European Journal of Pharmaceutics and Biopharmaceutics 79 (2011) 406–415

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

Development of potential novel cushioning agents for the compaction of coated multi-particulates by co-processing micronized lactose with polymers

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ARTICLE INFO

Article history:
Received 19 September 2010
Accepted in revised form 25 March 2011
Available online 31 March 2011

Keywords:
Micronized lactose
Cushioning effect
Spray drying
Hydroxypropylcellulose
Hydroxypropylmethylcellulose
Polyvinylpyrrolidone

ABSTRACT

This work aimed to explore the potential of lactose as novel cushioning agents with suitable physicomechanical properties by micronization and co-spray drying with polymers for protecting coated multi-particulates from rupture when they are compressed into tablets. Several commercially available lactose grades, micronized lactose (ML) produced by jet milling, spray-dried ML (SML), and polymer-co-processed SMLs, were evaluated for their material characteristics and tableting properties. Hydroxypropylcellulose (HPC), hydroxypropylmethylcellulose (HPMC), and polyvinylpyrrolidone (PVP) at three different levels were evaluated as co-processed polymers for spray drying. Sugar multi-particulates layered with chlorpheniramine maleate followed by an ethylcellulose coat were tableted using various lactose types as fillers. Drug release from compacted multi-particulate tablets was used to evaluate the cushioning effect of the fillers. The results showed that the cushioning effect of lactose principally depended on its particle size. Micronization can effectively enhance the protective action of lactose. Although spray drying led to a small reduction in the cushioning effect of ML, it significantly improved the physicomechanical properties of ML. Co-spray drying with suitable polymers improved both the cushioning effect and the physicomechanical properties of SML to a certain degree. Among the three polymers studied, HPC was the most effective in terms of enhancing the cushioning effect of SML. This was achieved by reducing yield pressure, and enhancing compressibility and compactibility. The combination of micronization and co-spray drying with polymers is a promising method with which new applications for lactose can be developed.

1. Introduction

Multi-particulate dosage forms generally consist of coated or/and uncoated multi-particulates that are conventionally filled into hard gelatin capsules. There is increasing interest to prepare multi-particulates in compressed tablets as tableting confers several advantages such as reduced risk of product tampering, lower cost by higher throughput production, flexibility in dosing regimen by allowing scoring tablets without loss of sustained release property, easier swallow ability compared with capsules [1], and avoidance of animal-derived gelatin. Following oral administration, tablets containing compacted multi-particulates need to disintegrate quickly and release the individual multi-particulates. This will enable the multi-particulates to spread uniformly throughout the gastrointestinal tract and maintain their advantages as a multiple-unit dosage form, which include the reduced risk of local irritation and dose dumping, good bioavailability, and long retention times within the gastrointestinal tract.

However, compacting multi-particulates poses considerable challenges during formulation and process development, especially if they are polymer coated. The polymeric coating must possess sufficient elasticity to withstand the compaction force without rupturing while the core should have some degree of plasticity to accommodate stresses associated with deformation during tableting. It has been reported that the ability of films to withstand pressure followed the order: films cast from acrylic polymers ≫ films cast from organic ethylcellulose solution > films cast from aqueous ethylcellulose dispersion [1]. Excipients with a variety of particle sizes, rheological properties, and bulk densities have been investigated, either alone or in combination, as cushioning agents to minimize the deleterious effects of compaction force and hence, to protect the coated multi-particulates

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doi:10.1016/j.ejpb.2011.03.024

dispersed within. These include microcrystalline cellulose (MCC) [2,3], lactose, cornstarch, L-HPC, mannitol and carmellose calcium [2], freeze-dried beads [4], wax beads [5–7] and beads composed of MCC alone [8] or in combination with other excipients like waxy and plastic polyethylene glycol [9,10], brittle and plastic lactose [11], and brittle dibasic calcium phosphate dihydrate [12]. In terms of the tableting process, the latest developments in tablet compaction such as extending dwell time could be explored to prepare tablets that contain multi-particulates by capping the maximum compaction pressure, which in turn, prevents the coat from rupturing.

In the present work, lactose, one of the most widely used fillers in tablets, was examined for its potential to act as a cushioning agent. Firstly, the effect of the particle size of lactose on its cushioning effect was studied. In light of the finding that particle size reduction improved the cushioning effect, micronized lactose (ML) was co-processed with several polymers by spray drying to determine whether such co-processing could improve the physico-mechanical performances of ML while maintaining or, ideally, further enhancing the cushioning effect during the tableting of ethylcellulose-coated multi-particulates.

2. Materials and methods

2.1. Materials

Spray-dried lactose (Pharmatose DCL 11, DMV, Veghel, Netherlands) and α-lactose monohydrate (Pharmatose 80 M, 150 M, 200 M, and 450 M, DMV, Veghel, the Netherlands), hydroxypropylmethylcellulose (HPMC; Methocel E3, Dow Chemical, Midland, MI, USA), hydroxypropylcellulose (HPC; Klucel EF, Hercules, Wilmington, DE, USA), polyvinylpyrrolidone (PVP; Kollidon K17, BASF SE, Ludwigshafen, Germany), cross-linked polyvinylpyrrolidone (PVPP; Polyplasdone XL, ISP, Wayne, NJ, USA), magnesium stearate (Riedel-de Haën, Seelze, Germany), sugar cores with a fraction size of 500–600 μm (Nu-pareil, Hanns G Werner GmbH, Tornesch, Germany), and aqueous ethylcellulose dispersion (Surelease, Colorcon, West Point, PA, USA) were used as supplied. Chlorpheniramine maleate (CPM; BP grade, China) was used as the model drug.

2.2. Preparation of the micronized lactose (ML)

Pharmatose 80 M was micronized by jet milling in a fluidized-bed opposed jet mill (AFG100, Hosokawa, Augsburg, Germany). The mill was operated at a pressure of 0.4 MPa and classifying wheel speeds of 5000 and 18,000 rpm to produce ML particles with volume median diameters of approximately 2 and 10 μm, respectively. Particle size was determined by laser diffraction (Wet Module, LS230, Coulter Corporation, USA).

2.3. Preparation of ML-polymer particles via spray drying

In order to prevent ML from undergoing a dissolution-precipitation cycle during processing, ML of approximately 2 μm was homogeneously dispersed in ice-cold saturated water solutions of lactose containing various amounts of dissolved polymer on an ice bath to form the feed dispersions. Three polymers, HPC EF, HPMC E3, and PVP K17, were used at different levels. For HPC, concentrations of 5%, 10%, and 15% (w/w) were used while 5%, 15%, and 25% (w/w) were used for HPMC and PVP. The ratio of dispersed ML to dissolved lactose in the feed dispersions was fixed at 2.23. Each prepared feed dispersion was immediately spray-dried using a pilot scale spray dryer (Mobile Minor, Niro, Søborg, Denmark) with a rotary atomizer operated under the following conditions: inlet temperature, 160 °C; outlet temperature, 80 °C; atomizing wheel speed, 23,000 rpm; and feed rate, ~40 ml/min. The spray-dried particles collected were further dried in a hot-air oven at 60 °C for 3 h and then sealed in plastic bags and stored in desiccator at room temperature until further tests.

