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Research paper

Novel compaction techniques with pellet-containing granules

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ABSTRACT

Objective: The purpose of this investigation was to introduce a new concept of admixing coated pellets with excipients to obtain a segregation-free combination of pellet-containing granules and cushioning granules during mixing and compression.
Methods: Acrylic polymeric-coated pellets were granulated by centrifugal granulation method with excipients; then, the pellet-containing granules were compacted into tablets with the cushioning granules, which were prepared in mixer or fluidized bed-granulator. Tablets were also made in a traditional method by directly compressing the mixtures of coated pellets and cushioning granules for control. Drug-release profiles, weights and drug content of tables were tested to compare this new method with the traditional method.
Results: The granulation process changed the surface morphology of coated pellets from smooth to rough and increased the angle of repose of pellets to close to that of the cushioning granules. Weight and drug content RSD values of tablets prepared by pellet-containing granules were much lower than those of tablets prepared by coated pellets. The similarity factor f_2 values for drug-release profiles of tablets prepared from pellet-containing granules and the original coated pellets were above 50 when microcrystalline cellulose (MCC), Polyplasdone® XL (PVPP), and lactose were used as granulating excipients.
Conclusions: The granulation process could roughen the surface of coated pellets and increase the angle of repose and uniformity of the mixture with cushioning granules. Compared with the tablets directly compressed from coated pellets, the tablets prepared by pellet-containing granules showed improved uniformity in both weight and drug content. The granulation and compression processes did not significantly influence the drug-release behavior of coated pellets, and the enteric dissolution was retained.

1. Introduction

Compared with single-unit dosage forms, multiple-unit dosage forms offer several advantages such as improved bioavailability and prevention of high local drug concentration in gastrointestinal tract [1,2]. Capsule is commonly employed as a dosage form to facilitate the oral administration of pellets as multiple-unit systems, while another form, tablet containing pellets was induced. Compared with hard gelatin capsules, tablets containing pellets offer many advantages, such as lower production cost by skipping complex process control on capsule filling, easier to swallow, higher patients' compliance, lower risk for the technology process being copied by competitors, and the dividable property of the dosage [3]. Though pellet tablets hold various superiorities, it is a challenge to prepare qualified tablets [4,5] as: (1) the polymeric coating film must be flexible enough to withstand the compaction forces and to maintain its integrity after tableting and (2) it is necessary to achieve non-segregated mixture of coated pellets and filler/binders to ensure the weight and drug content uniformity of the tablets. Acrylic polymers are widely used to increase flexibility [6,7], and plasticizers were incorporated to enhance elongation [8]. Abbaspour [9] reported to use acrylic polymer to prepare plastic pellets for compacting. It successfully avoided the coating process but resulted in exorbitant acrylic polymer consumption. According to the literature, the shape, size, and bulk density of the cushioning excipients would significantly influence the homogeneity of tablets during both mixing and further tableting process [8,10,11]. Up till now, the manual operation was employed to compress pellets into tablets in most investigations. Wagnera and coworkers [4] investigated the pellets distribution within the machine-compressed tablets and drew a conclusion that pellets distribution was influenced by the machine speed. Ando [12] used a special tableting machine and dry-coating technology to produce tablets which functioned like capsules by encapsulating the pellets inside. This method avoided the segregation of pellets from cushioning granules by skipping the mixing process. It was also reported that the similar

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particle size and bulk density of the cushioning granules and the pellets advantaged to achieve the uniform tablets [4,11,13]. Several researchers studied the properties of cushioning granules, which might affect the tablet homogeneity, but the influence of the pellet shape has not been mentioned.

The purpose of this study was to adopt a new method of centrifugal granulation to change the surface and micromeritical properties of the coated pellets, intending to obtain a non-segregated blend of coated pellets and cushioning granules for producing qualified tablets.

