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ORIGINAL ARTICLE

The effect of spray drying on the compaction properties of hypromellose acetate succinate

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Abstract

Background: The aim of this study was to evaluate the compaction behavior of a model two-component amorphous spray-dried dispersion system compared with the unprocessed excipients, using simulated rotary tablet press production conditions. *Method*: In this study, the stabilizing polymer, hypromellose acetate succinate (HPMCAS), was solubilized and spray dried with and without sodium lauryl sulfate (SLS). The impact of compression force and speed on the tabletting process was quantified by means of tablet tensile strength, compaction energy, and Heckel analysis. *Results*: Addition of the surfactant SLS, spray dried or as a physical mix, reduced the tablet strength. However, a lesser impact on the unprocessed excipients was observed in comparison with the spray-dried excipients. In the presence of 1% (w/w) SLS, tablets displayed a tendency to cap when compressed at higher speeds, supported by high elastic energy values indicating high uniaxial stress upon decompression. In the presence of 3% (w/w) SLS, tablets could not be produced at high speeds. Heckel analysis revealed a greater strain rate sensitivity of HPMCAS when spray dried in the presence of surfactant. Exposure of samples to a range of relative humidities before compaction had no effect on tablet strength. *Conclusion*: This study has shown that spray drying of HPMCAS in the presence of a surfactant affects the compressibility of the material, resulting in decreased tablet strength, increased elastic deformation, and capping.

Key words: Amorphous dispersion, capping, elastic energy, rotary press simulator, strain rate sensitivity, surfactant

Introduction

Crystalline active pharmaceutical ingredients are routinely converted to amorphous forms to obtain favorable properties in terms of solubility, dissolution, or bioavailability. Such amorphous systems typically incorporate stabilizing polymers and surfactants, which on their own may dictate the eventual tablet-forming properties and can be spray dried and directly compressed to form a finished drug product. Powder blends undergo elastic and plastic deformations within the range of forces encountered during commercial tablet production, and relating these to the capping and lamination tendencies of a formulation is critical toward understanding the behavior of the drug product.

In optimizing the oral delivery of poorly soluble drugs, the use of solid dispersions combines the benefits of an increase in solubility and maximizes the surface area of the compound that comes into contact with the dissolution medium as the carrier dissolves[1]. Solid dispersions prepared using a range of hydrophilic carriers have been shown to improve the dissolution rate of poorly soluble drugs such as indomethacin[2] and piroxicam[3]. The dissolution rate of solid amorphous dispersions of the BCS Class IV drug ritonavir and PEG 8000 resulted in improved dissolution profiles[4] and oral bioavailability[5], whereas a solid dispersion carrier system comprising a water-soluble polymer (PEG 3350) and surfactant (polysorbate 80) greatly enhanced the bioavailability of a poorly water-soluble drug[6].

Spray drying is a common method for the preparation of solid dispersions and can also modify the crystallinity of a material, which can subsequently affect the compression behavior, and Di Martino et al.[7] found that

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spray-dried acetazolamide particles exhibited improved compression properties and reduced capping tendency compared with the original material. Berggren et al.[8] hypothesized that the properties of spray-dried particles, such as flowability and compactibility, could be modified by the addition of a small amount of surfactant and found that the tablet-forming ability of spray-dried amorphous lactose was influenced by the presence of surfactants in the spray feed solution. Fichtner et al.[9] studied the influence of surface energy on the compactibility of lactose particles following spray drying with or without polysorbate 80 and concluded that a decrease in tablet strength correlated to the decrease in powder surface energy observed with increased proportion of the surfactant.

Hypromellose acetate succinate (HPMCAS) is a cellulose ester bearing acetyl and succinoyl groups and is commonly used as an aqueous enteric coating material. Curatolo et al.[10] patented compositions comprising a spray-dried dispersion of a sparingly soluble drug in HPMCAS. Tanno et al.[11] evaluated the use of HPMCAS as a carrier in solid dispersions and found that the polymer suppressed the recrystallization of nifedipine more efficiently than other polymers.

The aim of this study was to evaluate the compaction properties of HPMCAS, before and after spray drying in the presence and absence of sodium lauryl sulfate (SLS), under simulated rotary tablet press production conditions.

Materials and methods

Materials

HPMCAS is a granular grade of cellulose ether with 22–26% methoxyl, 6–10% hydroxypropyl, 10–14% acetyl, and 4–8% succinoyl substitution on the cellulose backbone (Aqoat® type AS-HG, Shin Etsu, Tokyo, Japan). SLS is a commonly used anionic surfactant (Texapon® K12 P PH, Cognis GmbH, Dusseldorf, Germany). Lithium bromide, magnesium chloride, and copper chloride salts were all obtained from Sigma Aldrich (Dorset, UK).