2.4. Characterization of the spray-dried materials

2.4.1. Moisture content

An accurately weighed sample was dried at 105 °C in a hot-air oven until a constant weight was achieved. The dried sample was then cooled in a desiccator overnight before weighing. The moisture content was calculated by dividing the weight loss after drying with the original weight of the sample.

2.4.2. Physical states of lactose

The physical states of lactose in the materials studied were examined by X-ray diffraction and differential scanning calorimetry (DSC). X-ray diffractograms of the materials were obtained using an X-ray diffractometer (XRD 6000, Shimadzu, Kyoto, Japan). A monochromatic Cu Kα radiation source was operated at 40 kV and 30 mA with a step size of 0.02° and a scan speed of 2°/min over a range of 5–50° (2θ). The diffractometer was calibrated using a silicon standard. The percentage of crystallinity was calculated using the integral method introduced by Wakelin et al. [13]. The diffraction pattern of the lactose prepared by the spray drying of an aqueous solution of lactose was used as the amorphous reference and the pattern of the lactose re-crystallized from an aqueous solution of lactose at 60 °C was used as the crystalline reference. The thermal properties of samples were observed by DSC (DSC-50, Shimadzu, Kyoto, Japan) in the temperature range of 50–250 °C with a scanning rate of 2 °C/min. Calibration was carried out with indium and tin standards. The weighed dried samples were sealed into aluminum pans and measured under a nitrogen atmosphere.

2.4.3. Particle size and size distribution

Particle size was determined by laser diffraction (Dry Powder Module; LS230, Coulter Corporation, USA). All materials were pre-sieved with a 500 μm aperture size sieve before size analysis. Materials were steadily delivered to achieve an obscuration of 4–7%. Sampling time was fixed at 60 s. The volume weighted mean particle size (D_{50}) was automatically determined while particle size distribution was represented by span and calculated using the following equation:

$$\text{Span} = \frac{D_{90} - D_{10}}{D_{50}} \quad (1)$$

where D_{10}, D_{50}, and D_{90} are the diameters of sample at the 10th, 50th, and 90th percentiles of the cumulative percent undersize plot, respectively. Three replicates were carried out for each measurement.

2.4.4. Flowability

The angle of repose was determined to indicate the flowability of the materials. An appropriate amount of powders was first passed through a sieve with a 500 μm aperture size and then poured through a glass funnel in a controlled manner onto a platform until a stable and height-fixed heap was formed. The angle of repose was measured as the angle made by the inclined plane of the heap with the horizontal.

2.4.5. Apparent particle density

The apparent particle density of the materials was determined by helium displacement (Penta-Pycnometer, Quantachrome Instruments, USA). Measurements were performed in duplicates.

2.4.6. Compressibility

A tapping apparatus (Stampfvolumeter, JEL, Germany) was used for the compressibility studies. The sample was pre-sieved with a 500 μm aperture size sieve and flowed continuously from an appropriate height into a measuring cylinder, which was exactly cut to 50 cm^3, until it was full. After the excessive powder was scraped off, the weight of the filled powder was recorded. Tapping was carried out until no further change in volume was achieved. The bulk (ρ_b) and tapped (ρ_{ta}) densities were calculated as quotients of the weight of the powder to its volumes occupied before (V_0) and after tapping (V_{ta}), respectively. The Hausner ratio and the percent compressibility (PC) were calculated by Eqs. (2) and (3), respectively.

$$\text{Hausner ratio} = \frac{\rho_{ta}}{\rho_b} \tag{2}$$

$$\text{PC} = \frac{V_0 - V_{ta}}{V_0} \times 100\% \tag{3}$$

2.4.7. Compactability

The materials were compacted on a universal testing machine (Autograph, AG-100kNE, Shimadzu, Kyoto, Japan) using 10 mm, round flat-faced tooling with a compaction pressure of 64, 96, 127, or 159 MPa. The target compact weight was 440 mg. After 48 h of storage, thickness and diameter of five compacts at each compaction force were determined using a digital micrometer (Mitutoyo, Japan). The breaking force (F) of the compacts was determined by a crushing force tester (Sotax HT1, Switzerland). The compact tensile strength (σ) in MPa was calculated using Eq. (4) [14]:

$$\sigma = \frac{2F}{\pi D t} \tag{4}$$

where F is the breaking force of the compact (N), D is the compact diameter (mm), and t is the compact thickness (mm). The compactibility of the materials, which was defined as the ability of the materials to be transformed into a compact with a certain mechanical strength, was determined from the calculated tensile strengths of the compacts as a function of compaction pressure.

2.4.8. Yield pressure

The "off-die" method was used so as to eliminate the effect of elastic deformation on determination. The compact weight for each material was adjusted to obtain a compact thickness of 4.0 mm at zero porosity based on the apparent particle density of the material as determined previously via helium pycnometry. The compaction was carried out as above using 10 mm flat-faced tooling with compaction forces of 5.0, 7.5, 10.0, 12.5, and 15.0 kN, respectively. After 0 and 48 h of storage, thickness and diameter of three individual compacts at each compaction force were determined using the digimatic micrometer. The Athy–Heckel Eq. (5) was used to analyze the volume reduction mechanism during compaction [15–17] and to determine the mean yield pressure of the material (P_y).

$$\ln\frac{1}{1-D} = KP + A \tag{5}$$

where D is the relative density of the compact at pressure P; K is a material constant and is the slope of the linear portion of the plot. The reciprocal of K is P_y, which is inversely related to the ability of the material to deform plastically under pressure. Typically, lower values of P_y indicate the onset of plastic deformation at lower applied pressures.

2.4.9. Scanning electron microscopy

The samples were gold sputter-coated (JFC-1100, Jeol Ltd., Tokyo, Japan) and then examined under a scanning electron microscope (SEM; JSW-6510 LV, Jeol Ltd., Tokyo, Japan).

2.5. Preparation of controlled-release multi-particulates

Sugar cores were coated with two consecutive functional layers in tandem, namely, the drug deposition layer followed by the controlled-release layer using the Precision coater module of the multiprocessor (MP-1, GEA Aeromatic-Fielder, Eastleigh, UK). For drug loading, 1 kg of the sugar cores was coated under the following conditions: airflow rate 80 m^3/h, atomizing air pressure 0.2 MPa, spray rate 11.8 g/min, and inlet air temperature 70 °C. The Precision coater module was fitted with an accelerator insert with inlet air diameter of 24 mm and a partition column with a partition gap of 18 mm. The aqueous coating solution, containing 10% (w/w) HPMC, 1% Plasdone C-15, and 5% (w/w) chlorpheniramine maleate, was delivered through a two-fluid spray nozzle with a nozzle tip of 0.5 mm, an air cap diameter of 2.5 mm, and a nozzle tip protrusion that was 1 mm from the flushed position. The drug-loaded multi-particulates were tray-dried at 60 °C for 12 h in the oven. The fines and agglomerates were removed using appropriate sieves.

