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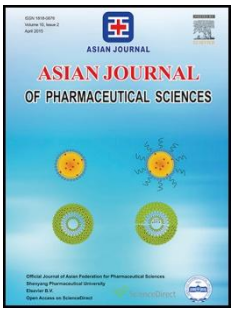

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Formulation design of granules prepared by wet granulation method using a multi-functional single-punch tablet press to avoid tableting failures

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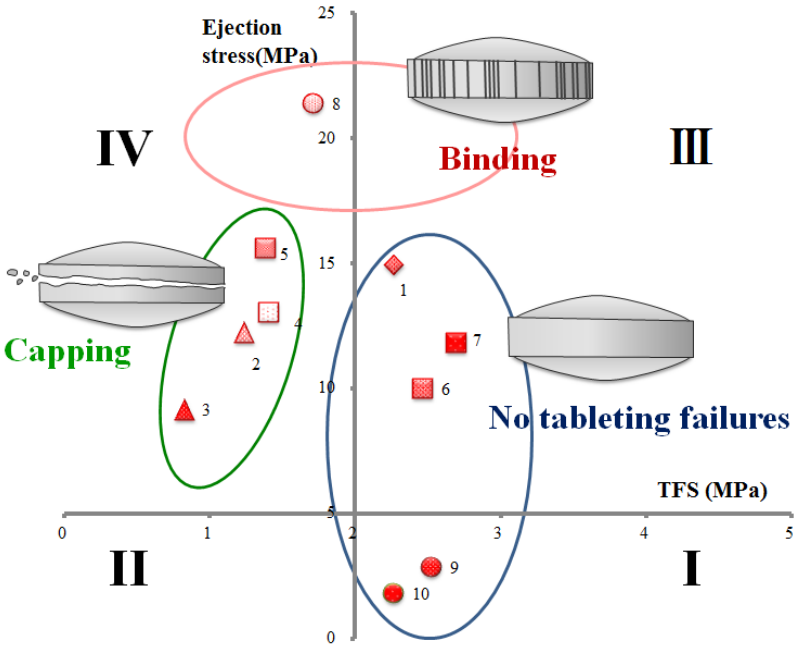
Graphical Abstract



Abstract:

We previously determined "Tableting properties" by using a multi-functional single-punch tablet press (GTP-1). We plotted "Compactability" on the x-axis against "Manufacturability" on the y-axis to allow visual evaluation of "Tableting properties". Here, we examined whether this evaluation method can be used in the formulation design of tablets prepared by wet granulation. We used the GTP-1 to measure "Tableting properties" with different amounts of binder, disintegrant, and lubricant, and compared the results with those of tableting on a commercial rotary tableting machine. Tableting failures (capping and binding in particular) occurred when samples that had been evaluated as having poor "Compactability" or "Manufacturability" on the GTP-1 were compressed on the rotary tableting machine. Thus, our evaluation method predicted tableting failure at the commercial scale. The method will prove useful for scaling up production.

Keywords: tableting; formulation design; wet granulation; capping; binding; single-punch tablet press

1. Introduction

When tablet formulations are designed, it is necessary to understand “Tableting properties” and to determine the optimum type, grade, and amount of ingredients. “Tableting properties” consist of “Compressibility”, “Compactability”, and “Manufacturability”. “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]. If the powder has poor “Compactability”, for example, the resultant tablet hardness will be low, and tablet defects, including breakage, may result. “Manufacturability” concerns tableting failure (e.g., sticking, capping, and binding). If friction between powders and die wall is high (that is, “Manufacturability” is poor), for example, the risk of tableting failures such as sticking and binding during manufacture will be high. 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]. When the amount of lubricant in the tablet formulation is too little, “Manufacturability” becomes poor, leading to tableting failures such as sticking and binding [10, 11]. Too much lubricant in the formulation reduces “Compactability” and thus tablet strength [12]. The frequency of occurrence of tableting failures depends also on the punch used to produce the required tablet shape [13, 14].

