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The application of factor analysis to evaluate deforming behaviors of directly compressed powders☆

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ABSTRACT

In this study we present an approach that describes plasticity and deformation behavior of well-known materials based on analysis of plasticity, elasticity and fragmentary behavior. The powders were compressed using Korsch XP1, and the correlations between compaction and physical parameters were analyzed by canonical correlation analysis (CCA). Factor analysis (FA) was employed to normalize compaction work, yield pressure measurements (*YP*) and determine elastic stretch for all our sample; these were scored and ranked accordingly. The canonical variables showed that true density (ρ_a), compression degree (C_p) and mean particle size (D_{50}) were associated with plastic coefficient (*PL*), *YP*, and fast elastic stretch (*FES*). When factor scores were used in combination with original data, the plasticity of our samples was sorted and ranked as high, intermediate, or low, which are in accord with plasticity rankings previously reported in literature [10]. Hence, physical and compaction data interval was established that evaluated powder deformation behavior during compaction. Finally, FA was used to further characterize deformation behavior during compaction.

1. Introduction

The Korsch XP1 is an inductive single-punch press, which can record the applied pressure to a powder bed, calculate punch displacement, measure die wall force, and obtain the contact time between punches and the powder bed. Once absolute tablet density and weight are input, the compaction work, Heckle equation, and other compression parameters can be obtained. Furthermore, such tablet machines can be controlled online and therefore are able to provide a more productive and research environment.

Direct compression of tablet formation has a number of advantages during production, such as less machine space, lower labor costs, less processing time and less energy consumption, which favors the pharmaceutical industry over traditional wet granulation methods [1,2]. However, poor compressibility and low mechanical strength can result from direct compression. Furthermore, slow disintegration rates can occur when high doses of active ingredient are used, especially those with poor flow properties and unexpected compactabilities. Therefore, the application of direct compression in producing tablets requires further developments.

Before addressing such issues, it is necessary to fully comprehend the deforming behavior and compactability of the excipients used in the direct production of tablets. In fact, because the excipient constitutes a large portion of the tablet, it can profoundly affect or dominate compaction properties. Therefore, the selection of appropriate excipients is regarded as the most important aspect of tablet development and design. The most compressible excipients frequently used in industry include cellulose, lactose, polyols, starch and mineral salts. At present deformation mechanisms can be mainly explained as plastic flow, brittle fracture and elastic recovery which are linked to surface contact and bonding formation of the tablet [3,4]; while high elasticity can reduce mechanical strength and give rise to capping or lamination [5,6]. Compression behavior greatly depends on how the physical properties of the powder will respond to pressure. The physical properties of various excipients can be used to predict compression behavior such as deformation characteristics, quality, functionality as well as aid in the design of pharmaceutical formulations [7].

The main methods employed to describe deforming behavior include the compression model, which is obtained based on the relative

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volume reduction, relative density increment or relative porosity changes with applied force, and the compaction energy consumption, which is obtained by integrating the force-displacement profile. Unfortunately both approaches are known to have limitations after long-term research [8,9]. Another widely used method for describing deformation behavior is multivariable analysis namely principle component analysis (PCA) [10,11], which transforms highly cross-correlated variables into a new system of principle component variables to shed light on the physical and mechanical properties of the powder. Factor analysis (FA), another multivariable analysis method, is an extension and expansion of PCA. Here, more complicated and mixed correlation variables can be integrated into several factors and applied to explore the measured and relative indicators, which can be simultaneously classified on the basis of combinative evaluation on extracted factors.

However, whether these above methods can be universally utilized to quantify a variety of materials, especially powder mixtures, has not been identified and verified. This is, in part, due to the time-consuming and uneconomical nature of the task at hand. We propose that the cheapest and easiest way to predict and identify the deformation characteristics of a powder or powder mixture is through a physical and compression data interval like an "ES" (expert system) [12,13]. The functional area of an ES not only can solve such a problem successfully but also can be used to make recommendations, decisions or predictions.

In this study, we have established a data interval applicable in characterizing the tablet behaviors of powder blends during compaction. We first analyzed the correlation between the physical properties and compression parameters for a range of powder types according to canonical correlation analysis (CCA). We then investigated the assortment of directly compressed powders using an analysis of composite factor scores.

Nineteen materials widely were selected that are widely used and well characterized in tablet production. These were ranked according to plastic deformation levels and then resulting compaction parameters were obtained. The ranking and sortation were in agreement with others in the literature [10,14–16]. The parameters obtained from the samples were used to establish our compressible and physical data intervals. As reference values, which subsequently were used to predict and analyze deforming behaviors of some unknown pharmaceutical powder or powder mixture. We therefore provide a validated and verified data interval for the evaluation of powder compression behavior that can be taken into account in future pharmaceutical research.