Subsequently, the drug-layered multi-particulates were coated with Surelease under the following conditions: airflow rate 100 m^3/h, atomizing air pressure 0.2 MPa, spray rate 14 g/min, and inlet air temperature 65 °C. The Precision coater module was fitted with an accelerator insert with an inlet air diameter of 20 mm and a partition column gap as above. The coating dispersion was delivered through a two-fluid spray nozzle with a nozzle tip of 1 mm, and an air cap diameter, and a nozzle tip protrusion as above. After coating, the multi-particulates were tray-dried and sieved as above.

2.6. Mechanical testing of coated multi-particulates

The crushing strength of coated multi-particulates was determined by using a tensile tester (EZ test-100 N, Shimadzu, Japan) mounted with a 100 N capacity load cell. A randomly sampled particulate with a size range between 500 and 600 μm was crushed diametrically between two platens at a rate of 0.5 mm/min, and the maximum load (N) required to crush the particulate was recorded from the force–time profile. A total of 104 measurements were carried out, and the averaged crushing strength of the coated multi-particulates used in this study was found to be 4.29 ± 0.71 N.

2.7. Tableting of coated multi-particulates

Each 1 g tablet was composed of 50% coated multi-particulates, 44% the material studied, 5% Polyplasdone XL, and 1% magnesium stearate as the drug delivery system, filler, disintegrant, and lubricant, respectively. The ingredients for each tablet were weighed out individually and mixed in a 25 ml beaker for 2 min with a spatula. The tablets were made using the universal testing machine with a tableting force of 5 kN. A 15-mm round flat face punches and die set was employed.

2.8. Evaluation of tablets

2.8.1. Dissolution testing

The dissolution tests were carried out on both uncompacted multi-particulates and tablets in an Optimal DT-1 dissolution tester (Optimal Instruments, USA) using USP apparatus II (500 ml deaerated purified water, 100 rpm, 37 °C, $n = 3$). Samples were withdrawn at predetermined time points and measured spectrophotometrically (UV-1201, Shimadzu, Japan) at 262 nm. In order

to minimize the effect of disintegration on drug release, tablets with a disintegration time of more than 3 min were carefully broken manually into several pieces to lower their disintegration time to less than 3 min before the dissolution test. Additional experiments were carried out on fast-disintegrating tablets to confirm that the breaking up of tablets did not damage the multi-particulates contained.

The similarity factor f_2, which was calculated by Eq. (6), was used to determine whether dissolution profiles were different; generally, an f_2 value between 50 and 100 is taken as the criterion for equivalence [18]. Dissolution data time points below 85% drug release and only one sampling time point above 85% were used in the calculation of f_2 [19].

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^{n} W_t (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\} \quad (6)$$

where n is the number of time points, R_t is the dissolution value of the reference formulation (i.e. uncompacted multi-particulates in this study) at time t and T_t is the dissolution value of the test formulation at time t.

In addition, the MDT values were calculated by Eq. (7) [20] to represent the release rate. The 92% drug release, which was directly determined from each dissolution curve, was set as the ending point of calculation.

$$\mathrm{MDT} = \sum \overline{t}_i \cdot \Delta M_i / \sum \Delta M_i \quad (7)$$

where $\overline{t}_i$ is the midpoint of the time period during which the fraction ΔM_i of the drug has been released from the dosage form, i.e., $\overline{t}_i = (t_i + t_{i+1})/2$ and $\Delta M_i = (M_{i+1} - M_i)$.

2.8.2. Disintegration testing

The disintegration time was determined on six tablets (USP method; DT2, Sotax, USA) in purified water that was maintained at 37 °C ± 1 °C. The European Pharmacopoeia requires that rapid release tablets disintegrate in a maximum of 15 min. This rule can also be applied to tablets containing multi-particulates for multiple-unit sustained release [21,22]. Disintegration time measurements, as such, are indicative of whether and when the tablet formulations start to act as true multiple-unit preparations [21].

2.8.3. Mechanical testing of tablets

Tablet crushing force was determined using a crushing force tester (Sotax HT1, Switzerland). Five tablets from each formulation were determined and results averaged.

3. Results and discussion

As described by several investigators [4,11], an ideal cushioning agent or filler should have the following desirable properties. Firstly, when compressed, it should deform much more readily than the drug-loaded multi-particulates so as to ameliorate the detrimental effects of compaction pressure. Deformation may occur directly and plastically or by fragmentation at low pressures, followed by plastic deformation with the further build-up of pressure. This is important, as effective protection of the coated multi-particulates requires a filler that is capable of effectively filling the voids between multi-particulates so as to protect them from the compressive impact brought upon by volume reduction due to compaction forces. Secondly, the filler should blend homogeneously with the multi-particulates and should be handled without segregation. Thirdly, the filler should facilitate the formation of compacts of adequate mechanical strength but with fast disintegration times. Last but not least, there should be, at most, minimal changes to the drug release kinetics of the coated multi-particulates after compaction.

3.1. Effect of particle size of lactose on the cushioning effect

The effect of lactose particle size on the cushioning effect was significant (Figs. 1 and 2). Regression analysis revealed a linear correlation between the similarity factor f_2 values (Y) of the release profiles and the logarithmic values of mean particle sizes (X) of the non-spray-dried lactose batches ($Y = -10.1 \ln X + 67.5$; $R^2 = 0.992$). A decrease in the lactose particle size results in a corresponding increase in: (i) pressure required for particle fracture, (ii) plastic flow of bulk particles, and (iii) elasticity of each particle. This resulted in a change of the main consolidation mechanism during compaction from fragmentation to plastic deformation [23]. Consolidation by plastic deformation is less harmful than fragmentation to the coatings of multi-particulates due to various reasons. Firstly, plastic deformation causes a material to deform into a shape that fits the voids, hence creating better contact among the constituent particles. Secondly, fragmentation may create sharp edged fragments that could pierce into the coatings of the multi-particulates. In addition, finely divided excipients would adhere as a powder coat onto the surface of the large coated multi-particulates, minimizing the impact of compression forces. For ML, "soft tableting" [24,25] can take place due to the increased elasticity of the single particle, contributing possibly to its excellent cushioning effect. On the other hand, amorphous lactose showed a lower yield pressure than crystalline lactose, indicating that the amorphous lactose particles were more deformable than the crystalline grades [26]. Spray-dried lactose powders generally contain approximately 80–90% fine primary crystalline particles along with 10–20% amorphous lactose; thus, it is unsurprising that the f_2 values of tablets using SML or Pharmatose DCL 11 as filler deviated upwards from the trendline as mentioned above (Fig. 2).

