP} \tag{8}$$

Eq. (8) corresponds to the relationship between the apparent volumes of compact (V_p) and the applied pressure (P). In this new equation, the parameters of K and V_∞ are called as the compression coefficient and the true volume, respectively. Theoretically, V_∞ is the volume of compact while the applied pressure value $P\to\infty$.

Eq. (8) can be transformed into Eq. (9) as follows:

$$\frac{V_P - V_\infty}{V_0 - V_\infty} = e^{-KP} \tag{9}$$

$$\frac{V_0 - V_P}{V_0 - V_\infty} = 1 - e^{-KP} \tag{10}$$

Cooper-Eaton's equation is expressed as the following equation, i.e. $\frac{V_0 - V_P}{V_0 - V_\infty} = Ae^{-\frac{C_1}{P}} + Be^{\frac{C_2}{P}}$. There are four parameters and two exponential terms in Cooper-Eaton's equation, while there is only one parameter in the new proposed equation. The new equation was expressed as a more simplified model to describe the compression behavior of substances.

It is presumed that

$$R = \frac{V_0 - V_P}{V_0 - V_\infty} \tag{11}$$

Then,

$$R = 1 - e^{-KP} \tag{12}$$

The parameter of R is named as the ratio of compression. That is the ratios of the compacted volume at a certain pressure P to the maximal compressible volume. As the applied pressure value $P\to0$, the ratio of compression is close to 0. While the applied pressure value $P\to\infty$, the value of R is

gradually near to 1.

According to Eq. (8), the relationship between the volume of compact and the applied pressure depends on two parameters of powder, i.e. K and V_∞. The set of V_p−P data are fitting with the non-linear least square method and then the values of parameters could be obtained.

In this new compression equation, the value of parameter K could demonstrate the strength of the resist force of powder to the applied pressure. That is to say that the parameter K expresses the compressibility of materials. A bigger value of K indicates the powder is easier to be compressed. K might be a representative parameter for material compressibility.

Interpretation of the constants in the Kawakita equation One of the empirical compression models is the equation proposed by Kawakita, which will be compared with the fitting results from the new compression equation:

$$C = \frac{V_0 - V_p}{V_0} = \frac{abP}{1 + bP} \tag{13}$$

Which is reformulated to:

$$V_p = \frac{V_0 \cdot (1 + bP - abP)}{1 + bP} \tag{14}$$

Where V_0 is the initial volume and a and b are constants. The constant a is commonly used to represent filling and flowability of the material, which is correspondent with the limiting value of C at infinite pressure. The physical meaning of the constant b or $1/b$ is more complex. Mathematically $1/b$ is the pressure needed to compress the powder to one half of the total degree of volume reduction estimated as a. $1/b$ could used to express the compressibility of materials. The value of parameter $1/b$ is much lower, the compressibility of materials is much better.

Experimental

Materials Microcrystalline celluloses-Avicel PH 101® (PH101, FMC Corporation, Philadelphia, PA, USA); microcrystalline celluloses-KG 802® (KG802), microcrystalline celluloses-SCP 100® (SCP100), microcrystalline celluloses-PH301® (PH301) (Nippon Asahi Kasei Corporation, Japan); Plasdone S-630® (Co-PVP, ISP Corporation, USA), Magnesium stearate (Shanghai Yuanji Chemical Ltd., China).

Compaction experiments The powders of various types of MCC were mixed with 0.5% (*w*/*w*) magnesium stearate in the V-blender (Shanghai Zhenchun Powder Equipment Corporation, China) for 15 minutes, separately. The mixture was directly compressed to tablets on a tablet-compressing machine equipped with an inductive force transducer and signal transduction system (MiNi PRESS-Ⅱ SF, Karnavati Engineering Ltd., India). Eleven millimeters diameter flat circular compacts of 500 mg weight were prepared and the mainly compression forces of the compacts were recorded by the computer connected to the tableting machine and the main compression forces ranged from 50 MPa to 500 MPa. Compaction pressures were adjusted by controlling the punch displacement at the point of maximum compression. The dimensions of the compacts were measured with a vernier caliper (Shanghai measurement tools factory, China). Ten of tablets were prepared at each pressure setting to obtain the average of tablet dimensions. Before each compaction, the punches and die were lubricated with a suspension of 1% magnesium stearate in ethanol.

Data treatment Non-linear least square regression program (proposed by Prof. Zhu Jia-bi) was employed to fit the Eq. (8) and Eq. (14) by minimizing AIC and SS. The SS was calculated as $\sum (V_{\text{measure}} - V_{\text{predict}})^2$ where V_{measure} was the determined value and V_{predict} was the relative volume predicted by the model. The AIC was calculated as $N\ln\sum w_i(V_{\text{measure}}-V_{\text{predict}})^2+2M$, where N was the number of the observations and M was the number of the parameters and w_i was the weight factor. These two values were used to evaluate the quality of the curve fitting.

Results and discussion

1 Goodness-of-fit of the proposed model

Five kinds of commonly used excipients powder were compacted at the pressure in the range of 50−500 MPa. These sets of experimental data were fitted with the proposed model [Eq. (8)] according to the principle of least squares, as shown in Figure 1. It was clear that experimental data almost lay on the fitting lines given by Eq. (8), which implied that Eq. (8) could well predict the variation of volume with compaction pressure for pharmaceutical powders.

