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Characterization of tableting properties measured with a multi-functional compaction instrument for several pharmaceutical excipients and actual tablet formulations

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ABSTRACT

Before designing tablet formulations, it is important to understand the "Tableting Properties" of excipients and API (active pharmaceutical ingredient) powders. Those properties refer to "Compressibility", "Compactability" and "Manufacturability", which are difficult to evaluate quantitatively. In this study, we aimed to evaluate the "Tableting Properties" by using a benchtop single-punch tablet press, developed recently to measure these parameters using a single device. In order to facilitate understanding of the results visually, we proposed a new plot, where the X-axis showed the tensile fracture stress and the Y-axis showed the ejection stress. This plot, which is composed of four regions, shows the combination of "Compactability" and "Manufacturability". We confirmed the ability of this device to evaluate the characteristics of typical pharmaceutical additives as a value of "Tableting Properties". Losartan potassium was used as an API, and Dilactose R and MCC as an excipient with good "Tableting Properties". The ejection stresses of losartan potassium and Dilactose R were very high. An increase in magnesium stearate shifted the point along the Y-axis in this plot, and it meant an improvement in "Manufacturability". It was confirmed that the device and plot are useful in designing formulations efficiently using a small amount of sample powders.

1. Introduction

Many kinds of powders such as excipient, binder, disintegrating agent and lubricant, are used to develop a tablet formulation. To obtain a final tablet formulation efficiently and quickly, it is important to know the compression properties of each powder. Generally, the "Tableting Properties" of powders can be evaluated mainly in terms of "Compressibility" and "Compactability". "Compressibility" is estimated by measuring the changes in the bulk density of the powder bed continuously when it is pressedcompressed. Various researchers have studied this property using Kawakita, Heckel and other equations, which are frequently used as an indicator of "Compressibility" (Kawakita and Ludde, 1969; Heckel, 1961a,b; Klevan et al., 2010). On the other hand, "Compactability", which relates to the binding force between particles that is caused by applying pressure, shows the extent of tablet strength. The fact that powders have a high degree of plastic deformability means that the contact area between particles can be increased efficiently, and plastic deformability is thus a desirable property for good "Compactability" (Tesfai and Goran, 1999). Conversely, elastic deformability may be an undesirable property with respect to "Compactability". However, it is not actually easy to evaluate the plasticity or elasticity of a single particle directly. "Compactability", by measuring the hardness of the resulting tablets, is commonly regarded as an indicator (David and Augsburger, 1977). Furthermore, when manufacturing actually, we should consider "Manufacturability" alongside "Compressibility" and "Compactability". For example, friction between the tablet and die wall causes binding (i.e., tablet failure) on the side of tablet when the compressed tablet is ejected from the die. It means that formulations should be designed to have less ejection stress. In other words, preparing tablets calls for favorable conditions in terms of these three measures of performance ("Compressibility",

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"Compactability" and "Manufacturability"), which are comprehensively evaluated to provide the "Tableting Properties".

When the formulation is designed, it is necessary to determine the types, grades, and amounts of additives to be added to the preparation. However, in general, these selections and decisions are often based on designers' rules of thumb and formulation design is almost never done with an understanding of the "Tableting Properties". Therefore the overlooked problems may lead to production troubles in the case of mass production or defects in products after distribution. For this reason, if the "Tableting Properties" can be firmly understood, it could conceivably lead to a formulation design without complications. Recently, a variety of additives have been developed for the purposes of tablet manufacture and many additives are also being used during the direct compression method of tablet production. However, since the direct compression method is a simple method of production where the powders are mixed, and then compressed into tablets, the additives included in the formulation for direct compression should show sufficient "Tableting Properties". Mannitol and lactose granulated by methods such as the spray dry method or the fluid-bed method of wet granulation are examples of additives that may be used with the direct compression method, and they are generally reputed to be additives with excellent "Compressibility" and "Compactability" (Ilic et al., 2009). Nevertheless, "Tableting Properties" are rarely compared quantitatively, and they are often treated as nothing more than formulation designers' rules of thumb.

It is difficult to evaluate "Tableting Properties" quantitatively. Recently the "Gamlen Tablet Press (GTP-1, benchtop single-punch tablet press)" has been developed for measuring "Compressibility", "Compactability" and "Manufacturability" in a single device. That is, this machine make it possible to measure pressure and displacement in the compression process, as well as the friction during ejection and then the hardness of the resulting tablets. It is expected that GTP-1 will enable the accurate measurement of not only "Compressibility", but also "Compactability" and "Manufacturability".