3.2. Co-spray drying of ML with polymer

Although ML (~2 μm) was found to have an excellent cushioning effect in the first part of this study, it is impractical to use it directly in production due to its extremely poor flowability and compactability. Therefore, spray drying, one of the commonly used particle engineering technologies, was used in an attempt to produce porous and free-flowing particles, which were believed to be composed of a solid dispersion of primary micronized crystalline

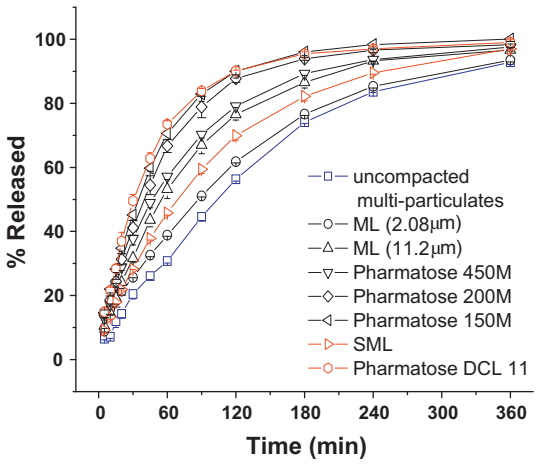

Fig. 1. *In vitro* release profiles of chlorpheniramine maleate from tableted EC-coated multi-particulates with various lactose types as fillers. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

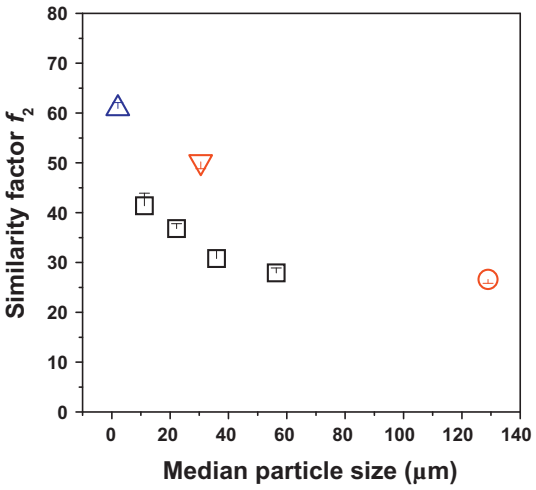

Fig. 2. Effect of particle size of lactose on the similarity factor f_2 of release profiles of chlorpheniramine maleate from tableted EC-coated multi-particulates. □ Pharmatose 150 M, 200 M, and 450 M and ML with a volume median diameter of 11.2 ; △ ML with a volume median diameter of 2.08; ▽ SML; ○ Pharmatose DCL 11. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

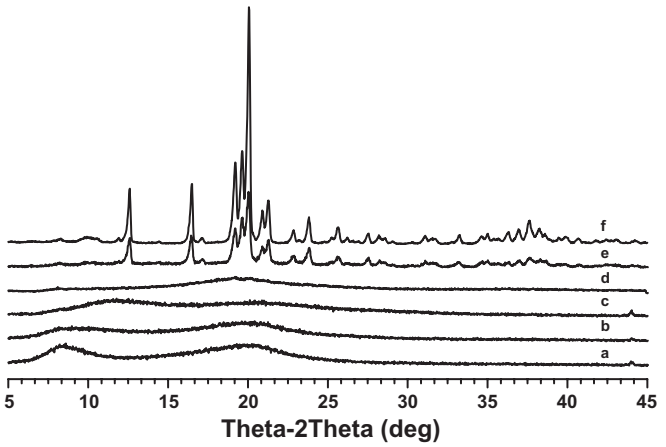

Fig. 3. Representative X-ray diffractograms of the materials studied. (a) HPC EF; (b) HPMC E3; (c) PVP K17; (d) Amorphous lactose; (e) SML-25% PVP; (f) Recrystallized lactose.

particles in amorphous lactose and, thus, possess improved physical and mechanical performances while maintaining or, ideally, further enhancing the cushioning effect.

Co-spray drying of ML with water soluble polymers was believed to provide the following advantages: (i) to increase the feed viscosity or precipitate on the surface of ML during spray drying and hence effectively inhibit the phase transition of ML; (ii) to further improve the tableting performance of spray-dried particles; and (iii) to effectively inhibit the recrystallization of amorphous lactose during storage when the polymer has a high glass transition temperature (T_g). However, the addition of polymer should not significantly retard the disintegration of the formed tablets. HPC EF, HPMC E3, and PVP K17 were selected for the study as they possess the following properties. They are commonly used in tablets as a binder, are reported to be able to inhibit solid phase transition [27–29], and are the low-viscosity grade in each polymer group. Their T_gs are high at approximately 130 °C, 170 °C, and 140 °C, respectively. The highest levels of HPC EF and HPMC E3 were set at 15% and 25% in spray-dried products, respectively. Concentrations higher than these will result in feeding difficulties during spray drying. For PVP K17, although levels above 25% can be used without feed issues, product lumping will occur due to the hygroscopicity of PVP.

3.3. Material characteristics (Tablet 1)

The characteristics of the commercially available spray-dried lactose Pharmatose DCL 11 were also determined to act as a control in order to compare against the materials produced and the methods used in this study.

3.3.1. Moisture content

The moisture contents of the materials studied remained below 2.60% throughout the study and were not markedly different. Thus, the effect of moisture on the differences between their properties should be very small, if any.

3.3.2. Physical states of lactose

The physical states of lactose in the materials were investigated by X-ray diffraction and DSC. Some key information was obtained from the X-ray diffractograms (Fig. 3). For example, the crystal structure of lactose did not change during micronization and spray drying. The crystalline form of lactose in the spray-dried materials was mainly α-monohydrate, since diffraction peaks at 10.6° and 12.6° (2θ) were reported as confirmation of the presence or absence of crystalline β- and α-monohydrate, respectively [30]. The calculated percent crystallinity showed that the crystalline portions in the spray-dried products were similar to those in the feeds (Table 1). These results suggested that the ML portion was effectively maintained during spray drying.

The DSC thermograms of the lactose-containing materials were characterized by peaks at approximately 112 °C, 150–180 °C, and 213 °C (Fig. 4), which represented the release of water of hydration, the recrystallization of amorphous lactose, and the melting of lactose α-monohydrate, respectively. They also showed that the materials produced in this study were composed of a high percentage of crystalline lactose α-monohydrate and a small amount of amorphous lactose. Compared with the raw material Pharmatose 80 M, the ML-based materials exhibited certain different thermal properties. The most prominent one was the broadened and left-shifted DSC peak for the release of crystal water, which was attributed to the markedly enhanced activity of crystal water after micronization, especially if it was located at high energy surfaces and lattice defects [31]. Additional determination without N_2 flow was carried out to confirm that there was no interference of water moisture on the peak. In the absence of N_2 flow, the onset temperature of the peak shifted from ~80 °C to ~117 °C and, more importantly, no peak was detected at 100 °C (Fig. 4j).

