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Prediction of effects of punch shapes on tableting failure by using a multi-functional single-punch tablet press

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ABSTRACT

We previously determined "Tableting properties" by using a multi-functional single-punch tablet press (GTP-1). We proposed plotting "Compactability" on the x-axis against "Manufacturability" on the y-axis to allow visual evaluation of "Tableting properties". Various types of tableting failure occur in commercial drug production and are influenced by the amount of lubricant used and the shape of the punch. We used the GTP-1 to measure "Tableting properties" with different amounts of lubricant and compared the results with those of tableting on a commercial rotary tableting machine. Tablets compressed with a small amount of lubricant showed bad "Manufacturability", leading to sticking of powder on punches. We also tested various punch shapes. The GTP-1 correctly predicted the actual tableting results for all punch shapes. With punches that were more likely to cause tableting failure, our system predicted the effects of lubricant quantity in the tablet formulation and the occurrence of sticking in the rotary tableting machine.

1. Introduction

In developing a tablet formulation, it is necessary to understand "Tableting properties" and to determine the optimum type, grade, and amount of ingredients. "Compressibility" is evaluated by loading pressure onto a powder bed while measuring the bulk density of the bed. The properties of formulated powders have been investigated by using the equations of Kawakita and Ludde [1], Heckel [2,3], and Klevan et al. [4]. Some constants in these equations are frequently used as indicators of "Compressibility". "Compactability" is typically evaluated by measuring the tensile fracture stress (TFS) of tablets as a function of compaction pressure [5,6]. "Manufacturability" concerns tableting failure (e.g., sticking, capping, and binding). Sugimori et al. proposed that capping could be predicted from

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residual die wall pressure [7]. Urabe et al. suggested that estimation of general tableting properties and failures was possible by using a micro-powder characterizer with infinitesimal quantities of powder sample [8,9].

Combining these separate tests, the Gamlen Tablet Press (GTP-1; Gamlen Tableting Ltd., Nottingham, UK), a benchtop single-punch tablet press, measures pressure and displacement during compression, the friction between die and tablet during ejection (ejection stress), and the strength of the tablet (TFS) in a single device. In our previous study, we suggested the use of TFS as an indicator of "Compactability" and ejection stress as an indicator of "Manufacturability", as die wall friction can be problematic when the tablet is ejected from the die [10]. We evaluated "Compressibility", "Compactability", and "Manufacturability" with a GTP-1 and plotted TFS (i.e., "Compactability") on the x-axis against ejection stress (i.e., "Manufacturability") on the y-axis to allow visual evaluation of the quantitative "Tableting properties" of formulations. This method makes it possible to reach an optimum tablet formulation quickly. We demonstrated the usefulness of the method by using losartan potassium as an active pharmaceutical ingredient, microcrystalline cellulose as an excipient, and magnesium stearate (MgSt) as a lubricant in a model formulation. We confirmed quantitatively that the microcrystalline cellulose increased the "Compactability", and that the amount of MgSt and mixing time affected both "Compactability" and "Manufacturability".

Commercial drug production uses rotary tableting machines with much more dynamic tableting conditions than the GTP-1. We therefore need to determine the relationship between the results obtained with each apparatus. Pitt et al. reported that "Compactability" determined by the GTP-1 agreed with that produced by an industrial tableting machine (Fette; Fette Compacting, Germany) [11]. They found that measurement of the ejection stress using the GTP-1 was useful in predicting the occurrence of capping during commercial-scale tableting of formulations with different levels of microcrystalline cellulose. In general, tableting failures are strongly affected by the amount of lubricant in the formulation and the shape of the tablet (i.e., the punch shape). A lack of lubricant lowers "Manufacturability" and leads to tableting failure [12,13]. On the other hand, too much lubricant reduces "Compactability" and thus tablet strength [14]. In addition, some punch shapes are more prone to tableting failure, notably punches that have secant lines, embossed marks, and large curves on their surfaces [15,16]. When these types of punches are used, more lubricant is needed in the formulation to prevent tableting failure. When predicting "Tableting properties" at the production scale by using the GTP-1, both "Compactability" and "Manufacturability" need to be satisfactory, and the shape of the punch must be chosen to minimize tableting failure.

Here, we prepared four formulations with different amounts of lubricant. We measured the "Compactability" and "Manufacturability" of these formulations with the GTP-1, plotted the results, and compared them with the results of production-scale tableting. We also compared "Tableting properties" using punches of various shapes. The aim of this study was to examine the usefulness of measuring "Tableting properties" with the GTP-1 for the development of formulations in commercial drug production.

2. Materials and methods

2.1. Materials

We purchased granulated lactose (Dilactose R; Freund Corporation, Japan), microcrystalline cellulose (MCC: Ceolus PH302, Asahi Kasei Chemicals, Japan), partly pregelatinized starch (Starch 1500; Nippon Calorcon, Japan), magnesium stearate (MgSt; Taihei Chemical, Japan), and losartan potassium (LP; Kolon, Korea).

2.2. Methods

2.2.1. Sample preparation

Tablets with the formulations listed in Table 1 were prepared by direct compression. In all cases the quantity was 450 g, which is enough to make 3000 tablets of 150 mg each at the manufacturing scale. LP, Dilactose R, MCC, and Starch 1500 were mixed in a plastic bag and sieved through a 12-mesh sieve. The sieved powder was mixed for 10 min at 10 rpm in a rotary mixer (CB1-5/10; 10 L; Picks Technica, Japan). MgSt was added to the mixture at 0, 0.5, 1, or 3 mg per tablet (Table 1) and then samples B (MgSt 0.5), C (MgSt 1), and D (MgSt 3) were mixed for a further 60 min.

2.2.2. Evaluation of formulations on the GTP-1

The GTP-1 measures the upper punch pressure and displacement during compression, the ejection force (the friction between the die wall and the tablet during ejection), and the strength of the tablet (TFS) after ejection. To make a tablet, 100 mg of powder is placed in the die of the GTP-1 and compressed at 4.9 kN by the upper punch (a flat punch 6 mm in diameter) at a fixed 30 mm/min. All formulations were pressed and measured three times. The methods of calculation and plotting are described in our previous report [10].

2.2.3. Evaluation of formulations on the rotary tableting machine

Four types of formulation (A to D, Table 1) with various amounts of lubricant were compressed on a rotary tableting machine (Virgo-512, Kikusui Seisakusho, Japan). About 600 tablets (150 mg each, 90 g total) were continuously compressed at around 6.0 kN and 30 rpm. Four different types of punch were used: Type 1, flat punch with a secant line; Type 2, convex cup punch (R [major cup radius] = 11 mm); Type 3, compound cup punch (R = 9 mm, *r* [minor cup radius] = 3 mm); and Type 4, convex cup punch with a secant line and embossed marks (R = 9) mm (ø 7.5 mm each; Fig. 1). The cup radius was taken as a single arc generated from the tablet's centerline (midpoint) across the tablet's diameter, minor axis, or major axis. In Types 2 and 4,

Table 1 – Formulations.

Sample	A	B	C	D
Losartan potassium (LP) (mg)	50	50	50	50
Dilactose R (mg)	26	25.5	25	23
Ceolus PH302 (MCC) (mg)	59	59	59	59
Starch 1500 (mg)	15	15	15	15
Magnesium stearate (MgSt) (mg)	0	0.5	1	3
Total	150	150	150	150