In our previous paper [15], we tried to evaluate all three properties by using the Gamlen

Tablet Press (GTP-1; Gamlen Tableting Ltd., Nottingham, UK), a benchtop single-punch tablet press, and demonstrated that the strength of the tablet (TFS) and the friction between die and tablet during ejection (ejection stress) can be used as an indicator of "Compactability" and "Manufacturability", respectively. We evaluated "Compactability" and "Manufacturability" by plotting TFS (i.e., "Compactability") on the x-axis against ejection stress (i.e., "Manufacturability") on the y-axis. We have empirically known that the critical tablet properties for commercial products, TFS and ejection force, are 2MPa and 5MPa, when compressed at a compaction pressure of 200 MPa. The tablets having these properties such as a TFS of 2 MPa or higher and an ejection stress of 5 MPa or lower, are suitable to manufacture stably and withstand the transportation and the use of end-user. Thus, we centered the intersection point of the two lines, where TFS (on the X-axis) equals 2 MPa and ejection stress (on the Y-axis) equals 5 MPa in the plot. As shown in Figure 1, this plotting makes it possible to visualize the quantitative characterization of "Tableting properties", and thus to reach an optimum tablet formulation quickly.

We successfully predicted the effects of the amount of lubricant on "Tableting properties" ("Manufacturability") and determined the appropriate amount and mixing time of lubricant in a formulation design by this plot [15, 16]. This evaluation method also proved able to predict the results of commercial-scale tablet production regardless of punch shape [16]. It could also detect subtle differences in the amount of lubricant, and predict sticking problems on a rotary tableting machine. Therefore, we assessed the utility of our method in the formulation design of tablets to prevent tableting failures.

In this study, we tried to apply this method considering the three factors, "Compressibility", "Compactability", and "Manufacturability", with the single-punch tablet press (GTP-1) to set up the final formulation for a commercial tablet. The drug is called "active pharmaceutical ingredient A" (API-A), which is used as a treatment for osteoporosis.

We designed a 240-mg tablet containing 60 mg API-A. As the primary component of API-A tablets is a fine powder with an average diameter of about 10 μm, which is highly adhesive and has poor flowability, we used a wet granulation method for tablet production, in contrast to the direct compression method in our previous reports [15, 16]. In the early stage of formulation design, we formulated several tablets on a small scale and then reached the best formulations at the large scale. We also examined the usefulness of our evaluation method to improve "Tableting properties" during the scaling up of production.

2. Materials and methods

2.1. Materials

API-A has a melting point of about 259 °C and a molecular weight of 510.04, and is prepared with an average particle diameter of about 10 μm. As formulation additives, we bought anhydrous lactose (DCL21, DMV, The Netherlands), granulated lactose (Dilactose S, Freund Corporation, Japan), crospovidone (CPD: Polyplasdone XL-10, ISP Technologies, USA), povidone (PVP: K-30, Dai-ichi Kogyo Seiyaku, Japan), polysorbate 80 (Nikkol TO-10M, Nikko Chemical, Japan), and magnesium stearate (MgSt; Taihei Chemical, Japan).

2.2. Methods

2.2.1. Preparation of sample granules

Each 240 mg tablet contained 60 mg of API-A, along with anhydrous lactose and granulated lactose as vehicles, CPD as a disintegrant, PVP as a binder, polysorbate 80 as a

solubilizing agent, and MgSt as a lubricant in the quantities shown in Table 1. First, API-A, anhydrous lactose, granulated lactose, and CPD (1) were mixed in a fluidized bed granulator. The flowing powder mixture was sprayed with a solution of PVP and polysorbate 80 and granulated in the fluidized bed granulator. The granules were dried and passed through a 22-mesh screen. They were then mixed with CPD (2) and MgSt in a rotary mixer to prepare the sample granules.

Sample granules were prepared at two manufacturing scales. At the small scale, 720 g (3000 tablets' worth) was prepared in a small fluidized bed granulator (MP-01, Powrex, Japan) and a 5-L rotary mixer (VM-5 V-shaped blender, Tokuju, Japan). At the large scale, 4800 g (20 000 tablets' worth) was prepared in a large fluidized bed granulator (FLO-5, Freund Sangyo, Japan) and a 30-L rotary mixer (VM-30 V-shaped blender, Tokuju).