Although the recrystallization energy of amorphous lactose was reportedly used to calculate the amorphicity by assuming that the recrystallization energy was directly proportional to the initial amorphicity of the samples [32], the results would be inaccurate in this context due to both the low percentage of amorphous portion and, more particularly, the interaction between the amorphous portion and the 5–25% polymer portion. In terms of the altered shape of the recrystallization peak (Fig. 4h and i), such interactions might be different due to the existence form and the hydrogen bond-forming ability of polymer. For example, PVP is soluble in water at high temperatures and has a basic chemical group capable of donating electrons and thereby forming hydrogen bonds with other substances [33]. As a result, it might form a continuous network in amorphous lactose and interact intensively with it after co-spray drying.

In contrast, HPC is insoluble in hot water and precipitated as a highly swollen floc at a temperature between 40 °C and 45 °C.

Table 1
Characteristics of the different materials studied in this work.

Materials	MC (%)[a]	PS and SD		Cr (%)	AR (°)	ρ_{ap} (g/cm^3)	ρ_b (g/cm^3)	ρ_{ta} (g/cm^3)	HR	PC (%)	YP (MPa)[c]	
		D_{50} (μm)	Span								0 h	48 h
ML	1.24–1.78	2.08 (0.09)[b]	0.72 (0.37)	89.5	–	1.545	0.193 (0.005)	0.297 (0.001)	1.54	35.0	–	–
Pharmatose DCL 11	0.23–0.47	129 (4)	1.29 (0.04)	84.6	31.7 (0.7)	1.543	0.585 (0.007)	0.760 (0.001)	1.30	23.0	207.8	206.8
SML	1.48–2.08	30.5 (0.1)	1.84 (0.00)	79.5	39.3 (1.1)	1.542	0.399 (0.008)	0.590 (0.004)	1.48	32.3	163.7	165.2
SML-5%HPC	2.05–2.45	24.6 (0.4)	1.38 (0.14)	74.3	43.7 (1.2)	1.519	0.298 (0.006)	0.496 (0.004)	1.67	40.0	146.8	147.1
SML-10%HPC	2.17–2.46	24.4 (0.3)	1.31 (0.02)	69.8	40.8 (1.0)	1.494	0.330 (0.005)	0.538 (0.001)	1.63	38.7	124.2	124.4
SML-15%HPC	2.03–2.57	26.2 (0.7)	1.19 (0.21)	65.7	38.3 (0.4)	1.487	0.385 (0.005)	0.580 (0.004)	1.51	33.7	119.3	118.7
SML-5%HPMC	1.95–2.30	35.4 (0.4)	1.43 (0.01)	71.9	35.8 (0.5)	1.528	0.290 (0.003)	0.444 (0.005)	1.53	34.7	162.7	164.2
SML-15%HPMC	1.68–2.03	41.1 (0.6)	1.21 (0.02)	63.6	31.8 (0.4)	1.500	0.316 (0.004)	0.482 (0.004)	1.52	34.3	132.4	133.5
SML-25%HPMC	1.63–2.07	42.2 (0.4)	1.26 (0.00)	51.0	28.5 (0.8)	1.475	0.447 (0.002)	0.637 (0.002)	1.43	29.9	110.4	111.7
SML-5%PVP	1.96–2.52	31.5 (0.8)	1.26 (0.02)	71.1	33.7 (1.0)	1.518	0.340 (0.008)	0.517 (0.012)	1.52	34.1	146.8	149.0
SML-15%PVP	1.72–2.44	32.8 (0.2)	1.53 (0.02)	53.3	33.9 (0.8)	1.481	0.363 (0.003)	0.552 (0.005)	1.52	34.1	132.0	133.1
SML-25%PVP	1.45–2.15	37.5 (0.8)	1.35 (0.00)	47.4	38.9 (0.7)	1.444	0.394 (0.004)	0.672 (0.006)	1.70	41.3	138.8	140.1

MC, moisture content; PS and SD, particle size and size distribution; Cr, percent crystallinity; AR, angle of repose; ρ_{ap}, apparent particle density; ρ_b, bulk density; ρ_{ta}., tapped density; HR, Hausner ratio; PC, percent compressibility; YP, yield pressure.
[a] The moisture content of the materials was determined at the beginning and end of this study, respectively.
[b] Standard deviation.
[c] The yield pressures of Pharmatose 80 M determined after 0 and 48 h of storage of compacts were 254.8 and 256.8 MPa, respectively.

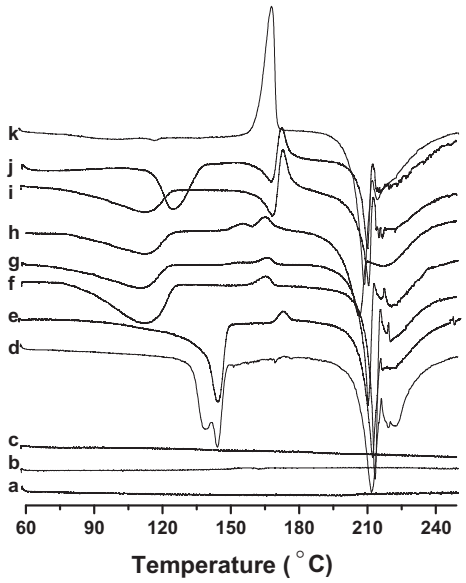

Fig. 4. Representative DSC thermograms of the materials studied. (a) HPC EF; (b) HPMC E3; (c) PVP K17; (d) Recrystallized lactose; (e) Pharmatose 80 M; (f) ML with a volume median diameter of 2.08; (g) SML-15% HPC; (h) SML-25% HPMC; (i) SML-25% PVP; (j) SML-25% PVP determined without N_2 flow; (k) Amorphous lactose.

Therefore, it would precipitate on the surface of ML particles or their aggregates before the feed was sprayed into the drying chamber, which meant that HPC would precipitate before the formation of amorphous lactose and hence they should exist much more independently in the co-spray-dried products. An intermediate situation would exist for HPMC in terms of both its higher heat-gelling temperature (~70 °C) and its high concentration in the feed. In addition, it was found that there were approximately 8.36% and 10.7% of amorphicity (calculated by recrystallization energy) in Pharmatose 80 M and ML (Fig. 4e and f), respectively, suggesting that only very little amorphous lactose was produced by solid phase transition during jet milling.

It was also clearly observed from scanning electron microscopy that these co-spray-dried products did consist mainly of primary ML particles, which were connected together by amorphous lactose and polymer (Fig. 5).

3.3.3. Particle size and size distribution

The volume median particle size of the spray-dried products ranged from 24.4 to 42.2 μm. The particle size distribution was narrow with the span value not exceeding 1.84. An increase in particle size was observed as the concentration of polymer increased. Spray-dried particle sizes usually increased as the feed concentration or viscosity increases [34]. The relatively smaller particle size of HPC-containing SMLs was believed to attribute to the full heat-gelling of HPC before spraying.