2. Materials and methods

2.1. Materials

The combinations of Eudragit® FS 30D and Eudragit® L 30D-55 were used to coat pellets for good flexibility, and these acrylic polymers were donated by Evonik Röhm GmbH (Darmstadt, Germany). Triethyl citrate (TEC, Jingqiu Co., Ltd., China), glyceryl monostearate (GMS, Xilong Co., Ltd., China), and Tween 80 (Tianjin Yaohua Chemical Reagent Co., Ltd.) were used as plasticizer and anti-sticking agents during coating process. Microcrystalline cellulose (MCC, Hopetop Co., Ltd., China), Polyplasdone® XL (PVPP, ISP, USA), mannitol (ISP, USA), α-lactose monohydrate (Lactoes, DMV, Veghel, The Netherlands), and Starch 1500 (Colorcon, USA) were used to prepare cushioning granules for good compressibility. Alginate, which was reported for soft-tableting, was also used to produce pellet-containing granules. Polyvinylpyrrolidone K-30 (PVP K-30, ISP, USA) and Polyvinylpyrrolidone K-90 (PVP K-90, ISP, USA) were used as adhesive during granulation, and Methocel® E3 (HPMC-E3, Colorcon, USA) was used for subcoating to prevent the immigration of drug.

2.2. Preparation of doxycycline hydrochloride pellets

A batch of 500 g 210–250-μm MCC pellets was layered in a fluidized bed coater (Glatt GPCG-1.1, Germany) with drug solution containing doxycycline hydrochloride/PVP K-30/distilled water. The spraying rate was 3.4 g/min with a 1.0-mm nozzle (bottom spray, Wurster coating) at an automation air pressure of 1.0 bar. The inlet temperature was adjusted to maintain the outlet temperature at 28–32 °C. After the drug layering, the pellets were subcoated with 2% (w/w) HPMC-E3 to prevent the potential drug/enteric polymer interaction and/or immigration of drug into the enteric coating [16]. Drug-layered pellets were sieved manually, and then, 250–300-μm pellets were stored in a desiccator at room temperature. The actual doxycycline hydrochloride content (theoretically 12%, w/w) was determined by drug assay in the pellets using UV spectrophotometry at 276 nm in pH 1.0 HCl solution.

2.3. Preparation of coated pellets

The drug-layered pellets were coated with Eudragit® polymer suspension, which was a combination of Eudragit® FS 30D and Eudragit® L 30D-55 at the ratio of 2:1, in a fluidized bed coater (Glatt GPCG-1.1, Wurster coating) to 30% weight gain. TEC (5% on dry polymer, w/w) as a plasticizer and GMS (5% on dry polymer, w/w) as an anti-sticking agent were added in the coating suspension [4,13,14], and the solid concentration of the suspension was adjusted using distilled water to approximately 20% (w/w). During coating process, the spraying rate and the inlet air temperature were adjusted as necessary to maintain the product temperature at 30 °C. Coated pellets were sieved manually, and 250–300-μm pellets were collected to cure at 40 °C in an oven for 4 h and then stored in a desiccator at room temperature.

Table 1
Excipient formulations for pellet-containing granules (%, w/w).

Formulations	MCC	PVPP	Lactose	Mannitol	Sodium alginate	Starch 1500
F1	90	10	–	–	–	–
F2	90	–	10	–	–	–
F3	90	–	–	10	–	–
F4	90	–	–	–	10	–
F5	90	–	–	–	–	10

2.4. Preparation of Pellet-containing granules

The coated pellets, 150 g per batch, were granulated with five different formulations of excipients as listed in Table 1 using a centrifugal granulation machine (BZJ-360MII, Beijing Long March Tianmin Hi-tech Co., Ltd., China) with the central rotary speed of 60 rpm. The adhesive solution, 5% (w/w) PVP K-90 in pH 1.0 hydrochloric acid, was sprayed at a rate of 5 g/min, and the excipient powder was fed at 8 g/min. Then the pellet-containing granules were dried at 40 °C in an oven for 12 h and sieved to collect granules in a size range of 300–420 μm for further investigation. The yield of the pellet-containing granules was calculated as following:

$$Yield\ (\%) = \frac{\text{weight of pellet contained granules (dried and sieved)}}{\text{weight of excipients} + \text{weight of coating pellets} + \text{weight of dryPVP K-90}} \times 100\%$$