2.2.2. Evaluation of "Tableting properties" using 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 [15].

2.2.3. Evaluation of formulations on the rotary tableting machine

Samples were compressed on a rotary tableting machine (Virgo, Kikusui Seisakusho, Japan) in the formulations shown in Table 1. Each 240-mg tablet was compressed at 11 kN

(in some cases at 16 or 20 kN) and 30 rpm, in an oval shape with a major axis diameter of 12 mm and a minor axis diameter of 6.5 mm. We set the target physical properties of tablets as a hardness of at least 60 N, a thickness of 4.40 mm, and a disintegration time in water of within 7 min. Hardness of 5 tablets was measured in the direction of the minor axis with a tablet hardness tester (PC-30, Okada Seiko, Japan). Thickness of 5 tablets was measured with a dial thickness gauge (MFG, Ozaki, Japan). Disintegration time of 6 tablets was tested with a disintegration tester (HM-61E, Toyama Sangyo, Japan) without the support disk according to the method described in the Japanese Pharmacopoeia. We also tested friability of 20 tablets in a tablet friability tester (Friabilator TFT-120, Toyama Sangyo, Japan), looking for cracking or capping after 1000 to 4000 rotations.

3. Results and discussion

3.1. Evaluation of "Tableting properties" using the GTP-1

Using our method for evaluating "Tableting properties", we plotted TFS on the x-axis against ejection stress on the y-axis (Fig. 1). When tablet hardness is sufficient, the point will be plotted on the positive side of the x-axis. When friction is negligible, the point will be plotted on the negative side of the y-axis. Therefore, range (I) indicates superior "Compactability" and "Manufacturability". In contrast, range (IV) indicates tablet weakness and high friction on the die wall, meaning poor "Compactability" and "Manufacturability".

3.1.1 Amount of disintegrant

We examined the effect of disintegrant on TFS. Each tablet contained CPD at 14.4 mg (6%) in Sample 1, 28.8 mg (12%) in Sample 2, or 43.2 mg (32%) in Sample 3 (Table 1). TFS

was >2 MPa in Sample 1, and the point was plotted in range (III) (Table 2; Fig. 2). TFS was <2 MPa in Sample 2 and <1 MPa in Sample 3, and the points were plotted in range (IV), indicating poor "Compactability" and, in Sample 3, insufficient hardness.

3.1.2 Amount of binder

We examined the effect of binder on TFS in formulations with 14.4 mg of disintegrant per tablet. Each tablet contained PVP at 4 mg in Sample 4, 8 mg in Sample 5, 12 mg in Sample 1, 18 mg in Sample 6, or 24 mg in Sample 7 (Table 1). TFS was <2 MPa in Samples 4 and 5, and the points were plotted in range (IV), indicating poor "Compactability" (Table 3; Fig. 3). Therefore, ⩾12 mg of binder is needed to give sufficient hardness (Table 3; Fig. 3).

3.1.3 Amount of lubricant

Formulations giving sufficient tablet hardness were Sample 1 (12 mg PVP + 14.4 mg CPD), Sample 6 (18 mg PVP + 14.4 mg CPD), and Sample 7 (24 mg PVP + 14.4 mg CPD). However, because Samples 6 and 7 contained a lot of binder, delayed disintegration time could be expected. We therefore further examined Sample 1-based formulations.

We have previously shown that it is advisable to design formulations to optimize both "Compactability" and "Manufacturability", but the results of Samples 1, 6, and 7 showed high ejection stress (⩾5 MPa), and the points were plotted in range (III), indicating poor "Manufacturability". Insufficient MgSt causes tableting failures such as sticking and binding [16]. To improve "Manufacturability", we added different amounts of MgSt to Sample 1-based formulations. Each tablet contained 0.6 mg MgSt in Sample 8, 1.2 mg MgSt in Sample 1, 2.4 mg MgSt in Sample 9, and 3.2 mg MgSt in Sample 10. The ejection stress decreased as the amount of lubricant increased (Table 4; Fig. 4). That of Sample 8 was extremely high, and the sides of the tablets were deeply damaged during ejection. For this

reason, TFS of Sample 8 was low. Samples 9 (2.4 mg MgSt) and 10 (3.6 mg MgSt) were plotted in range (I), indicating good "Compactability" and "Manufacturability" (Table 4; Fig. 4).

3.2 Evaluation of formulations on the rotary tableting machine

To validate the results described in section 3.1, we prepared samples on a rotary tableting machine and tested the "Manufacturability" and physical properties of the tablets (Table 5).