3.3.4. Flowability

HPMC was the most effective in improving the flowability of SML, while HPC was the worst. An increase in flowability was observed as the level of HPMC or HPC increased, which was believed to be related to both the increased particle density and the smoothing of the particle surface (Fig. 5).

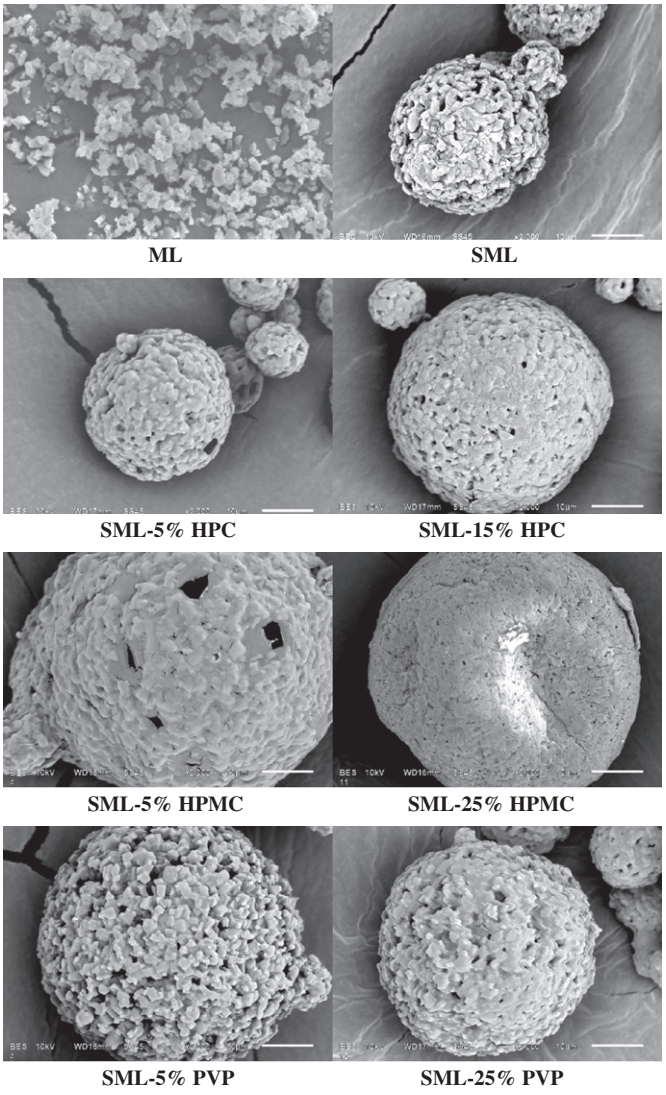

Fig. 5. Representative scanning electron photomicrographs of the materials studied (2000×).

3.3.5. Apparent particle density and compressibility

The apparent particle density of the materials coincided well with their theoretical polymer level and calculated crystallinity. Compared with Pharmatose DCL 11, the materials produced in the study had much smaller bulk and tapped densities as well as much greater Hausner ratios and percentage compressibility. This indicated that they were more porous and compressible. For all three tested polymers, an increase in bulk and tapped densities were observed as the polymer level increased. SMLs with up to 15% polymer had even smaller bulk densities than SML, which suggested that a low level of polymer is favorable in the creation of more porous particles. With the exception of SML that contained 25% HPMC, all of the other polymer-containing SMLs showed a better compressibility than SML. High porosity and compressibility are generally considered to favor the cushioning effect of a material.

3.3.6. Compactibility

Compared with Pharmatose DCL 11 and Pharmatose 80 M, ML-based spray-dried particles formed compacts that had 2.86- to 7.42-fold higher tensile strength over the compaction pressure range of 60–160 MPa (Fig. 6). Typically, particles with smaller

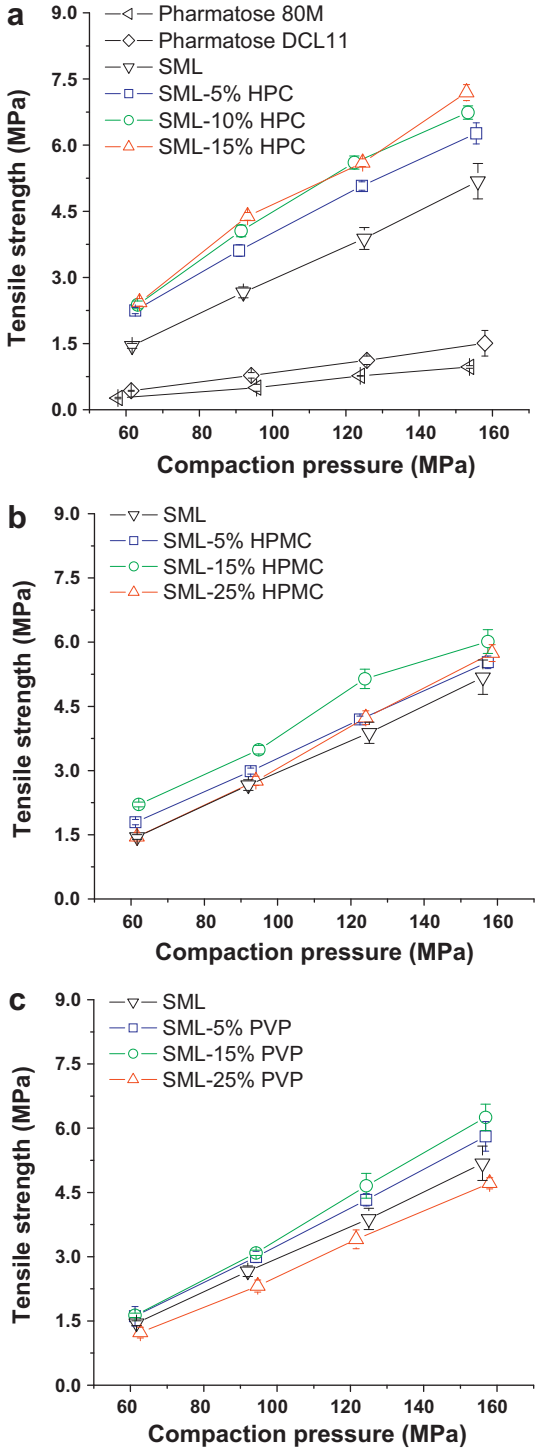

Fig. 6. Effect of polymer type and levels on the compactibility of SML. (a) HPC EF; (b) HPMC E3; (c) PVP K17. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

original particle sizes tended to produce stronger tablets [26,35]. Amorphous lactose was also found to produce tablets of higher tensile strength than crystalline lactose due to its higher deformability and inter-particulate bonding capacity [26,35]. In this study, the micro-sized primary particles, which dispersed extensively in the spray-dried secondary particles, were likely to contribute more to the significantly improved tensile strength than the coexisting amorphous portion, as Pharmatose DCL 11 also contains a comparable amount of amorphous lactose.