Spray drying

HPMCAS and mixtures of HPMCAS containing 1% (w/w) SLS (Table 1) were spray dried using a Buchi 190 spray dryer, with a 0.7-mm two-fluid nozzle at inlet and outlet temperatures of 50 and 40°C, respectively, with 1 mL/min feed rate. Stainless steel tubing was used to deliver the solutions to the nozzle. A high-performance cyclone (BÜCHI Labortechnik AG, Flawil, Switzerland) was used to capture dried particles. All mixtures (HPMCAS, HPMCAS + 1% SLS) had similar viscosities of ~9.6 cP at 5°C determined using a Brookfield viscometer (Brookfield Engineering Laboratories, Inc., Middleboro, MA, USA). After spray drying each sample was dried in a vacuum oven at 50°C for 30 hours. An additional sample of HPMCAS + 3% (w/w) SLS was prepared by spray drying and used for further compaction studies only.

Powder blending

Physical mixtures of HPMCAS and 1% (w/w) SLS or spray-dried HPMCAS and 1% (w/w) SLS (Table 1) were produced by blending for 5 minutes in a turbula mixer (Type 2B, WAB, Muttenz, Switzerland).

Percent relative humidity studies

Samples of HPMCAS, all spray-dried materials, and physical mixtures were stored at 6, 33, and 66% (±1%) relative humidity (RH) by placing in sealed dessicators above saturated solutions of lithium bromide, magnesium chloride, and copper chloride salts, respectively, for 1 week. Percent RH and temperature (25 ± 1°C) were monitored using a digital hygro-thermometer (Extech Instruments, Waltham, MA, USA).

Tablet compaction and analysis

The compression behavior of the spray-dried materials was compared to that of the pure excipient HPMCAS and the physical mixtures. Tablets (300 mg) were produced using a Stylcam® 100R rotary press simulator (Medel'Pharm, Lyon, France) fitted with 11.28 mm round flat punches. The Stylcam® is a high-precision, single station press capable of producing up to 2400 tablets/h using an automatic feeder, or operating in single cycles with manual die feeding, as in this study. Traditionally, compaction simulators have been operated in single-ended rather than double-ended compaction mode and carry the liability of not being a realistic representation of tabletting on a rotary tablet press[12]. The Stylcam® operates using a mechanical cam, which produces a biaxial compaction profile analogous to that of a rotary

Table 1. Composition of model blends evaluated for compression behavior (% w/w).

Blend name	HPMCAS	SLS	HPMCAS spray dried	HPMCAS: SLS spray dried
HPMCAS	100	—	—	—
SD HPMCAS	—	—	100	—
HPMCAS + 1% SLS MIX	99	1	—	—
SD (HPMCAS + 1% SLS)	—	—	—	99:1
SD (HPMCAS + 1% SLS MIX)	—	1	99	—
*SD (HPMCAS + 3% SLS)	—	—	—	97:3

*This sample was used for further tablet compaction studies only.

tablet press. Five tablets (300 mg) were compressed at 10 or 30 kN and rates of 10 or 30 rpm (equivalent to rotary press production rates of approximately 40,000 or 120,000 tablets per hour and dwell times of 30 and 10 ms, respectively). The crushing strength, P (kP), of each tablet was determined using a model 6D tablet tester (Dr. Schleuniger Pharmatron, Solothurn, Switzerland). Tablet thickness, t (mm), and diameter, d (mm), were measured using a digital micrometer (Mitutoyo, Andover, UK). Radial tensile strength (σ_t), which measures tablet failure as a result of the application of tensile stress only[12], was calculated according to Equation (1)[13]

$$\sigma_t = \frac{2P}{\pi d t} \quad (1)$$

Compaction energies, calculated from force–displacement profiles, were determined using the Analis® software (v. 2.01.22, Medel'Pharm, France) associated with the Stylcam®. For a system where both punches are mobile during compaction, punch movement may be plotted against applied force and the area under this curve will be the energy of compaction[14]. The characteristic shape of the force–displacement curve, recognizable in terms of its slope and elastic recovery, can be correlated to the ability of material to undergo plastic deformation[12].