3.2.1 Amount of disintegrant

Samples 2 (28.8 mg CPD) and 3 (43.2 mg CPD) showed poor "Compactability" in section 3.1. On the rotary tableting machine, sample 1 (14.4 mg CPD) reached the target tablet thickness (4.40 mm) when compressed at 11 kN (Table 5). However, Sample 2 exceeded the target thickness at 4.47 mm. To reduce the thickness to 4.40 mm, we had to increase the pressure to 16 kN. Sample 3 exceeded the target thickness even more at 4.54 mm, and was still 4.50 mm thick at 20 kN. All three samples disintegrated within the target of 7 min. All also reached the target hardness of 60 N, but Samples 2 and 3 tended to crack in capping layers (laminar separation) during hardness testing (Fig. 5(A)). Tablets that crack in this way during transportation will split, potentially leading to capping. For this reason, we tested the friability of these samples (Table 6). Sample 1 did not crack in capping layers even after 3000 rotations. Sample 2 tablets compressed to 4.47 mm did not crack even after 3000 rotations, but among the tablets reduced to 4.40 mm, 2 tablets cracked after 2000 rotations and 4 cracked after 3000 rotations. Furthermore, among the tablets of Sample 3, 10 tablets 4.54 mm thick and all 20 tablets 4.50 mm thick cracked. Thus, Samples 2 and 3 (TFS $\leqslant$ 2 MPa by GTP-1) were likely to experience capping-like breakage when made on a rotary tableting machine. Tablets with >14.4 mg of disintegrant were at high risk of capping failure.

Therefore, the appropriate amount of disintegrant per tablet was 14.4 mg. The poor predicted "Compactability" of Samples 2 and 3 was reflected in the actual tableting results.

3.2.2 Amount of binder

Evaluation using the GTP-1 showed that ⩾12 mg of binder is needed for sufficient hardness. We compressed Samples 4 (4 mg PVP), 5 (8 mg PVP), 1 (12 mg PVP), 6 (18 mg PVP), and 7 (24 mg PVP) on the rotary tableting machine (11 kN, 30 rpm) and tested their "Manufacturability" and physical properties (Table 5). Every sample reached the target thickness of 4.40 mm and the target hardness of 60 N. In particular, the formulations that had good "Compactability" in the GTP-1 results (Samples 7, 6, and 1) had high tablet hardness. The target disintegration time was within 7 min, but, as predicted (section 3.1.3), that of Sample 6 was near the upper limit, and that of Sample 7 exceeded the target. Tableting failures did not occur, but capping-like breakage tended to occur in Samples 4 and 5, which had relatively low TFS in the GTP-1 evaluation. In the friability tests, Sample 4 showed a capping-like breakage after 3500 rotations, and Sample 5 after 4000 rotations (Table 7). The poor predicted "Compactability" of Samples 4 and 5 was also reflected in the actual tableting results.

3.2.3 Amount of lubricant

Evaluation using the GTP-1 showed that ejection stress decreased as the amount of lubricant increased. Samples 9 (2.4 mg MgSt) and 10 (3.6 mg MgSt) were plotted in range (I), indicating good "Compactability" and "Manufacturability". We compressed Samples 8 (0.6 mg MgSt), 1 (1.2 mg MgSt), 9, and 10 on the rotary tableting machine (11 kN, 30 rpm) and tested their "Manufacturability" and physical properties (Table 5). Every formulation reached the target thickness of 4.40 mm. As shown in Fig. 5(B), binding of Sample 8 occurred soon

after the start of compression; granule adhesion to the inner wall of the die was severe, and damage to the sides of the tablets occurred. The other formulations were compressed without manufacturing failures. Sample 8 had the worst "Manufacturability" in the GTP-1 evaluation and on the rotary tableting machine. When the amount of lubricant was changed in samples 1, 9 and 10, every formulation reached the target hardness of 60 N. It is well known that excessive amount of lubricant in the tablet formulation decreases hardness and prolongs disintegration time of resultant tablets, because hydrophobic lubricant cover the surface of granules too much. However, as on the GTP-1, tablet hardness did not decrease as the amount of lubricant was increased. As the range of lubricant amount used in the present study was not so much compared with usual tablet formulations, lubricant may not completely cover the surface of granules to weaken the binding between granules, while it can work as lubricant at the surface of die wall. Every formulation also reached the target disintegration time of within 7 min. Therefore, each tablet needs ⩾1.2 mg of lubricant to maximize "Manufacturability".