Among the three polymers studied, HPC was the most effective in improving the tensile strength of SML-based compacts while PVP was the worst (Fig. 6). As the polymer level increased, it appeared that all three polymers affected the tensile strength in a similar manner. Firstly, the tensile strength increased with polymer level up to a maximum, beyond which the tensile strength decreased with further increases in polymer levels. Regardless of the type of polymer used, 15% (w/w) was found to produce the hardest compacts. The distribution of the polymeric binder in such SML particles favored the surface due to the solute migration or heat-gelling during drying, which, firstly, modulated the plasticity of the particles and thus increased the contact area of the inter-particle joints and, secondly, affected the adhesiveness of the particles through the formation of binder bridges between the particles.

Irrespective of the compaction pressure used, lamination occurred when ML was compacted, which suggested that its properties, particularly the bulk density, were significantly improved by spray drying (Table 1) and should be attributed to both the weak bonding formed between crystalline ML particles during compaction and the volume recovery of excess air entrapped in the compact during ejection.

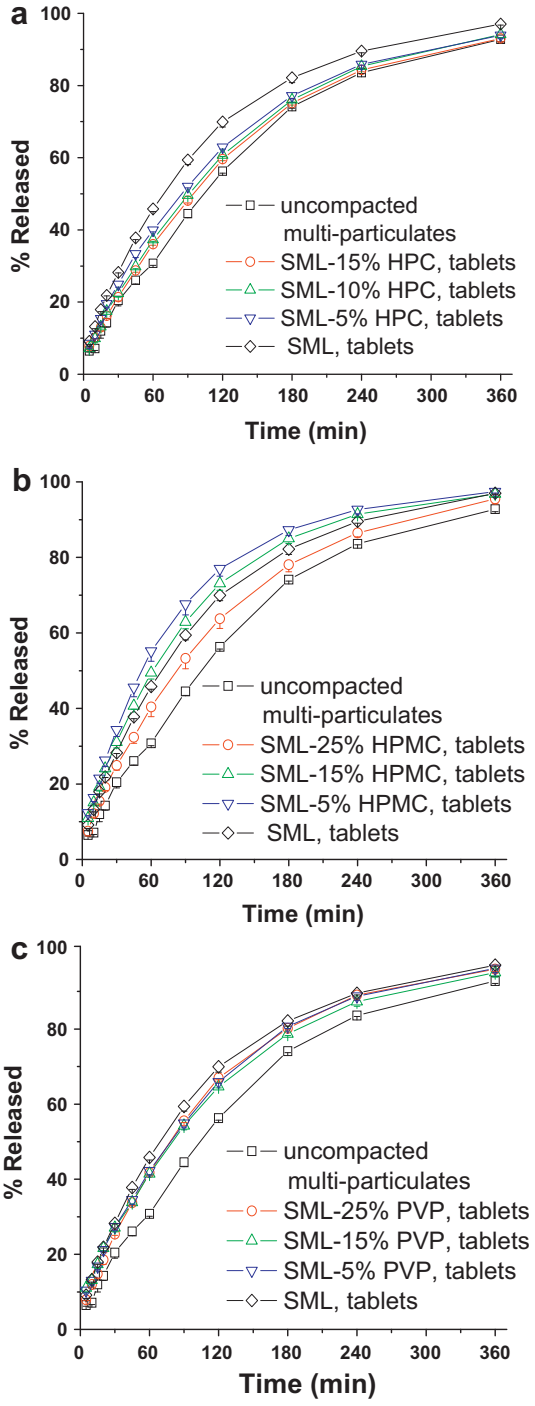

Fig. 7. Drug release profiles for tablets composed of EC-coated multi-particulates and various polymer-containing ((a) HPC EF; (b) HPMC E3; (c) PVP K17) SMLs as fillers. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3.3.7. Yield pressure (P_y)

Results revealed that the linear correlations of all the Athy–Heckel plots were accurate over the compaction pressure range of 58–189 MPa with correlation coefficients between 0.9962 and 0.9999. The addition of polymer resulted in a reduction in the P_y value of SML in the following order: HPC > HPMC > PVP; moreover, higher polymer levels led to a greater reduction. The P_y value of SML was reduced by ~36% when compared to Pharmatose 80 M. The addition of 5–25% polymer caused a further reduction in P_y of between 0.6% and 32%. In addition, the P_y values of compacts determined after 48 h storage were only slightly higher than those determined immediately after compact ejection, which suggested that the slow viscoelastic recovery of the materials, especially HPC-containing SMLs, was very limited. Plastic deformation at low pressure is an essential characteristic for a material to act as an excellent cushioning agent.

3.4. Tablet characteristics

The cushioning effects of the materials investigated in this study were indirectly reflected in the drug release behaviors of the multi-particulates before and after tableting. Results showed that tableting accelerated drug release to some degree no matter what kind of filler was used (Figs. 7 and 8 and Table 2). However, when the brittleness and thickness of the coating of the multi-particulates, which was cast from aqueous ethylcellulose dispersion and designed for only approximately 6-h sustained release,

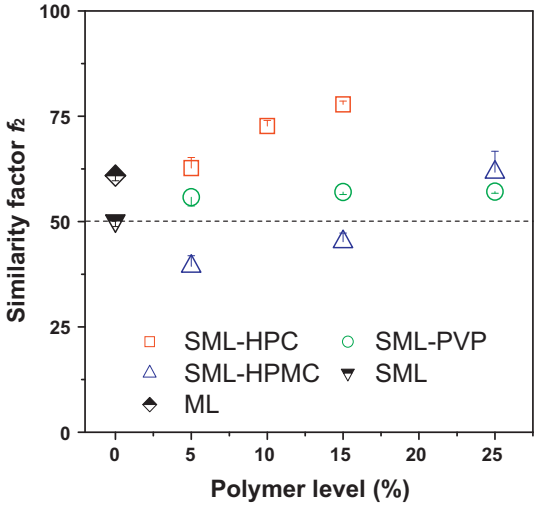

Fig. 8. Effect of polymer type and levels on the similarity factor f_2 of drug release profiles from tablets. The f_2 values were calculated with the dissolution values of uncompacted multi-particulates as reference. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2
Properties of multi-particulates-containing tablets prepared using different fillers.