Therefore, in this paper, using the aforementioned GTP-1, we have attempted to express the characteristics of typical pharmaceutical additives quantitatively as a value of "Tableting Properties". In other words, we compared finely powdered lactose and mannitol, which are not typically used in the direct compression method, with granulated lactose and mannitol, which are used in the direct compression method. From the results, we attempted to clarify the extent to which the "Tableting Properties" of additives for direct compression are superior. In addition, we also measured the "Tableting Properties" value of microcrystalline cellulose, which has excellent "Compressibility" and "Compactability", to check the applicability of the measurements of additives using the GTP-1 (Zhang et al., 2003; Jivraj et al., 2000).

Furthermore, we investigated whether GTP-1 and our plot are useful to decide the types, grades and amounts of additives in tablet formulation design. A tablet with Losartan Potassium (LP) was chosen as a model preparation.

2. Materials and methods

2.1. Materials

Fine powder lactose monohydrate (Pharmatose 200 M, DMV, The Netherlands), granulated lactose (Dilactose R, Freund Corporation, Japan), spraydried lactose (FlowLac 90, Meggle, Germany), fine powder mannitol (Mannitol P, Shigma-Aldrich, Sweden), granulated mannitol (Granutol R, Freund Corporation, Japan), spraydried mannnitol (Parteck M200, Merck, Germany), microcrystalline cellulose (MCC 102, Ceolus PH102, Asahi Kasei Chemicals, Japan), microcrystalline cellulose (MCC 302, Ceolus PH302, Asahi Kasei Chemicals, Japan), partly pregela- tinized starch (Starch 1500, Nippon Calorcon, Japan), magnesium stearate (Taihei Chemical, Japan), and losartan potassium (Kolon, Korea) were purchased.

2.2. Methods

2.2.1. Equipment

A benchtop single-punch tablet press used in this paper is the Gamlen Tablet Press (GTP-1). The upper punch pressure and displacement during the compression process, the friction between die and tablet in the ejection process (ejection stress), and the strength of the tablet (tensile fracture stress) after the ejection can be measured using this equipment. First, the sample powder is filled into a die of the GTP-1, and then an upper punch descends at a fixed speed (30 mm/min). Secondly, when the compressed tablet is ejected from the die, the friction force between the die and the tablet is measured. Finally, the hardness of the ejected tablet is measured by using the same equipment. One hundred mg of sample mixture loaded into die was compressed at a load of 500 kg by using the GTP-1 with a flat punch of 6 mm in diameter. The compression speed was 30 mm/minute, and all measurements were repeated three times. The sample powders indicated in 2.2.2 and 2.2.3 were evaluated.

2.2.2. Evaluation of pharmaceutical excipients

Pharmatose 200 as a fine powder lactose hydrate, Dilactose R as a lactose granule for direct compression, and FlowLac 90 as a spry-dried lactose granule for direct compression were evaluated. Mannitol P as a fine powder mannitol, Granutol R as a mannitol granule for direct compression, and Parteck M200 as a spray-dried mannnitol granule for direct compression were evaluated. MCC 102 and MCC 302 as a microcrystalline granules for direct compression were evaluated.

2.2.3. Evaluation of formulations

For the decision of the types of additives and their amounts in the formulation, the GTP-1 was used. Losartan potassium (hereafter LP) was chosen as a model active pharmaceutical ingredient. The formulations are indicated in Tables 1 and 2. The weight of each tablet was set to 150 mg, and the content of LP produced 3 standards (25 mg, 50 mg and 75 mg per a tablet).

Table 1
Formulations.

Sample	A	B	C	D	E	F	G	H	I	P
Losartan Potassium (LP)	25	25	25	50	50	50	75	75	75	50
Dilactose R	25	25	25	26	25.5	25	25	25	25	23
MCC 302	85	84.5	84	59	59	59	35	34.5	34	59
Starch 1500	15	15	15	15	15	15	15	15	15	15
Magnesium Stearate (MgSt)	0	0.5	1	0	0.5	1	0	0.5	1	3
total	150	150	150	150	150	150	150	150	150	150

(Unit: mg).