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.

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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
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 tabletting 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 tabletting 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 tabletting 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 tabletting 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 (φ 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,

| 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|
the convex cup punches had a single radius, whereas in Type 3, the convex cup punch had two radii. The surface of every tablet was visually inspected. Tableting was terminated when failure occurred. Tablet hardness was measured five times with a hardness tester (Portable Checker PC-30, Okada Seiko, Japan).

3. Results and discussion

3.1. “Tableting properties” of model formulations with different amounts of lubricant

Our method for visually assessing “Tableting properties” plots TFS (hardness) on the x-axis and ejection stress (“Manufacturability”) on the y-axis [10]. The graph is divided into four ranges (Fig. 2). If a point is plotted in range (I) (lower right), the formulation has superior “Compactability” and “Manufacturability”. Conversely, if a point is plotted in range (IV) (upper left), the tablet is soft and die wall friction is high, indicating problems with both “Compactability” and “Manufacturability”.

Four types of formulation (samples A to D in Table 1) with different levels of lubricant were prepared, and then compressed by using the GTP-1 (Table 2). Sample A (MgSt 0) had good “Compactability” (TFS ≥ 2 MPa), but bad “Manufacturability” (ejection stress ≥ 5 MPa), and so was plotted in range (III). Samples B and C, with increasing amounts of MgSt, were plotted in range (I), indicating much better “Manufacturability”. Samples with insufficient lubricant, which lowers “Manufacturability”, are plotted in range (III) or (IV) [12,13].

Sample D (MgSt 3) had reduced “Compactability” (TFS = 1.83 MPa), but good “Manufacturability” (ejection stress = 1.01 MPa), and was plotted in range (II). Too much lubricant decreases “Compactability” and thus tablet hardness (Shah and Mlodozeniec, 1977). This corresponds to plotting in range (II) or (IV). Our method makes it possible to visualize the effects of lubricant quantity on “Tableting properties”. The placement of samples B and C in range (I) indicated no problems with “Compactability” or “Manufacturability”. In contrast, the placement of sample A in range (III) indicated problems with “Manufacturability” (sticking and binding); and the placement of sample D in range (II) indicated potentially low tablet hardness. Optimization of formulations so that the data fall in range (I) will achieve durable physical properties during distribution and use [17,18].

3.2. Comparison of “tableting properties” predicted by using each apparatus

We tested the ability of the method described in section 3.1 to predict the results of tableting on a commercial rotary
A tableting machine using a Type 1 punch (flat punch with a secant line; Fig. 3A). Samples B (MgSt 0.5), C (MgSt 1), and D (MgSt 3) were tableted without any problems. Sample A (MgSt 0) left materials stuck to the surface of the punch (Fig. 3B), which interfered with the tableting process after 130 to 140 presses (Fig. 3; Table 3). This result was consistent with the plotting of sample A in range (III) in section 3.1. The prediction for sample D (MgSt 3) placed it in range (II), indicating poor “Compactability”, because tablet hardness decreases as the amount of lubricant is increased. As predicted, the tablet hardness of sample D was lower than those of samples A, B, and C (Table 4, Type 1).

### 3.3. Evaluation of “tableting properties” on the rotary tableting machine with various punches

The results in section 3.2 agreed with those in section 3.1 when a flat punch with a secant line was used. We also tested different punches with curved surfaces (with different curvatures), secant lines, and embossed marks (Fig. 1). When a Type 3 compound cup punch was used, the particles at the center of the tablet did not deform as much as those at the periphery (Fig. 4). This difference indicates that use of a compound cup punch may make it difficult to compress tablets evenly across the surface. On the other hand, the use of a flat punch is not prone to sticking on the punch surfaces. Therefore, punches with a suitable shape have to be chosen carefully, depending on the powder formulation.

### Table 2 – “Tableting properties” of model formulations with different amounts of lubricant evaluated with the benchtop single-punch tablet press.

| Sample | “Compactability”: TFS (MPa) | “Manufacturability”: ejection stress (MPa) | “Compressibility”: elastic recovery (%) | Plot range |
|--------|-----------------------------|------------------------------------------|----------------------------------------|------------|
| A (MgSt 0) | 2.88 ± 0.10 | 8.21 ± 0.78 | 32.97 ± 0.56 | III |
| B (MgSt 0.5) | 2.66 ± 0.16 | 3.25 ± 0.77 | 35.03 ± 1.03 | I |
| C (MgSt 1) | 2.27 ± 0.07 | 1.54 ± 0.00 | 36.64 ± 0.26 | I |
| D (MgSt 3) | 1.83 ± 0.04 | 1.01 ± 0.09 | 38.78 ± 0.38 | II |

### Table 3 – Numbers of tablets successfully produced with punches of each type in GTP-1.

| Sample | Plot range | “Manufacturability” | Type 1 | Type 2 | Type 3 | Type 4 |
|--------|------------|---------------------|--------|--------|--------|--------|
| A (MgSt 0) | III | Bad | 130–140 | 165–175 | 5–15 | 20–30 |
| B (MgSt 0.5) | I | Good | 600a | 600a | 5–15 | 95–105 |
| C (MgSt 1) | I | Good | 600a | 600a | 105–115 | 600a |
| D (MgSt 3) | II | Good | 600a | 600a | 600a |

Type 1: flat punch with a secant line; Type 2: convex cup punch (R = 11); Type 3: compound cup punch (R = 9, r = 3); Type 4: convex cup punch with a secant line and embossed marks (R = 9).

