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Original Research Paper

Evaluation of fundamental and functional properties of natural plant product powders for direct compaction based on multivariate statistical analysis

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ABSTRACT

Direct compaction (DC) is the preferred choice for tablet manufacturing; however, its application in natural plant product (NPP) tablets is still extremely immature. In this study, NPP powders prepared by three commonly used methods were evaluated on their suitability for DC. Extensive characterizations of their physical properties were performed. Multivariate statistical analysis was utilized to explore the influence of preparation technology on the properties of NPP powders and identify the dominating factors that influence their DC properties. The results demonstrated that (i) the 27 kinds of model NPP powders selected randomly in this study could to some degree represent most NPP powders used in actual production; (ii) ~81.5% of the NPP powders exhibited both poor compactibility and flowability, and none of the NPP powders could be compacted into tablets via DC; (iii) the physical properties of NPP powders prepared by direct pulverization were significantly different from those of extracted ones, while there were no significant differences between the water and ethylalcohol extracted ones; and (iv) the DC properties of NPP powders could be improved through controlling some physical properties (e.g., density, particle size, morphology, and texture parameters) reasonably. Overall, this study comprehensively evaluated the current status and application of NPP powders in DC, and is significant in facilitating the development and modernization of NPPs through DC.

1. Introduction

Originated before christ, natural plant products (NPPs) have long been used for their health functions in clinical practice [1]. Nowadays NPPs attract more and more attention, receive an increasing acceptance, and experience a rise in popularity from a global scope because of their vital role in prevention and treatment of diseases and their nontoxicity to living organisms [1,2]. However, there are still many barriers hindering the modernization and globalization of NPPs. One is the preparation and administration inconvenience of decoctions (the most common and important dosage form for NPPs). Additionally, most of NPPs are needed to be taken chronically. Therefore, NPP tablets are now the preferred choice due to their multifarious merits, e.g., no need of extemporaneous preparation, easiness to be stored and taken, and accurate dose [3].

Tablets, as a conventional platform, continue to be the dosage form of choice and constitute about half of solid dosage forms in contemporary use [4–6]. Direct compaction (DC) is the preferred choice for tablet production due to its simplicity and continuous nature, cost and time effectiveness, and elimination of heat and moisture effects [5,7–11]. However, most NPP powders cannot be

Abbreviations: AR, angle of repose; AUTCC, area under tensile strength versus compaction force curve; CF, compaction force; ChP, Chinese Pharmacopeia; CR, compaction ratio; d(0.5), particle size; DC, direct compaction; DP, direct pulverization; E-E, ethylalcohol extraction; EF, ejection force; E_{SP}, net energy per unit of quality; E_T, total energy; E_1, friction energy; E_2, energy retained during unloading; E_3, energy loss during unloading; f, equilibrium hygroscopic moisture content; FES, fast elastic stretch; k, absorption moisture rate constant; MC, moisture content; NPP, natural plant product; PL, percentage of net energy except friction energy; ρ_b, bulk density; ρ_t, tapped density; ρ_{true}, true density; R_i, percentage of each energy; R^2, square of the correlation coefficient; RMSE, root mean square error; Span, particle size distribution; SSE, sum of squares for error; TS, tensile strength; UDWF, upper die wall force; W-E, water extraction.

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Table 1
27 kinds of common NPP powders selected based on three preparation technologies.

Ethylalcohol extraction powders	Code	Water extraction powders	Code	Direct pulverization powders	Code
Paeoniae Radix	A1	Andrographis Herb	B1	Andrographis Herb	C1
Rhodiolae Crenulatae Radix et Rhizoma	A2	Taraxaci Herba	B2	Taraxaci Herba	C2
Puerariae Lobatae Radix	A3	Astragali Radix	B3	Puerariae Lobatae Radix	C3
Salvia Miltiorrhiza Radix et Rhizoma	A4	Salvia Miltiorrhiza Radix et Rhizoma	B4	Salvia Miltiorrhiza Radix et Rhizoma	C4
Polygonati Rhizoma	A5	Citri Reticulatae Pericarpium	B5	Citri Reticulatae Pericarpium	C5
Silybi Fructus	A6	Gardeniae Fructus	B6	Gardeniae Fructus	C6
Ziziphi Spinosae Semen	A7	Sterculiae Lychnophorae Semen	B7	Ziziphi Spinosae Semen	C7
Zingiberis Rhizoma	A8	Sophorae Flos	B8	Sophorae Flos	C8
Poria	A9	Ganoderma	B9	Poria	C9

processed into tablets via DC because of their poor functional properties (e.g., poor flowability and compactibility) [5,8,9]. Furthermore, the relevant researches on the functional properties for DC mainly focus on excipients and chemical drugs [12–14], rather than on NPPs. Compared to the two formers, NPP powders often have a much more complex composition, leading to their complex properties. Moreover, NPP powders commonly exhibit high hygroscopicity, low glass transition temperatures, poor flowability and compactibility, and high doses, all of which severely decrease their DC suitability. Therefore, it is of great importance to research the DC properties of NPP powders and explore the barriers that prevent the development and application of DC in production of NPP tablets.