Because the weight of dry PVP K-90 was a relatively very small part, the above equation could be simplified as:

$$Yield\ (\%) = \frac{\text{weight of pellet contained granules (dried and sieved)}}{\text{weight of excipients} + \text{weight ofcoating pellets}} \times 100\%$$

2.5. Preparation of cushioning granules

2.5.1. Mixer-granulated cushioning granules

Three-hundred grams of MCC and PVPP were blended at the ratio of 9:1 in a mixer-granulator (Okada Seiko Co., Ltd., Japan) for 5 min. With the central rotary speed set at 350 rpm, 300 g 10% (w/w) PVP K-30 binder solution was added at the rate of 10 g/min and then the wet mass was granulated by sieving through a 0.5-mm sieve. Finally, the granules were dried at 60 °C in an oven for 12 h and then sieved to collect smaller granules in a size range of 250–300 μm for preparing tablets with original coated pellets. The larger cushioning granules in a size range of 300–420 μm were collected for preparing tablets with pellet-containing granules.

2.5.2. Fluidized bed-cushioning granules

The same formulation of MCC and PVPP was blended in a fluidized bed granulator (Glatt GPCG-1.1, top spraying) for 5 min, and the same formulation of PVP K-30 binder solution was added at the rate of 10 g/min with the air flow of 15 m^3/h, the inlet temperature of 35 °C, the outlet temperature of 25 °C, and the product temperature around 27 °C. Upon completion of spraying, the granules were dried at 40 °C for 5 min in the fluidized bed and then oven-dried at 60 °C for 12 h. The dry product was sieved, and granules in the size ranges of 250–300 μm and 300–420 μm were collected separately for further investigation.

2.6. Characterization of the particles

Bulk and tapped densities, together with angle of repose, were all determined by a BT1000 powder test (DanDong Bettersize Instruments Ltd., China) for the obtained pellets and granules. The mean of three tests was reported.

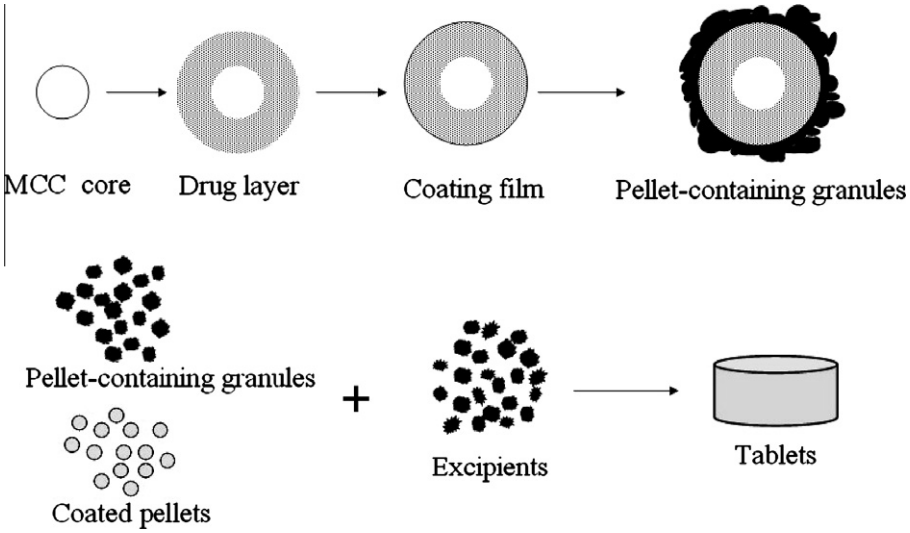

Fig. 1. The process of preparing tablets using the traditional method (coated pellets) and the new method (pellet-containing granules).

Table 2
Formulations of tablets (%, w/w).

Formulations	Pellet-containing granules	Coated pellets	Cushioning granules	
			Mixer-granules	Fluidized bed-granules
T1	50	–	50	–
T2	50	–	–	50
T3	–	50	50	–
T4	–	50	–	50

2.7. Preparation and characterization of tablets

The process flow chart for preparing tablets using both traditional method and pellet-containing granules was showed in Fig. 1.