During tabletting, the reduction in volume of the compact upon application of force can be calculated using the Heckel equation[15] (Equation 2)

$$\mathrm{Ln}\left(\frac{1}{1-D}\right) = KP + A \quad (2)$$

where D is the relative density of the compact in die at pressure P, K and A are regression coefficients of the linear portion of the curve, and the reciprocal of K is the mean yield pressure (Py), which is generally considered to reflect the effective deformability of the particles during compression[16]. The true densities of materials were determined using helium pycnometry (Multipycnometer, Quantachrome, Boynton Beach, FL, USA). Heckel plots were constructed using the Analis® software and mean yield pressures were determined at low (Py_1) and high compression rates (Py_2). The strain rate sensitivity (SRS) of each material was calculated according to Equation (3)[17]:

$$\text{Percent SRS} = \frac{Py_2 - Py_1}{Py_2} \times 100 \quad (3)$$

SRS is traditionally used to compare materials according to their respective increases in yield pressures at two different punch speeds[12]. SRS increases as the plastic deformation becomes the more dominant mechanism during the compaction process[17].

Thermal analysis

Differential scanning calorimetry (DSC) was performed with indium being used for temperature calibration. Samples were analyzed in hermetically sealed aluminum pans using a Pyris 1 DSC (Perkin Elmer, Waltham, MA, USA) equipped with a liquid nitrogen-cooling accessory. An empty hermetically sealed aluminum pan was used as reference. DSC thermograms were recorded at a heating rate of 10°C/min.

Thermogravimetric analysis (TGA) was performed using a TGA 2050 (TA Instruments, New Castle, DE, USA) equipped with a high-precision balance. TGA thermograms were recorded at a heating rate of 10°C/min.

Scanning electron microscopy

The surface structure of samples and compressed tablets were studied using scanning electronic microscopy (SEM; Inspect S SEM, FEI, Hillsboro, OR, USA). Samples were examined at 20 Kv accelerating voltage with low vacuum.

Particle size analysis

The particle size of spray-dried materials were determined through image analysis using the Scion Image software (Scion Corporation, Frederick, MD, USA). A minimum of 400 particle diameters for each material were measured.

Bulk powder density and flowability

Poured bulk powder density (ρB_{min}) was determined by filling a known weight of material into a volumetric cylinder. Tapped bulk density (ρB_{max}) was determined manually 'tapping' the cylinder in a drop-box until a constant volume was reached (minimum 250 times). Percentage flowability was determined using the Carr's index (Equation 4)

$$\text{Carr's index}\,(\%) = \frac{\rho B_{max} - \rho B_{min}}{\rho B_{max}} \times 100 \quad (4)$$

Statistical analysis

The impact of surfactant and RH on tablet strength was evaluated using the Minitab software package. Analysis of variance was used to determine any significant ($P < 0.05$) differences in tablet strength.

Results and discussion

Analysis revealed that the particle size of spray-dried HPMCAS was reduced in the presence of SLS (Table 2).

Bulk and tapped density measurements were comparable for the model blends that were evaluated and the

Table 2. Particle size measurements (μm) for spray-dried HPMCAS in the presence and absence of 1% SLS.

	SD HPMCAS	SD HPMCAS + 1% SLS
D_{10}	7.9	5.3
D_{50}	13.0	9.7
D_{90}	23.6	18.5
Mean	14.8	11.3
SD	7.0	6.9

impact of surfactant on particle size was not reflected in the flowability of the materials (Table 3). HPMCAS, because of its granular nature, displayed markedly lower Carr's index values, indicating superior flowability compared with the spray-dried materials.

SEM images (Figure 1) show the granular nature of the HPMCAS starting material and the spherical shape of the spray-dried materials. Surface morphology nor particle size seemed to be affected by the presence of SLS.

DSC thermograms of the model spray-dried blends did not show a crystalline melt indicating that spray-drying process produced an amorphous blend (data not shown).

TGA data revealed a similar weight loss as a function of temperature (0.64–0.78%) for the spray-dried HPMCAS in the presence and absence of 1% SLS, and there were no significant differences in moisture content of any samples (data not shown).

Increasing compression force resulted in higher tablet tensile strengths for all samples. HPMCAS when compressed alone produced robust tablets and showed little dependence on the compression speed used. When physically mixed with 1% SLS, tablet strength was reduced, presumably because of the distribution of surfactant acting as a barrier to interparticulate bonding during compression of the granular HPMCAS. When spray dried (HPMCAS), tablet strength was reduced and was equivalent to that of the pure excipient when physically mixed with 1% SLS. Addition of 1% SLS as a physical mix with the spray-dried HPMCAS did not reduce the tablet strength further, which may be explained by considering the increased surface area of the spray-dried powder. It is probable that increased concentration or a longer mixing time would be required to distribute the surfactant sufficiently to disrupt bonding when mixing with spray-dried particles.