3.3 Scaling up

Because Samples 1 (1.2 mg MgSt), 9 (2.4 mg MgSt), and 10 (3.2 mg MgSt) did not cause problems in "Manufacturability" or quality at the small manufacturing scale (720 g), we scaled up production (4800 g). Evaluation using the GTP-1 showed no change in "Tableting properties" (Tables 4, 8). We compressed samples prepared at the large scale on the rotary tableting machine (11 kN, 30 rpm) and tested their "Manufacturability" and physical properties (Table 5). No tableting failure was observed, and 20 000 tablets were compressed in each sample. We conclude, therefore, that at whatever manufacturing scale, the results are reliably predicted by the GTP-1. Therefore, scaling-up will be simplified if done according to the target "Tableting properties" determined experimentally by using our evaluation method.

4. Conclusion

It is important to design tablet formulations so as to avoid potential manufacturing failures. Previously, we assessed our evaluation method in the design of formulations prepared by direct compression. Here, we assessed it in the design of formulations prepared by wet granulation. We optimized the amounts of binder, disintegrant, and lubricant and prepared samples by fluid bed granulation, and evaluated the "Tableting properties" of the samples using the GTP-1. Tableting failures (capping and binding in particular) occurred when samples that the GTP-1 had evaluated as having poor "Compactability" or "Manufacturability" were compressed on an actual rotary tableting machine. In particular, the tablets were at risk of capping when TFS measured by the GTP-1 was $\lesssim$1.5 MPa, and of binding when ejection stress was $\gtrsim$20 MPa. Thus, problems predicted by the GTP-1 were confirmed in actual tableting. We would therefore be able to design tablet formulations that avoid tableting failures at the commercial scale by optimizing the composition through evaluation on the GTP-1. We would also be able to scale up production on the same basis.

Acknowledgements

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Fig. 1. Plot of "Tableting properties".

I: good "Compactibility", good "Manufacturability"

II: poor "Compactibility", good "Manufacturability"

III: good "Compactibility", poor "Manufacturability"

IV: poor "Compactibility", poor "Manufacturability"

Fig. 2. "Tableting properties" of formulations with different amounts of disintegrant, evaluated using benchtop single-punch tablet press.

Fig. 3. "Tableting properties" of formulations with different amounts of binder, evaluated using benchtop single-punch tablet press.

Fig. 4. "Tableting properties" of formulations with different amounts of lubricant, evaluated using benchtop single-punch tablet press.

Fig. 5. Tableting failures: (A) Capping and (B) Binding

Table 1 Formulations of tablets (mg).

Sample	1	2	3	4	5	6	7	8	9	10
API	60	60	60	60	60	60	60	60	60	60
Anhydrous lactose	120	120	120	120	120	120	120	120	120	120
Granulated lactose	30	15.6	1.2	38	34	24	18	30.6	28.8	26.4
Crospovidone (1)	9.6	9.6	9.6	9.6	9.6	9.6	9.6	9.6	9.6	9.6
Povidone	12	12	12	4	8	18	24	12	12	12
Polysorbate 80	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
Purified water	100	100	100	108	104	94	88	100	100	100
Crospovidone (2)	4.8	19.2	33.6	4.8	4.8	4.8	4.8	4.8	4.8	4.8
Magnesium stearate	1.2	0.6	1.8	1.2	1.2	1.2	1.2	0.6	2.4	3.6
Total	240	240	240	240	240	240	240	240	240	240

Table 2 “Tableting properties” of formulations with different amounts of disintegrant, evaluated using benchtop single-punch tablet press.

	Amount of disintegrant /tablet	“Compactability” TFS (MPa)	“Manufacturability” Ejection stress (MPa)	“Compressibility” Elastic recovery (%)	Plot range
Sample 1	14.4 mg	2.27 ± 0.48	14.94 ± 1.71	32.98 ± 1.03	III
Sample 2	28.8 mg	1.24 ± 0.24	12.22 ± 0.48	31.14 ± 0.25	IV
Sample 3	43.2 mg	0.83 ± 0.07	9.15 ± 3.10	30.49 ± 0.64	IV

Table 3 “Tableting properties” of formulations with different amounts of binder, evaluated using benchtop single-punch tablet press.