Pellet-containing granules using excipient formulations F1–F5 were mixed with fluidized bed-cushioning granules at equidimension separately, and the blends were compressed into tablets, which were labeled as F′1–F′5 accordingly for studying and comparing the drug-releasing profiles.

An essential tablet compress machine (ZYD-8, Shanghai Far-east Pharmaceutical Machinery General Factory, China) was utilized to prepare 10-mm-diameter tablets, and the compress force was adjusted to achieve a desirable hardness (30 N ± 3 N) for each tablet. Though fixed values of compress force were used to prepare tablets in most of the literatures [5], the compress force in current study was adjustable based on the properties of the granule blend to ensure consistent tablet hardness throughout the batch.

Pellet-containing granules with excipient formulation F1 was chosen to investigate the influence of different cushioning granules and different pellets on the tablet characteristics and dissolution performance. As specified in Table 2, T1 and T2 represented the tablets compressed from the combination of pellet-containing granules and two different cushioning granules, which were prepared in mixer-granulator and fluidized bed-granulator, respectively. T3 and T4 represented the tablets compressed from the combination of traditionally coated pellets and the above two different cushioning granules, respectively. The hardness of all the tablets was 30 N ± 3 N.

2.8. Drug-release studies

The USP 24 Method II (paddle) was used to investigate the release properties of doxycycline hydrochloride from the coated pellets and the tablets in 900 ml of pH 1.0 hydrochloric acid for 2 h, followed by in pH 5.5 potassium acid phthalate buffer for 4 h. The media were agitated at 50 rpm, and the samples were withdrawn at predetermined time points and measured UV spectrophotometrically (TU-1901, Beijing Purkinje General Instrument Co., Ltd.) at λ = 276 nm (acidic medium) and λ = 345 nm (potassium acid phthalate buffer medium), respectively.

2.9. Scanning electron microscopy

The cross-section surface of the tablets, the original coated pellets, and the pellet-containing granules were sputtered with gold

Table 3
Characteristics of the particles (n = 3).

Particles		Bulk density (mg/cm^3)	Tapped density (mg/cm^3)	Angle of repose (°)	Yield (%)
Coated pellets		728.3 ± 3.11	778.8 ± 1.6	22.0 ± 0.8	–
Cushioning granules	M[a]	724.5 ± 0.8	774.03 ± 3.6	34.3 ± 0.8	–
	F[b]	297.6 ± 4.2	334.1 ± 3.4	42.3 ± 0.2	–
Pellet-containing granules	F1	614.4 ± 1.0	620.3 ± 2.2	39.4 ± 0.8	64.7
	F2	616.9 ± 1.7	621.3 ± 1.6	35.9 ± 0.3	55.2
	F3	626.6 ± 3.1	631.2 ± 0.6	42.4 ± 1.2	77.8
	F4	617.3 ± 2.7	622.5 ± 1.5	38.6 ± 0.7	52.1
	F5	724.3 ± 0.5	774.0 ± 2.0	28.4 ± 1.0	26.2

[a] Cushioning granules prepared by mixer-granulator.
[b] Cushioning granules prepared by fluidized bed with the same formulation as M.

palladium and then observed with a scanning electron microscope (SEM JSM-6330F, JEOL, Japan).

3. Results and discussions

3.1. Characterization of the particles

Three kinds of particles, specifically the coated pellets, the cushioning granules, and the pellet-containing granules, were characterized for bulk and tapped densities and angle of repose, and the results were summarized in Table 3. Compared to the original coated pellets, the pellet-containing granules showed decreasing in sphericity, except formulation F5, with a significant increase in the angle of repose from 22.0° to about 40°, and decrease in bulk and tapped densities from 728.3 mg/cm^3 and 778.8 mg/cm^3 to 614.4–626.6 mg/cm^3 and 620.3–631.2 mg/cm^3, respectively. On the contrast, F5 pellet-containing granules presented properties approaching to those of coated pellets rather than other pellet-containing granule formulations. This exceptional result might be caused by the adhesion of Starch 1500 in the presence of water. The low yield of F5 also indicated that: (1) the excipients powder could self-granulate into individual pellets after absorbed enough water in the practice; (2) the individual pellets composed of excipients might be adhesive to coated pellets, instead of wrapping the coated pellets inside, then likely form aggregation and result in size increase; and (3) a large amount of excipients powder was adhesive to the inner wall equipment and the amount loaded on coated pellet surface was low.