2. Materials and methods

2.1. Materials

Microcrystalline cellulose (Avicel PH102®, Bath P209820920), co-processed mixture of mannitol and microcrystalline cellulose (HFE PH102®, Bath XN06817380) and croscarmellose sodium (Ac-Di-Sol SD711, Bath TN09820947) were gift samples from FMC biopolymer, Philadelphia, USA. Mannitol (Pearlitol 200SD-Mannitol®, Bath E665G), sorbitol (Sweetpearl P300DC®, Bath E200M), and Potato starch® (Bath VEK47) were donated by Roquette, Lestrem, France. Silicified microcrystalline cellulose (Prosolv SMCC90®, Bath P9S9269; and Prosolv SMCC50®, Bath P5S9041), co-processed compound of microcrystalline cellulose, micro-silica, sodium carboxymethyl starch and sodium fumarate (Prosolv EASYtab®, Bath 4381303X), as well as some calcium salts involving calcium carbonate (Vivapress®, Bath 794590504), diacalcium phosphate dihydrate (Emcompress®, Bath 7091), calcium phosphate dibasic anhydrous (Anhudriys Emcompress®, Bath 3009), and calcium sulfate (Compactrol®, Bath 08021C) were free samples from JRS Pharma, GMBH & CO.KG, Rosenberg, Germany. Lactose such as agglomerated lactose (Tablettose 100®, Bath L0946A4023) and spray-dried lactose (Flowlac 100®, L1006), as well as starches including partially pre-gelatinized starch (Starch 1500®, Bath IN517075), and co-processed blend of corn starch and pre-gelatinized starch (StarCap 1500®, Bath IN518146) were contributed by Meggle Pharma, Wasserburg, Germany and Colorcon Indianapolis, USA respectively. Copovidone (Plasdone S-630®, Bath 1272473ACJ5) was also given for free by ISP Pharmaceuticals, American. Potassium chloride (KCl®, Bath Q0275) was purchased from Shanghai Yaji Biotechnology Co. Ltd.

2.2. Experimental measurements of physical properties

2.2.1. Flow property

It has been demonstrated that the flow properties of pharmaceutical powders directly affect die fill characteristics and weight variations that are necessary for direct compaction. There are plenty of approaches used that evaluate flowability, these include, the velocity of flow, angle of repose (*AR*), Jenike shear index, Carr's index and Hausner ratio.

In the present work, the combination *AR* with compression degree (C_p) according to $F = 2\sqrt{AR*Cp}$ was used to characterize powder flowability (lower *F* value corresponded to increased flow property). *AR* and C_p were measured 3 times by a BT-1000 type instrument (Dandong Baite Instrument Co. Ltd., Dandong, China).

AR was measured as the maximum angle between the horizontal and the free surface of powder pile after a land slide has restored the pile to a metastable equilibrium slope [17]. C_p was defined as:

$$C_p = \frac{(\rho_t - \rho_b)}{\rho_t} * 100\% \quad (1)$$

where, ρ_b, bulk density ($g{\cdot}cm^{-3}$); ρ_t, tapped density ($g{\cdot}cm^{-3}$).

2.2.2. Particle size distribution

Particle size distribution of all substances, including D_{10}, D_{50} and D_{90} was determined using the dry method three times (Mastersizer 2000, Malvern Instruments Ltd., England). The *Span* was obtained from the following equation:

$$Span = e^{\frac{D_{90} - D_{10}}{D_{50}}} \quad (2)$$

where D_{10}, D_{50} and D_{90} were particle sizes (μm^{-1}) for 10%, 50% and 90% of particles respectively.

2.2.3. Moisture content (MC)

The samples (1–3 g) were tested using the Sartorius MA35 instrument (Sartorius scientific Instrument, Germany). Each sample was placed on an aluminum pan and heated to 105 °C, except for Plasdone S-630, which was heated to only 80 °C to prevent damage to the molecular structure. The percentage of *MC* was computed until the weight was constant. Each sample was tested three times.

2.2.4. Absolute density (ρ_a)

ρ_a was determined by helium pycnometry in triplicates upon ten repetitive purges cycles (Micromeritics AcuuPyc™II1340, Micromeritics Instrument Co., American).

2.3. Tablet preparation

The Korsch XP1 instrument (Korsch AG, Berlin, Germany) was used and the selected substances were tableted with the speed of 10 strokes·min^{-1}. Inhomogeneity of stress delivery during the compaction process may result in the density distribution gradient of the tablet being decreased as filling height is increased. Therefore, the filling depth was fixed at 8.0 mm [18], and each material was compressed by using four different pressures. Prior to compaction, the upper punch, lower punch and die-wall were lubricated with a suspension of magnesium stearate in acetone (the contribution of magnesium stearate was 5 w/v%). Powder from each sample was needed to fill into the feeder afterwards. Initially compressed tablets were abandoned because no signal could be recorded before the data recording software (Pharmaresearch) was initialized. The tablet was weighed and the mass (M) recorded