	Amount of binder /tablet	“Compactability” TFS (MPa)	“Manufacturability” Ejection stress (MPa)	“Compressibility” Elastic recovery (%)	Plot range
Sample 4	4 mg	1.41 ± 0.26	13.00 ± 2.93	35.55 ± 1.04	IV
Sample 5	8 mg	1.39 ± 0.09	15.60 ± 1.33	33.17 ± 0.41	IV
Sample 1	12 mg	2.27 ± 0.48	14.94 ± 1.71	32.98 ± 1.03	III
Sample 6	18 mg	2.47 ± 0.52	9.96 ± 0.91	31.56 ± 0.60	III
Sample 7	24 mg	2.70 ± 0.23	11.80 ± 3.80	31.14 ± 0.28	III

Table 4 "Tableting properties" of formulations with different amounts of lubricant, evaluated using benchtop single-punch tablet press.

	Amount of lubricant /tablet	"Compactability" TFS (MPa)	"Manufacturability" Ejection stress (MPa)	"Compressibility" Elastic recovery (%)	Plot range
Sample 8	0.6 mg	1.72 ± 0.23	21.38 ± 1.28	31.03 ± 0.46	IV
Sample 1	1.2 mg	2.27 ± 0.48	14.94 ± 1.71	32.98 ± 1.03	III
Sample 9	2.4 mg	2.53 ± 0.08	2.83 ± 0.40	36.55 ± 0.92	I
Sample 10	3.6 mg	2.27 ± 0.15	1.79 ± 0.97	36.47 ± 0.97	I

Table 5 Physical properties of tablets compressed by rotary tableting machine.

	Content per tablet (mg)			Tableting pressure (kN)	Tablet thickness (mm)	Tablet hardness (N)	Disintegration time (min)
	CPD	PVP	MgSt				
Sample 1 [a]	14.4	12	1.2	11	4.41 ± 0.01	76 ± 6	5.6 ± 0.0
Sample 2	28.8	12	1.2	11	4.47 ± 0.01	74 ± 7	5.2 ± 0.0
				16	4.40 ± 0.01	75 ± 5	–
Sample 3	43.2	12	1.2	11	4.54 ± 0.01	66 ± 4	5.2 ± 0.0
				20	4.50 ± 0.00	66 ± 15	–
Sample 4	14.4	4	1.2	11	4.40 ± 0.00	58 ± 8	3.2 ± 0.1
Sample 5	14.4	8	1.2	11	4.41 ± 0.00	70 ± 6	4.5 ± 0.1
Sample 6	14.4	18	1.2	11	4.40 ± 0.01	96 ± 4	6.9 ± 0.1
Sample 7	14.4	24	1.2	11	4.40 ± 0.00	104 ± 13	7.9 ± 0.2
Sample 8	14.4	12	0.6	11	4.38 ± 0.01	87 ± 3	6.4 ± 0.0
Sample 9	14.4	12	2.4	11	4.40 ± 0.00	77 ± 3	6.5 ± 0.0
Sample 10	14.4	12	3.6	11	4.39 ± 0.00	77 ± 2	5.8 ± 0.0
Sample 1-L [b]	14.4	12	1.2	11	4.40 ± 0.01	82 ± 2	6.1 ± 0.1
Sample 9-L	14.4	12	2.4	11	4.39 ± 0.01	76 ± 3	6.3 ± 0.1
Sample 10-L	14.4	12	3.6	11	4.38 ± 0.01	76 ± 3	6.3 ± 0.1

a. Samples 1–10 were prepared at the small scale.

b. Samples 1-L, 9-L, and 10-L were prepared at the large scale.

Table 6 Friability test of formulations with different amounts of disintegrant (to confirm capping-like breakage): data show number of breakages among 20 tablets.

	Amount of disintegrant/tablet	Tablet thickness Average (mm)	1000 rotations	2000 rotations	2500 rotations	3000 rotations
Sample 1	14.4 mg	4.41 ± 0.01	0	0	0	0
Sample 2	28.8 mg	4.47 ± 0.01	0	0	0	0
		4.40 ± 0.01	0	2	4	4
Sample 3	43.2 mg	4.54 ± 0.01	0	0	4	10
		4.50 ± 0.00	7	14	20	20

Table 7 Friability test of formulations with different amounts of binder (to confirm capping-like breakage): data show number of breakages among 20 tablets.