The largest change in angle of repose was attained by F3 pellet-containing granules, which indicated that under the same operation conditions, maximum surface modification of coated pellets could be achieved by F3 formulation. Thus, it was expected that when mannitol formulation was used for granulation, the least amount of excipients powder and the shortest process time could be applied to achieve the same level of surface modification. Moreover, the angle of repose of F3 pellet-containing granules was 42.4°, almost the same as that of fluidized bed-cushioning granules 42.3°. This characterization was definitely benefited to preparing non-segregation binary mixtures and compressing uniform tablets. The highest yield of 77.8% for F3 also proved that mannitol powder was the ideal excipient for granulating process. Besides, the bulk and tapped densities of F3 pellet-containing granules were greater than those of other pellet-containing granules, which might be due to the greater adhesive force of mannitol resulting in a more compact excipients layer.

PVPP was an excellent disintegration agent in tablet manufacture due to its good flowability and compressibility and was in favor of granulation as well. The angle of repose and yield of F1 pellet-containing granules were 39.4° and 64.7° respectively, just slightly lower than those of mannitol formulation. Lactose and sodium alginate revealed high adhesiveness with the presence of water. With good water solubility, lactose transformed to adhesive after absorbing water, and sodium alginate swelled into hydrogel when plenty water was present and increased the adhesiveness of excipients. The hydrophilicity of lactose and sodium alginate resulted in lower yield and angle of repose.

3.2. Effect of granulation process

For an acceptable pellets containing tablet product, the compressed tablets should disintegrate into individual pellets in the gastrointestinal fluids and the drug release should not be affected by the compacting process [2]. And in current study, the excipients laying onto the pellet-containing granules and the tablet compression should not influence the drug-release mechanism from the coated pellets, too. The coating acrylic polymers used in this study, Eudragit® FS 30D and Eudragit® L 30D-55, are both enteric materials, which dissolve in pH 5.5 and pH 7.0 media, respectively. If the tablets could maintain their enteric property after compacting, the liberation of drug from the compressed tablets within 2 h in pH 1.0 medium should not be more than 10% [4,14].

The similarity factor f_2 was introduced to compare the difference between the dissolution profiles. The value of f_2 greater than 50 represents the similarity of the two profiles, and the more f_2 approaching to 100, the greater equivalence between the two profiles. f_2 can be calculated as [17]:

$$f_2 = 50 \log \left\{ \left[1 + (1/n) \sum_{t=1}^{n} (Rt - Tt) \right] \right\}$$

where n is the number of sampling points, Rt and Tt are the percentage dissolved of the reference and the test product at each time point t.

Fig. 2 shows the release profiles of the original coated pellets and the pellet-containing granules (F1–F4) within the first 2 h in pH 1.0 HCl solution and then following 4 h in pH 5.5 buffer medium. Drug release from all four formulations of pellet-containing granules was less than 10% after 2 h in pH 1.0 medium, which indicated that the enteric coating remained its integrity after granulating operation. However, in pH 1.0 medium, the release rate of granulated formulations was slightly faster than that of original coated pellets. This could be because the coated film swelled during the wet granulation process, and the softened film was more vulnerable to mechanical property change or microstructure damage during the granulating process. Burst effect was observed in all the granule formulations except F4, which reflected the good disintegration of excipients laying for pellet-containing granules. The drug release from F1 granules quickly reached 4.35% after the first 5 min, then increased slightly, and finally achieved 6.5% at 2 h. The drug release reached platform at 5 min for F1 granules in acidic medium, and F2 and F3 granules attained release platform at 15 min and 30 min, respectively. These values were in accordance with the disintegrability of the excipients. The drug release of F4 increased slowly over the time, and no burst effect was observed. This might be because the hydrogel formed by sodium alginate was the hindrance for drug release.