* The tablets were manufactured without any failure using the total amount of formulated powders.

### Table 4 – Hardness (N) of tablets manufactured on a rotary tableting machine.

| Sample | Plot range | “Compactability” | Type 1 | Type 2 | Type 3 | Type 4 |
|--------|------------|------------------|--------|--------|--------|--------|
| A (MgSt 0) | III | Good | 61.0 ± 2.3 | 54.2 ± 5.4 | 42.0 ± 2.6a | 51.4 ± 4.8a |
| B (MgSt 0.5) | I | Good | 53.2 ± 3.3 | 44.4 ± 2.9 | 35.8 ± 2.0a | 39.0 ± 2.2 |
| C (MgSt 1) | I | Good | 49.2 ± 4.7 | 42.6 ± 4.3 | 35.6 ± 2.5 | 35.8 ± 1.9 |
| D (MgSt 3) | II | Bad | 34.6 ± 1.8 | 29.8 ± 1.6 | 28.0 ± 0.7 | 26.8 ± 1.3 |

Type 1: flat punch with a secant line; Type 2: convex cup punch (R = 11); Type 3: compound cup punch (R = 9, r = 3); Type 4: convex cup punch with a secant line and embossed marks (R = 9).

* Tablets could not be formed with these formulations. Therefore, the surface of the punches was lubricated with magnesium stearate and tableting was performed again.
When the Type 2 convex cup punch ($R = 11$) was used, samples B (MgSt 0.5), C (MgSt 1), and D (MgSt 3) were tableted without any failures (Table 3). However, after only 165 to 175 tablets were compressed, tablets of sample A (MgSt 0) would not separate from the surface of the punch and were caught on the scraper and broke apart. The surface of the punch was covered with powder. This result corresponded with the plotting of sample A in range (III) (Fig. 2), indicating poor “Manufacturability”.

When the Type 3 compound cup punch ($R = 9, r = 3$) was used, sample D (MgSt 3) was tableted without any failures (Table 3). In contrast, sample A (MgSt 0) adhered to the punch immediately, and the cup began to fill with powder. Sample B (MgSt 0.5) covered the surface of the punch as soon as compression began: only 5 to 15 tablets were pressed before the tablets became difficult to separate from the punch and broke apart. Sample C (MgSt 1) began to adhere to the center of the cup after 105 to 115 tablets had been pressed, and a dimple-like indentation appeared in the center of the tablet. Ejection stress (on the y-axis), which was associated with the occurrence of tableting failure, increased in the order of samples D < C < B < A. Therefore, the results obtained with the GTP-1 correctly predicted the tableting success on the rotary press.

Many tablets have both secant lines and embossed marks. Punches such as Type 4, with a complex surface shape, are often used in commercial tablet production. When such punches are used, tableting failures, such as sticking, tend to occur around secant lines and embossed marks. When the Type 4 punch was used, samples C (MgSt 1) and D (MgSt 3) were tableted without any problems (Table 3). In contrast, sample B (MgSt 0.5) covered the surface of the punch after 95 to 105 tablets were pressed, and became difficult to separate from the punch and broke apart. Sample C (MgSt 1) did not stick, but both B and C were plotted in range (I) (Table 3). The GTP-1 experiment correctly predicted the increased possibility of failure by the distance between samples B and C in the plot. Sample A (MgSt 0) filled the cups of all punches (Fig. 5), forcing us to stop the compression. Nevertheless, the number of tablets successfully compressed before sticking (Table 3) was associated with the degree of ejection stress, confirming the placement of sample A in range (III) (Fig. 2).

We measured the hardness of tablets manufactured on the rotary tableting machine with each type of punch (Table 4). We could not press sample A (MgSt 0) in the Types 3 and 4 punches, or sample B (MgSt 0.5) in the Type 3 punch, because of severe sticking during compression, so we coated the punch surfaces with MgSt by hand and then pressed the samples. The effects of lubricant content on tablet “Compactability” in the GTP-1 (Table 2) paralleled the effects on tablet hardness in the rotary tableting machine (Table 4). Sample D (MgSt 3) was plotted in range (II) (Fig. 2). Although sample D avoided tableting failure in all punches, its hardness was the lowest of all. Sample A (MgSt 0), which plotted in range (III), produced tableting failure in all punches, but its hardness was the highest of all. These differences indicate that in designing a formulation, it is necessary to comprehensively evaluate both “Compactability” and “Manufacturability”.

Fig. 4 – Electron micrographs of a tablet compressed with a compound cup punch.
4. Conclusion

For all punch shapes, the properties of tablets pressed on the GTP-1 reflected the results of tableting on a rotary machine. Sample A, plotted in range (III) (poor “Manufacturability”), resulted in tableting failure (sticking) at the manufacturing scale. Sample D, plotted in range (II) (good “Manufacturability”) was compressed without tableting failure on the rotary machine. Powders plotted in range (II) (poor “Compactability”) were weakest. Although samples B and C were both plotted in range (I) (ideal conditions), sample C’s position indicated better “Manufacturability”. With complex punch shapes (Types 3 and 4), as predicted, sample C gave better “Manufacturability” and had less tableting failure on the rotary machine than sample B.

Our evaluation method reliably predicted both the “Manufacturability” and “Compactability” of tablets prepared on a rotary tableting machine, confirming its capacity to evaluate formulations that avoid tableting failure with any punch shape, using only small sample amounts.

Conflicts of interest

The authors declare that there is no conflicts of interest.

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