It has been reported that the physical properties of powders can be divided into two groups: fundamental properties and functional properties. These properties are interdependent. Functional properties (e.g., flowability and compactibility) are determined by fundamental properties (e.g., particle morphology, size, shape, surface area, porosity, and density) [5,15], which, in turn, are mainly determined by particle structure. Therefore, it's reasonable to believe that the particle structure also affects functional properties of particles significantly [5]. The particle structure is mainly affected by the preparation technologies of powders. In the actual production, NPP powders are commonly prepared by three methods, i.e., direct pulverization (DP), water extraction (W-E), and ethylalcohol extraction (E-E). The DC properties of powders are also related to chemical properties (e.g., surface energy) more or less. Generally, there is a directly proportional relationship between tablet strength and particle surface energy [16–20]. Fichtner et al. have demonstrated that reducing the dispersive surface energy of particles would increase the pressure needed to form a compact with a predetermined tensile strength [16]. On the other hand, reducing the surface energy could improve the flowability and bulk density of particles [19]. In addition, the chemical composition of materials also affects their DC properties. For example, polar components are generally conducive to the compactibility.

In light of the above, this study aimed to evaluate the key DC properties (i.e., flowability and compactibility) of NPP powders and explore the key factors affecting them. Firstly, 27 kinds of commonly used NPP powders (Table 1) were randomly selected as the model materials. Next, their physical properties were fully characterized. Then, the multivariate statistical analysis was utilized to explore the influence of the preparation technology of NPP powders, evaluate the DC properties of NPP powders, and identify the dominating factors that influence these DC properties.

2. Materials and methods

2.1. Materials

Natural plant pieces were purchased from Shanghai Kangqiao Chinese Medicine Tablet Co., LTD (Shanghai, China). All the pieces were ground in an impact mill to the pulverization degree of 80 mesh except *Puerariae Lobatae Radix* (C3). C3 was prepared by an ultrafine grinder because of its fibrous nature. NPP extracts, including A1, A4, B2, B4, B6, B8, B9, were purchased from Liwah Plant Extract Co., LTD (Ningbo, China), and the other extracts were purchased from Hanzhong TRG Biotech Co., LTD (Xi'an, China).

2.2. Compactibility

Materials were compacted into tablets directly on a fully instrumented single punch press (Korsch XP1, Germany) using 8.5 mm and round flat-faced tooling. The compaction force was 3, 6, or 9 kN, and the compaction speed was 10 tablets/min. The tablet mass was approximately 200 mg. Magnesium stearate (MgSt) was compacted before every tableting for lubrication. The breaking force of tablets was measured immediately by a crushing force tester (YD-20KZ, TIANDA TIANFA-pharmaceutical testing instruments, Ltd., China). Tensile strength (TS) of tablets was calculated from the breaking force (F), tablet thickness (T), and diameter (D) using Eq. (1) [21]. Compactibility was characterized by the area under TS versus compaction force curve (AUTCC) from 3 kN to 9 kN [22].

$$TS = \frac{2F}{\pi DT} \tag{1}$$

2.3. Angle of repose (AR)

AR was characterized by using a fixed funnel, a base with known radius (r), and a retaining lip to allow of symmetric cone by the material. The materials were poured from the funnel at a certain height (6.3 cm) onto the selected base uniformly. The pouring of the material was stopped when the heap reached a qualified cone. The height (h) of the cone was measured, and AR (θ) was calculated from Eq. (2):

$$\tan\theta = \frac{h}{r} \tag{2}$$

2.4. Specific surface area, uniformity, d(0.5) (median particle size), and Span

These properties were determined by laser diffraction (Marlven 2000, Marlven Instruments Ltd., England; dry method) with a Scirocco dry module. The Dispersive Air and Vibration Feed were 1.5–1.8 bar and 25–30%, respectively. Span represented the width of a particle size distribution and was defined as Eq. (3). The specific surface area of powders was calculated from the particle size distribution data assuming a spherical particle shape [23].

$$Span = \frac{d(0.9) - d(0.1)}{d(0.5)} \tag{3}$$

where d(0.1), d(0.5), and d(0.9) were the particle size values at which 10%, 50%, and 90% of the particles fell below, respectively.

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