Fillers	MDT (min)[a]	f_2[b]	Disintegration time (min)		Crushing force (N)
			Intact tablets	Broken tablets	
ML	96.4 ± 1.3	60.9 ± 1.2	0.28 ± 0.14	–	<2.0
Pharmatose DCL 11	36.6 ± 1.6	26.6 ± 0.8	0.19 ± 0.05	–	<2.0
SML	78.9 ± 2.5	50.2 ± 1.4	0.47 ± 0.14	–	26.4 ± 2.7
SML-5% HPC	94.9 ± 1.9	62.7 ± 2.5	0.57 ± 0.13	–	27.8 ± 1.5
SML-10% HPC	99.8 ± 1.2	72.7 ± 1.3	1.42 ± 0.28	–	31.6 ± 2.5
SML-15% HPC	103.7 ± 0.6	77.8 ± 0.8	5.12 ± 0.59	2.09 ± 0.31	36.4 ± 4.4
SML-5% HPMC	62.7 ± 4.8	39.4 ± 2.5	0.75 ± 0.12	–	26.0 ± 1.6
SML-15% HPMC	71.2 ± 3.4	45.2 ± 2.1	4.49 ± 0.27	1.95 ± 0.19	37.8 ± 2.5
SML-25% HPMC	92.4 ± 5.1	61.7 ± 5.0	8.58 ± 0.45	2.62 ± 0.63	36.8 ± 5.3
SML-5% PVP	85.6 ± 2.1	55.8 ± 2.1	0.53 ± 0.08	–	24.8 ± 1.9
SML-15% PVP	89.4 ± 1.7	57.0 ± 0.6	1.65 ± 0.27	–	33.8 ± 5.6
SML-25% PVP	86.0 ± 1.1	57.1 ± 0.4	2.53 ± 0.23	–	28.4 ± 5.2

[a] MDT for uncompacted multi-particulates was 110.1 ± 0.1 min.
[b] The f_2 values were calculated with the dissolution values of uncompacted multi-particulates as reference.

were taken into consideration, the cushioning effects obtained should be satisfactory and promising.

Compared with ML, SML exhibited a slightly reduced cushioning effect, which was reflected by an approximately 18% reduction in the MDT value of the model drug, chlorpheniramine maleate. During tableting, SML particles underwent fragmentation to a minor degree in terms of their distinct structure (micro-sized primary particles connected together by amorphous lactose). Plastic deformation and densification dominated the compression process, which ensured a well-preserved cushioning effect of ML. On the other hand, the bulk density of ML was 2.07-fold smaller than that of SML. Therefore, ML particles might have already been fully adsorbed onto the surface of multi-particulates during mixing as a result of their much fluffier structure and higher surface energy, and then act well as an elastically deforming protection layer during compaction. In addition, once the system was homogeneously mixed, the poor flowability of ML actually reduced the possibility of segregation in the subsequent downstream processes. These might all be reasons why ML acted slightly better than SML as a cushioning agent.

Co-spray drying with polymers appeared to be able to improve the cushioning effect and compactibility of SML. Apart from SMLs that contained 5% and 15% HPMC, all of the other polymer-containing SMLs exhibited better cushioning effects than SML in the present study. They helped to form tablets with the f_2 values between 55.8 and 77.8. In particular, HPC-containing SMLs and SML that contained 25% HPMC showed even better cushioning effects than ML. The reduction in yield pressure of materials was found to be most correlated to their improved cushioning effects (Fig. 9). Linear regression analysis revealed the effect of yield pressure was statistically significant ($P = 0.001$). The slope of this relationship was around −0.454. The correlation coefficient was reasonably high ($R^2 = 0.885$) when the data for SMLs that contained 15% and 25% HPMC were excluded. The lower the yield pressure, the earlier and larger would be the plastic deformation of the spray-dried particles, occurring even at low pressures. Thus, all the distributed primary micro-sized lactose particles could act as a "soft tableting" [24,25] material at increased pressures and hence produced a better cushioning effect. Deviation from the trendline suggested that other factors might also contribute to the protection effects. For SMLs that contained 15% and 25% HPMC, the much smaller than expected f_2 values might be attributed to their excellent flowability, which resulted in their segregation from multi-particulates during die filling. Further studies are needed to explore possibilities of increasing particle size without compromising other desired properties, particularly the cushioning effect, to address the segregation issues. Such methods include, but are not limited to wet granulation with ethanol as the main granulating liquid, which can produce granules with high porosity and deformability and hence good cushioning effect [36,37] or fluidized spray drying, which combines the features of the spray drying process with fluid-bed granulation [38].

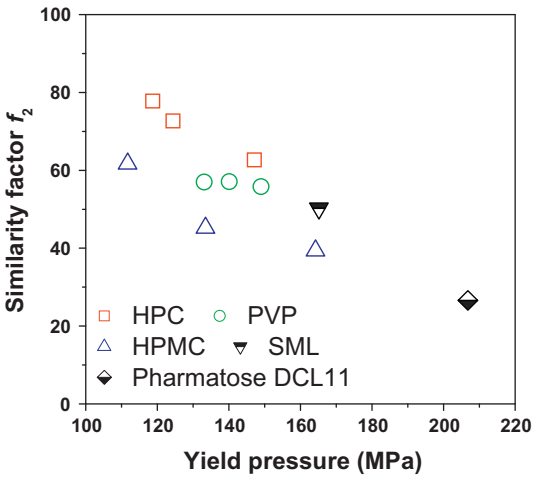

Fig. 9. Relationship between the similarity factor f_2 values of drug release profiles from tablets and the yield pressures of the fillers used. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Apart from drug dissolution, the crushing force and disintegration time of the multi-particulates-containing tablets were also determined (Table 2). The results obtained coincided well with those obtained in the compaction study on pure materials, and the crushing force of tablets with ML-based spray-dried materials as fillers was significantly higher compared to tablets that used ML or Pharmatose DCL11 as filler. The influences of polymer type and levels on the tablet crushing force were also similar to those for pure materials. In general, the existence of polymer enhanced the crushing force of tablets and the 15% (w/w) polymer level in SMLs produced the hardest tablets. As for disintegration, all the tablets met the 15 min requirement of the European Pharmacopoeia for rapid release tablets. Among the three polymers studied, PVP showed the least adverse effects on disintegration, which was attributed to its good solubility and relatively lower viscosity in water.

4. Conclusion

The cushioning effect of lactose mainly depends on its particle size. Micronization can effectively enhance the protection effect of

lactose on the multi-particulate coating cast from aqueous ethylcellulose dispersion during compaction. Although spray drying caused a small reduction in the cushioning effect of ML, it does significantly improve the physicomechanical properties of ML. Co-spray drying with the appropriate type of polymer(s) can improve both the cushioning effect and the physicomechanical properties of SML. Among the studied three polymers (HPC, HPMC, and PVP), HPC was found to be the most effective in terms of reducing the yield pressure, enhancing the compressibility and compactibility, and, most importantly, improving the cushioning effect of SML. In most cases, 15% (w/w) of polymer yielded the best improvements.

In light of the results obtained in this work, further studies on the physical stability of the materials, the particle size enlargement, and the combined use of polymers with different characteristics could be explored to further demonstrate their utility as cushioning agents for the tableting of any pressure-sensitive substances such as coated multi-particulates, microcapsules, biologically active macromolecules, as well as drugs that undergo polymorphic transformation under pressure.

Acknowledgements

This work was supported by the GEA-NUS PPRL Grant N-148-000-008-001, the National Sci-Tech Major Special Item of China (2009ZX09502-009), the Project of Shanghai Science and Technology Committee (09DZ2292000), the Key Discipline Project of Shanghai Education Committee (J50302) and the Xinglin Scholar Program of Shanghai University of Traditional Chinese Medicine.

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