The sum of SS and AIC were shown in Table 1. The SS values calculated from the models reflected the difference between the measured data and the predicted data. The AIC values were used to estimate the good-of-fit of the model to the experimental data. The results indicated that the predicted data of the model pharmaceutical powders calculated by the nonlinear

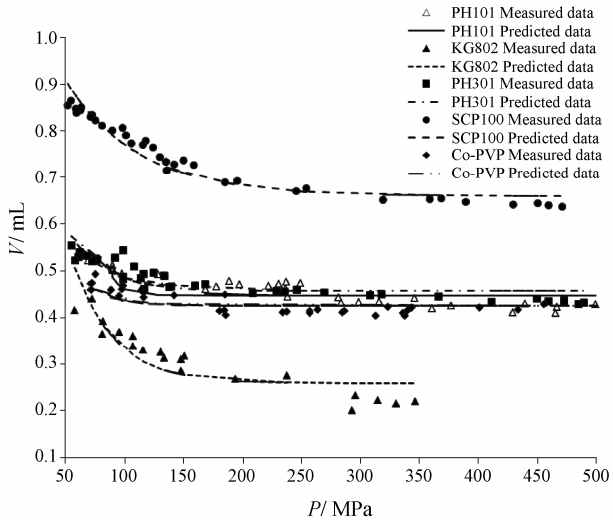

Figure 1 Volume (V)-compaction pressure (P) fitting curves of pharmaceutical powders wth the proposed compression model by non-linear least square regression

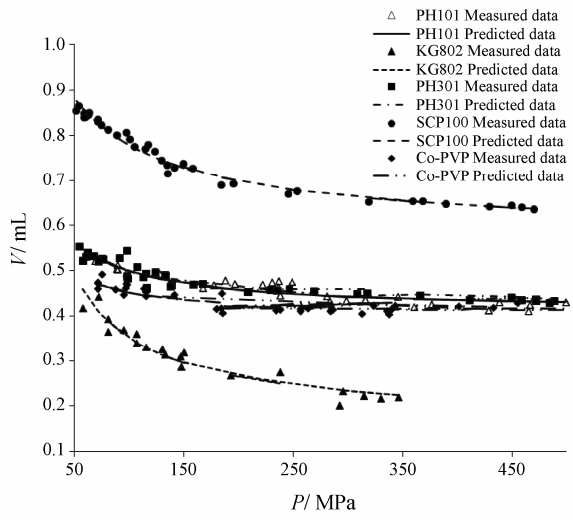

Figure 2 Volume (V)-compaction pressure (P) fitting curves of pharmaceutical powders wth Kawakita model by non-linear least square regression

Table 1 Calculated results of data-fitting with the proposed compression model. V_∞: The volume of compact while the applied pressure value $P\to\infty$; K: Compression coefficient representing for material compressibility; SS: Squared deviations; AIC: Akaikes informatics criterion

Powder	Parameter		SS	AIC
	V_∞	K		
PH101	0.259	28.750	2.622E-02	−72.463
KG802	0.448	33.162	1.236E-02	−132.183
SCP-100	0.660	16.047	1.415E-02	−153.545
Co-PVP	0.425	45.679	1.202E-02	−172.862
PH301	0.457	32.713	1.475E-02	−160.439

least square program were close to the corresponding measured data.

2 Goodness-of-fit of the Kawakita model

The compression behaviors of these pharmaceutical powders were evaluated with the Kawakita equation [Eq. (14)], as shown in Figure 2.

From this figure, the fitting results were similar to those of the new model, i.e. the experimental data points of these excipient powders almost fell on the predicted line calculated from the Kawakita model by means of non-linear regression method. Table 2 showed the results of the calculations of the Kawakita model. It was seen that the SS values and AIC values were in general small confirming the good-of-fit of Kawakita equation.

3 Analysis of the relationship between parameters and compaction mechanism

In the new proposed equation, the parameter

Table 2 Calculated results of data-fitting with Kawakita model. a: Parameter representing for the filling and flowability of materials; $1/b$: Parameter expressing the compressibility of materials

Powder	Parameter		SS	AIC
	a	$1/b$ (MPa)		
PH101	0.894	15.351	6.797E-03	−100.817
KG802	0.709	9.540	4.940E-03	−160.624
SCP-100	0.520	45.323	4.038E-03	−199.943
Co-PVP	0.722	4.965	5.305E-03	−205.564
PH301	0.639	11.935	5.616E-03	−198.100

K named compression coefficient represented the compressibility of powders. A comparison of the values of parameter K estimated from the proposed model indicated that the sequence of compressibility of these five kinds of materials was Co-PVP > KG 802 > PH 301 > PH 101 > SCP 100. The corresponding data were presented in Table 1.

The parameter $1/b$ estimated from Kawakita equation may be interpreted as the pressure needed to compress the powder to one half of the total degree of volume reduction estimated as a and as such they may be used as indicators of the tableting performance of the agglomerates. The smaller the parameter $1/b$ value, the better the compressibility. According to the values of parameter $1/b$ estimated from Kawakita equation, the compressibility of the pharmaceutical powders could be arranged in order as Co-PVP > KG 802 > PH 301 > PH 101 > SCP 100. This was consistent with the analysis result of the new proposed model.

Therefore, the new proposed model could be used as an alternate method of evaluating the compressibility

of pharmaceutical powders.

Conclusions

A new mathematical compaction model based on the compaction process and calculated through iterative non-linear regression was developed. It is concluded that the proposed model gave an excellent fit to the pressure-volume data. The quality of the curve fitting, evaluated from the SS and AIC, was at the same level as the Kawakita model. The information gained from the parameter of the model indicated quantitatively the fundamental compression mechanisms of the powder. Therefore, the model has the potential to evaluate of the deformation characteristics or compressibility of the powders.

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