	Amount of binder/tablet	Tablet thickness Average (mm)	1000 rotations	3000 rotations	3500 rotations	4000 rotations
Sample 4	4 mg	4.40 ± 0.00	0	0	1	1
Sample 5	8 mg	4.41 ± 0.00	0	0	0	1
Sample 1	12 mg	4.41 ± 0.01	0	0	0	0
Sample 6	18 mg	4.40 ± 0.01	0	0	0	0
Sample 7	24 mg	4.40 ± 0.00	0	0	0	0

Table 8 "Tableting properties" of formulations prepared at 20 000-tablet scale, evaluated using benchtop single-punch tablet press.

	Amount of lubricant /tablet	"Compactability" TFS (MPa)	"Manufacturability" Ejection stress (MPa)	"Compressibility" Elastic recovery (%)	Plot range
Sample 1-L [a]	1.2 mg	2.14 ± 0.07	11.85 ± 1.01	34.52 ± 1.58	III
Sample 9-L	2.4 mg	2.03 ± 0.06	2.79 ± 0.30	33.02 ± 0.17	I
Sample 10-L	3.6 mg	2.07 ± 0.06	1.58 ± 0.63	34.66 ± 0.33	I

a. Samples were prepared at the large scale.

Figures:

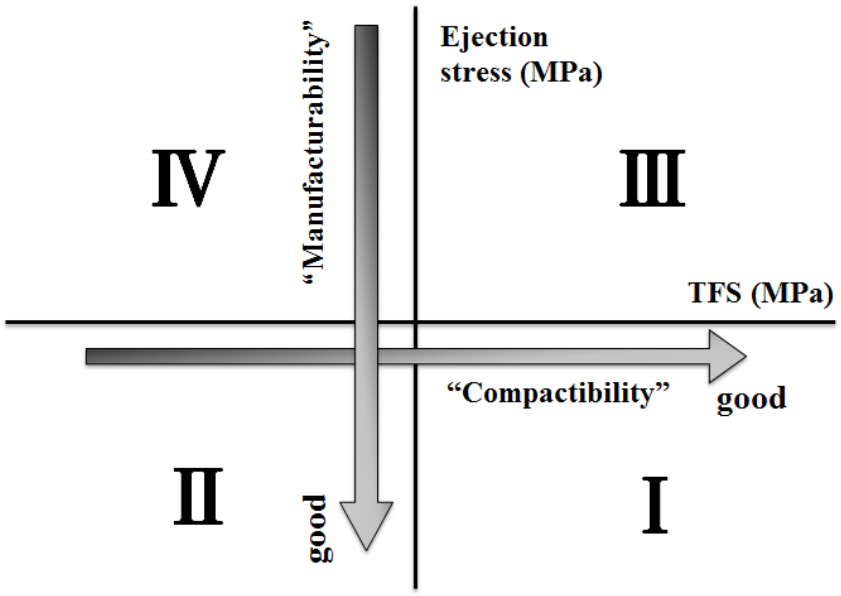


Fig. 1.

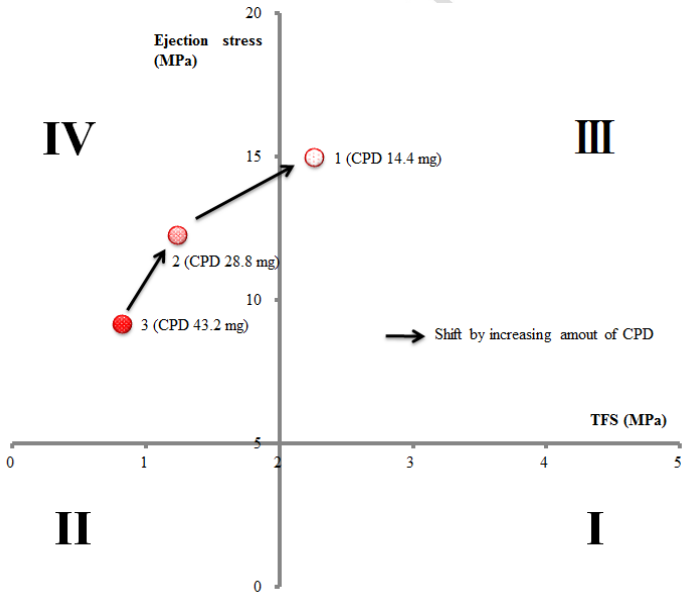


Fig. 2.