For the release profiles in pH 5.5 medium, the drug-release rate for pellet-containing granules was slightly faster than that for coated pellets, especially in the first 2 h. That was contributed by the accumulation amount of drug release in acid medium and the microstructure of acrylic coating films damaged during the granulating process because of the introduce of water and the external force.

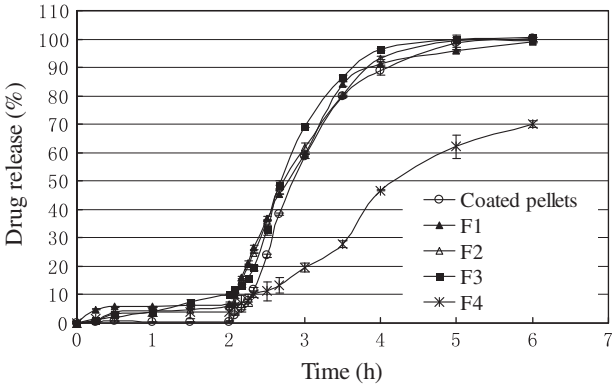

Fig. 2. Drug-release profiles of pellet-containing granules and the original coated pellets.

The f_2 values for release profiles of F1–F4 pellet-containing granules compared with that of the original coated pellets were 68.54, 62.86, 70.71, and 30.55, respectively. It was demonstrated that granulation process with formulations F1, F2, and F3 did not much impact the dissolution performance of the coated pellets. However, the drug release of pellets granulated with excipients containing sodium alginate (F4) was significantly delayed. Sodium alginate was reported for soft-tableting property and could decrease drug release from compressed pellets (coated with Eudragit® L 30D-55) from 56% to 21% [15]. But this polysaccharide compound (1) could not disintegrate completely in acid medium and the hydrogel might thicken the diffusion layer; (2) could stick to the coating film and slow down the hydration of the enteric film; and (3) could increase the viscosity of diffusion medium [18,19]. The first and last effects could reduce the dissolution rate of solid drug as described by Noyes–Whitney equation [20].

3.3. Effect of tableting process

Fig. 3 shows the drug-release profiles of tablets prepared by pellet-containing granules (F′1–F′3) compared with those of coated pellets. Similarly, the burst effect was observed for both F′1 and F′2 tablets in acid medium, and the burst onset time was increased to 15 min for F′1 and 30 min for F′2 comparing to 5 min for F1 and 15 min for F2, respectively. This phenomenon was due to the prolonged disintegration time for both tablets and excipients laying. Following the burst effect, the drug release of tablets F′1 and F′2 increased slightly instead of approaching a platform as the pellet-containing granules. After 2 h in acid medium, the release of tablets F′1 and F′2 finally attained 7.23% and 9.93%, respectively, which was higher than that of corresponding pellet-containing granules F1 and F2. This revealed that the coating film might be ruptured during compacting for both formulations; especially, the pellets located at the surface of the tablets were unavoidably compressed to deformation. The f_2 value of dissolution profile for F′1 and F′2 tablets compared with that of original coated pellets was 70.58 and 61.19, respectively, which proved that both tablet formulations maintained their enteric release mechanism. As mentioned above, the release rate of pellet-containing granules was slightly faster than that of coated pellets because the coated film swelled during the wet granulation and the softened film might rupture during the granulation. Further rupture of the coated film might occur during the tableting; however, the tablets disintegration and the close bonding of pellets and excipients powder formed during compaction might result in the delayed drug release from the tablet formulations. Because of the contribution of these two influences, the dissolution profiles of F′1 and F′2 tablets still showed great similarity to those of the original coated pellets, even the f_2 value of F'1 tablet was a little greater than that of the corresponding pellet-containing granules F1.