A significant ($P < 0.05$) impact of SLS on the tablet strength was observed in combination with spray drying

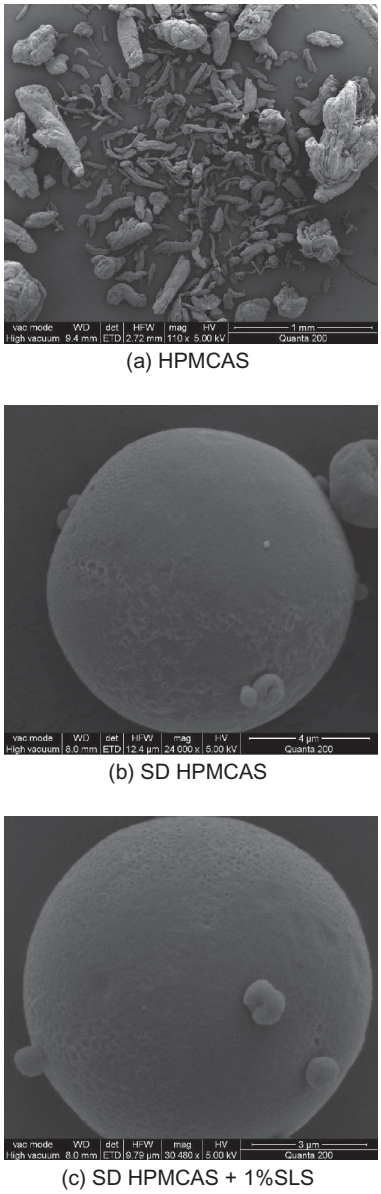

Figure 1. SEM images of (a) HPMCAS; (b) spray-dried HPMCAS; (c) spray-dried HPMCAS + 1% SLS.

of the excipients, suggesting a change in the compression mechanics and bond formation during tablet compaction. A higher compression speed caused a reduction in tensile strength of the tablets formed from the spray-dried HPMCAS in the presence of 1% (w/w) SLS (Figure 2), indicating dwell time is a contributing factor for the tablet-forming ability of the powder. Berggren et al.[8]

Table 3. Bulk density (ρB_{min}), tapped density (ρB_{max}), and Carr's index measurements on the different powder mixtures (mean values ± SD, $n = 3$).

	HPMCAS	SD HPMCAS	SD (HPMCAS + 1% SLS)
ρB_{min} (g mL^{-1})	0.333 (±0.001)	0.293 (±0.010)	0.340 (±0.012)
ρB_{max} (g mL^{-1})	0.417 (±0.003)	0.455 (±0.013)	0.511 (±0.009)
Carr's Index (%)	20.0 (±0.65)	35.6 (±2.13)	33.4 (±1.4)

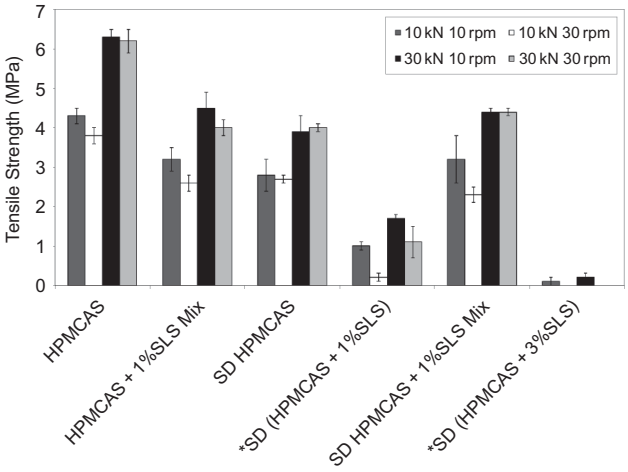

Figure 2. The effect of compaction force and speed on the tensile strength of HPMCAS tablets in the presence and absence of SLS, before and after spray drying (mean values ± SD, $n = 5$), *Significantly different data.