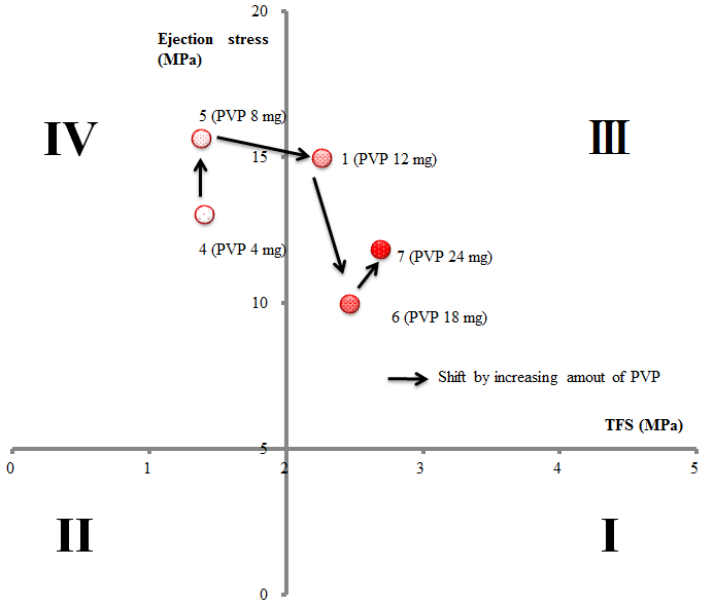


Fig. 3.

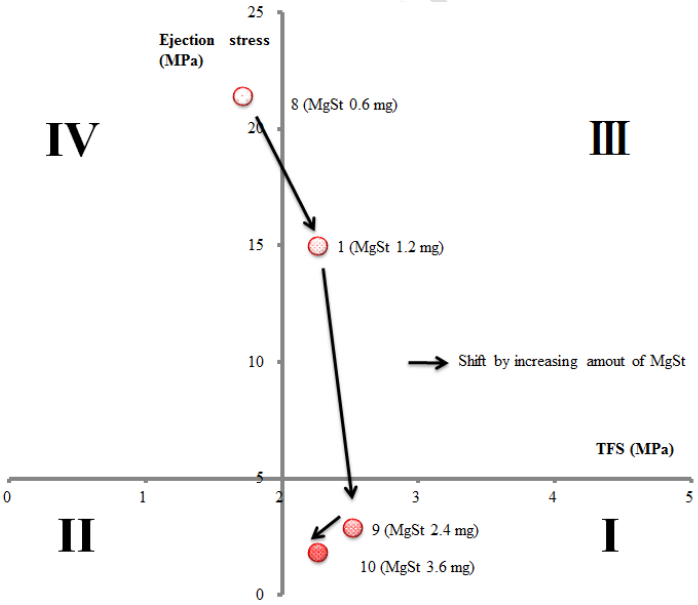
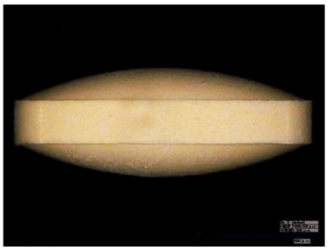
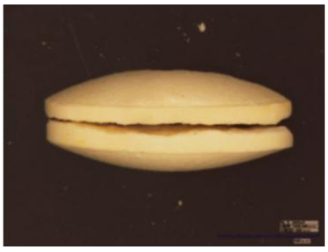


Fig. 4.

No tableting failures



(A) Capping



(B) Binding

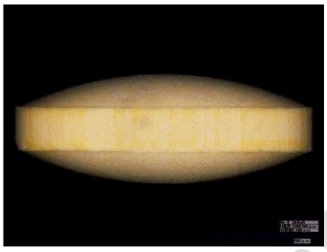


Fig. 5.