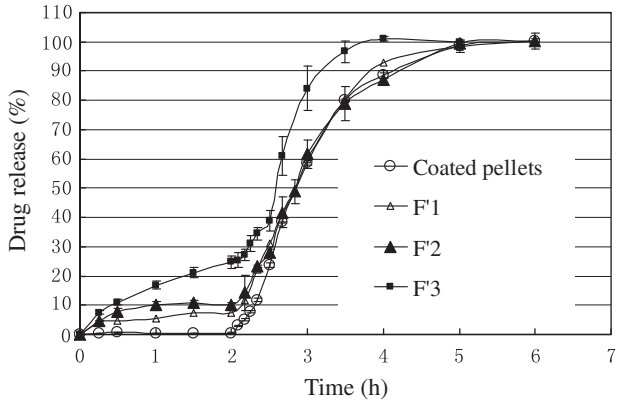

Fig. 3. Drug-release profiles of the tablets prepared by pellet-containing granules and the original coated pellets.

Tablets F′3 containing mannitol showed much faster drug release than other formulations. After initial 15 min, the drug release in pH 1.0 medium was nearly linear and the released amount after 2 h was up to 24.7%, which indicated the coating film cracked during compaction. Mannitol could not provide enough protection to the integrity of polymer coating, and this was in accordance with the literatures [3]. This could be due to the poor compressibility of mannitol, and thus, greater compress force was applied to prepare the tablets with required hardness. The higher hardness degree of mannitol particles than that of MCC might be another reason [21], which might create greater friction force during compaction, and the dissolving of mannitol in medium would result in persistent drug release.

Based on the above results, the formulation F1 of pellet-containing granules was chosen for manufacturing tablets by automachine. Same formulation of cushioning granules was prepared by two different methods as mentioned before. As shown in Table 3, fluidized bed-granules were porous and therefore had ideal compressibility, but their low density might lead to segregation in the pellets-cushioning granules mixture. In contrast, mix-granules had densified structure and therefore were more likely to achieve uniform distribution in combinations of pellets-cushioning granules; however, their higher yield pressure undermined the ability to absorb compaction forces during tableting.

3.4. Uniformity of tablets prepared by different methods

Table 4 reveals the weight and drug content standard deviation (SD) and RSD values for different tablet formulations. Both weight and drug content RSD values decreased when the pellet-containing granules took place of the original coated pellets, especially when the mixer prepared cushioning granules were used. This demonstrated that the granulation of coated pellets was benefit to the homogeneous blending of the pellets and cushioning excipients. Also, the enhanced densification of the mix-granules was an advantage to the homogeneous mixture of cushioning granules and pellets, as small RSD values were found for both T1 and T3 formulations. The worst scenario of tablet uniformity with weight and drug content RSD values of 9.53% and 22.86%, respectively, was found when original coated pellets was mixed with fluidized bed-granules (T4). Comparing the RSD values of T4 with T2, in which the coated pellets were granulated before mixing with the fluidized bed-granules, significant improvement of tablet uniformity was observed. It demonstrated that even mixing with the low-density fluidized bed-granules, the pellet-containing granules could still reduce the segregation.

3.5. The SEM photographs of particles/tablets

The SEM micrographs displayed in Fig. 4 illustrated the change in surface morphologies of pellets as a result of granulating. It

Table 4
Weight and drug content uniformity of the tablet formulations ($n = 9$).

Tablet formulations[a]		T1	T2	T3	T4
Weight	Average (mg)	402.35	407.13	405.30	407.11
	SD (mg)	5.40	8.22	12.32	38.8
	RSD (%)	1.34	2.02	3.04	9.53
Drug content	Average (%)	11.17	11.54	11.42	11.68
	SD (%)	0.16	0.17	0.30	2.67
	RSD (%)	1.43	1.47	2.62	22.86

[a] The formulations of T1–T4 were specified in Table 2.