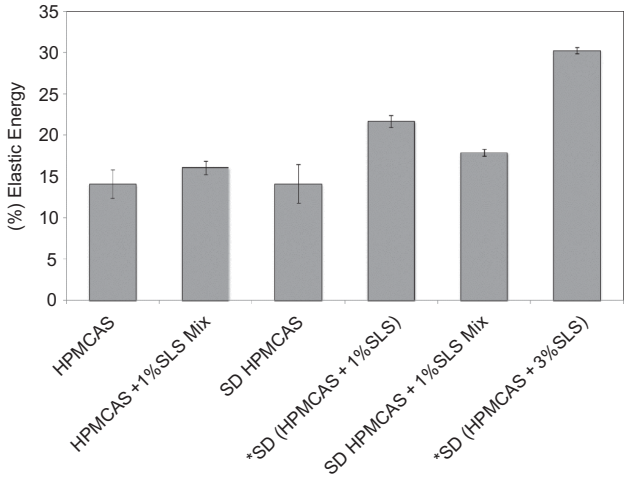

Figure 3. The percent elastic energies of HPMCAS tablets in the presence and absence of SLS, before and after spray drying (mean values ± SD, $n = 5$). Data shown are for tablets produced at 30 kN and 30 rpm, *Significantly different data.

claimed that the presence of a surfactant on the particle surface of spray-dried amorphous particles may have lowered the strength of the particle–particle adhesive joints. Millqvist-Fureby et al. [18](1999) determined that the coverage of the enzyme trypsin on the surface of particles after spray drying was significantly reduced by the presence of a surfactant in solution, which the authors ascribed to the more efficient adsorption of the surfactant at the air/water interface in the spray droplets. Fichtner et al.[9] reported that particle surface energy, lowered by the presence of surfactant during spray drying, reduced powder compactibility and ascribed this to a reduction in the strength of adsorption bonds formed during compression. In this study, it is thought that adsorption of SLS on the surface of the particles during spray drying may have restricted interparticulate bond formation during compaction and caused the subsequent reduction in tablet strength.

When spray dried in the presence of SLS, HPMCAS tablets also displayed a tendency to cap when compressed at higher speeds. This observation was supported by the high elastic energy values (Figure 3) indicating high uniaxial stress upon decompression. Elastic energy is not utilized for bonding during compression but is stored as deformation energy under stress[14]. The release of this energy, at the end of the compression cycle causes weak interparticulate bonds to break and the creation of a porous structure or, in the case of materials with a high resistance to an increase in porosity, the phenomenon of capping to occur[19]. Garr and Rubinstein[20] stated that capping is a problem that frequently occurs during tabletting and that a combination of low overall plasticity because of high compression speeds and relatively high elasticity after the compression force has been removed results in a greater tendency to cap. An increase in elastic energy was recorded at the higher compression speed for all samples in this study, which is a trend previously noted by other authors[19]. When spray dried in the presence of 3% (w/w) SLS, tablets could not be produced at high speeds because of capping upon ejection from the die. Heckel analysis revealed greater SRS of HPMCAS when spray dried in the presence of surfactant (Table 4) further supporting the dependence of the material on speed of compression and associated dwell times. Materials that undergo deformation independently of compression rate have low SRS values (2%) whereas materials that deform plastically (i.e., time-dependent deformation) have higher SRS values.[17] The low-yield pressures for the spray-dried HPMCAS, both with and without SLS, indicate a relatively deformable material. Whereas the yield pressure for the spray-dried material alone remained relatively constant, when spray dried in the presence of SLS, an increase in yield pressure at the higher compression rate was recorded, thus giving a greater SRS value.

Storage over a range of percent RH did not have a significant effect ($P > 0.05$) on tablet strength of HPMCAS, spray-dried materials, or physical mixtures studied (data not shown) indicating the environmental RH condition had negligible impact on the tabletting for this model system.

Table 4. True density, mean yield pressure, and strain rate sensitivity values for HPMCAS, spray dried in the presence and absence of SLS.

	SD HPMCAS	SD (HPMCAS + 1% SLS)
True density (g/cm^3)	1.4090	1.3743
Py–10 rpm	64.6	70.8
Py–30 rpm	65.5	82.5
%SRS	1.4	14.2

Conclusion

The presence of surfactant in the production of a solid dispersion formulation and the concentration used can have an impact upon compression properties. Furthermore, external addition of surfactant to the spray-dried dispersion can also influence tablet properties. This study has shown that spray drying of HPMCAS in the presence of a surfactant affects the compressibility of the material, resulting in decreased tablet strength, increased elastic deformation, and capping. During drug product concept selection, consideration should be given toward the incorporation of minimum quantities of surfactant or as a physical mixture with the spray-dried dispersion to achieve a commercially viable formula and process. Polymer selection during formulation development not only impacts the physicochemical stability but also manufacturability of the final drug product.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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