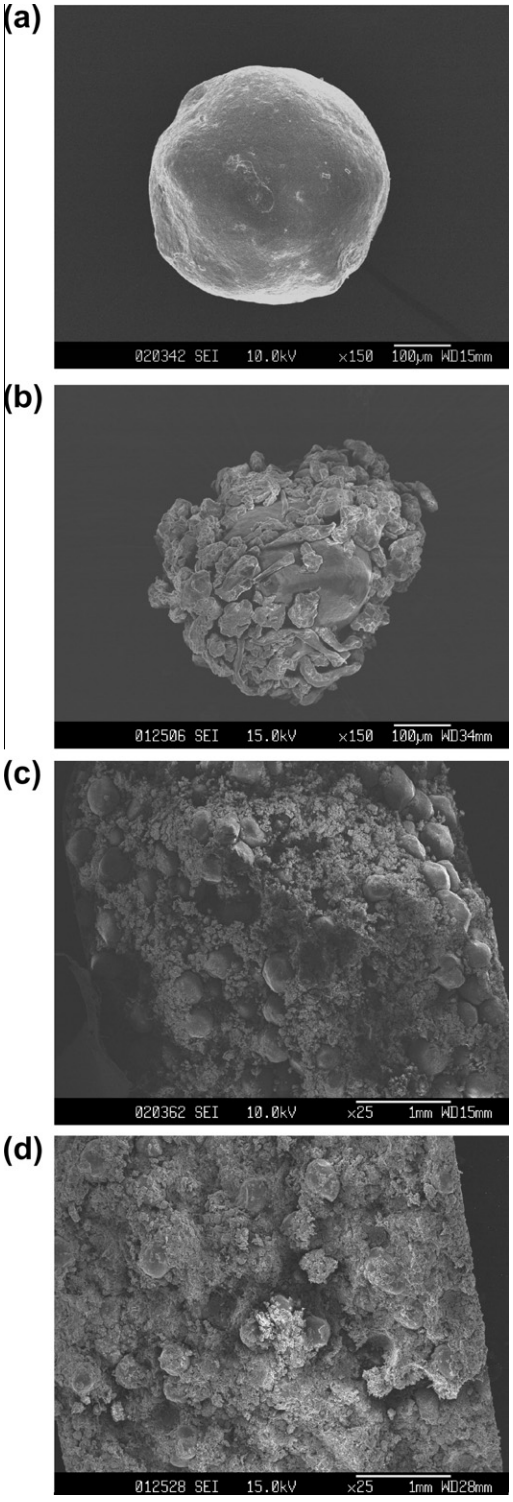

Fig. 4. SEM micrographs for original pellets, pellet-containing granules, and the cross-section of T2 and T4 tablets. (a) Coated pellets. (b) Pellet-containing granules. (c) Cross-section of T4. (d) Cross-section of T2.

clearly showed that the spherical coated pellets with smooth surface (Fig. 4a) became irregular shape pellets with rough surface (Fig. 4b) after granulating. Granules adhere to the surface of coated pellets, formed as pellet-containing granules showed in Fig. 4b. The granulated layer on the pellets' surface enables the pellets to be separated with each other even in mixing and compressing progress. And the rough surface also provided higher friction force in mixing phase for the combination of pellet-containing granules and cushioning granules. The friction force, which increased with rougher surface, was the inhibition of segregated combinations. Fig. 4c showed the cross-section micrographs of tablets prepared from the traditional mixture of coated pellets and cushioning granules. The aggregation of the coated pellets was observed, especially on the margin of tablets. And the aggregation could lead to damage of the coating films during compression as lacking of cushioning material for lubricating and absorbing the compaction force. Because of the fusion property of coated film during longtime storage, pellets aggregation could result in alternation of drug-release behavior. Fig. 4d was the sectional view of the tablets prepared from the blend of pellet-containing granules with cushioning granules. For the granulated layer, individual pellet was separated from each other, and the boundary between pellet-containing granules and cushioning granules was blurred. The pellets covered with granulated layer were well distributed inside the tablets, and no aggregation was observed.

4. Conclusions

Pellet-containing granules showed micromeritics parameters more similar to those of cushioning granules prepared by either fluidized bed or mixer-granulator than original coated pellets. Tablets prepared from the combinations of pellet-containing granules and cushioning granules showed improvement in both weight and drug content uniformity, even when the cushioning granules had distinguished different density. The pellet-containing granules with rough surface were isolated by granulated layers, which could protect coated films from contacting or fusing together during compacting and storage. During granulating and compressing, the polymeric coating films were abrased but not damaged, and the enteric drug-release behavior was maintained though the initial burst drug release in acid stage was observed.

Acknowledgements

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