Hollow Filler–Binders as Excipients for Direct Compaction

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Purpose. As an effect of their plastic deformation behavior, ductile materials create a large surface for bonding during compaction. However, a serious drawback is their high lubricant sensitivity, preventing the formation of strong bonds. The purpose of this study was both an increase in compactibility and a reduction of the lubricant sensitivity of ductile filler-binders by using hollow particles. This was illustrated for inulin.

Methods. Both solid and hollow inulin particles were prepared by spray-drying. Unlubricated tablets and tablets containing 0.5% magnesium stearate were compressed in a compaction simulator, operating at 300 mm/s. The tablet crushing strength was determined with a Schleuniger apparatus.

Results. The compaction of unlubricated, solid inulin particles showed that the product had good compatibility. This was caused by plastic deformation of the ductile, amorphous material under load, creating a large surface for bonding. After lubrication, however, the bonding properties decreased significantly, which was caused by the presence of a lubricant film. Hollow inulin particles have an increased compactibility as compared with solid particles and a strongly reduced lubricant sensitivity. Scanning electron micrographs show that hollow particles fragment before they start plastic deformation. This fragmentation behavior is supported by tablet surface area measurements and calculation of the buckling strength. This effect was responsible for both a higher crushing strength and a lower lubricant sensitivity as compared with solid inulin particles.

Conclusions. Compactibility of inulin particles can be increased, and lubricant sensitivity can be decreased by using hollow instead of solid particles.

KEY WORDS: inulin; direct compaction; filler-binders; lubricant sensitivity.

INTRODUCTION

One of the most important requirements for excipients for direct compaction is a good compactibility. In previous work, the effect of particle deformation on the compaction properties for directly compressible filler–binders has been studied (1). Brittle materials commonly break during compaction. Fragmentation prevents the formation of a large bonding surface. In contrast, ductile materials show plastic deformation. For the majority of ductile pharmaceutical materials the compaction force is higher than the yield strength but lower than the fragmentation strength, so they can be deformed to a large extent without fracture. This means that the bonding contact area is much larger for ductile materials than for brittle materials. So far, it seems that ductile materials should be preferred as directly compressible filler-binders because they create the largest surface for bonding. A serious drawback for ductile materials, however, is their high lubricant sensitivity, particularly when tablets are produced using high-speed tabletting machines, as is being done in the pharmaceutical industry (2,3). The lubricant sensitivity is strongly dependent on the fragmentation behavior of the material during the compaction process (2). During compaction of brittle materials, a lubricant film, formed during the mixing process, is destroyed as an effect of particle fragmentation. The interparticle bonding between the freshly formed, clean surfaces will be better than that of surfaces covered with a lubricant film. For plastically deforming materials, a lubricant film is not destroyed during consolidation because there is no fragmentation. This means that the tablet contains a continuous network or matrix of the lubricant (3). For this reason, the lubricant sensitivity of plastically deforming materials is usually high. Although there are different possibilities to limit the lubricant sensitivity of filler–binders (4), in pharmaceutical practice the reduction of the tablet strength as an effect of mixing with a lubricant is a well-recognized problem.

In this work, it was shown that using particles with a specific morphology can increase compactibility and can reduce the lubricant sensitivity of ductile materials. Recently inulin was introduced as a filler-binder for direct compaction of tablets (5). Although inulin is available in both an amorphous and a crystalline state, the best tabletting properties were found for amorphous inulin. As an effect of its ductile behavior under load, amorphous inulin has a high lubricant sensitivity. It was found, however, that the negative effect of lubricants on compactibility was reduced when particles containing large amounts of air were compressed (5). Obviously, entrapped air enhances fragmentation of ductile powder particles before they start to deform plastically, resulting in a breaking up of the lubricant film. In the present study, hollow excipient particles were introduced as a filler-binder for direct compaction of tablets. The effect of this special morphology on compactibility and lubricant sensitivity was investigated for both solid and hollow inulin particles.

MATERIALS

Two types of amorphous inulin, a solid and a hollow form, were obtained from Sensus (Roosendaal, The Netherlands). Both solid and hollow inulin particles were prepared by spray-drying of an aqueous solution, but under different conditions (6). Magnesium stearate (Ph.Eur) was supplied by Centra-Chemie (Etten-Leur, The Netherlands).

METHODS

The number average degree of polymerization of the inulins was determined as described previously (5). The particle size distribution of the inulins was determined using laser diffraction (Sympatec HELOS Compact KA with 500 mm lens; Sympatec, Clausthal, Germany). The powder was dispersed with a RODOS dry powder dispenser at a pressure of 0.5 bar.

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The moisture content of the filler-binders was determined in about 3 g inulin using an infrared drying balance (Sartorius MA 40 moisture analyser, Göttingen, Germany), operating at 105°C during 20 min.

The density of the inulins was determined using helium pycnometry (Quantasorb multipycnometer, Quantachrome, Syosset, NY, USA). The sample, as it was obtained, was measured to determine the amount of included air in the particles. After extensive milling in a coffee mill a true density of 1.480 g/cm^3 was found.

The elastic modulus of the inulins was measured as a function of deformation rate with dynamic mechanical analysis as previously described (7).

Flat-faced tablets of 500 mg and a diameter of 13 mm were prepared on a programmable compaction simulator (ESH testing, Brierley Hill, UK) at different compression forces. The speed of the upper punch was 300 mm/s. This high speed was chosen to simulate high-speed tabletting machines (8,9). The tablets were prepared from pure filler-binder or from blends of filler-binder and 0.5% magnesium stearate. Mixing with the lubricant was performed for 2 min in a Turbula mixer (model 2 P, W.A. Bachofen, Basle, Switzerland) at 90 rpm.

The specific surface area (BET) of inulin tablets was measured with a Quantasorp gas adsorption apparatus (Quantachrome Corp.) using nitrogen as adsorbate.

The tablet strength was determined (at least 30 min after compaction) with a Schleuniger 6 M tester (D. Schleuniger, Soloturn, Switzerland). The results presented are the mean of three measurements.

RESULTS AND DISCUSSION

Table I shows some physical properties of two types of amorphous inulin. Both inulins have a number average degree of polymerization of 11, an almost equal moisture content, and a comparable particle size distribution. Just as could be expected, the solid inulin particles have the highest density, which is close to the density 1.480 of the milled inulin. The difference shows that even the solid particles contain a small amount of entrapped air, which is quite common for spray dried inulin (5). The hollow inulin particles have a much lower density; the mean intraparticulate porosity, calculated from the densities, is about 20%. Figure 1 shows a scanning electron micrograph of the hollow inulin particles with, among other particles, a broken particle. Electron photographs of solid inulin particles are quite similar, but broken particles are not visible.

Figure 2 shows the compaction profiles for the two types of inulin, both unlubricated and lubricated with 0.5% magnesium stearate. The crushing strengths of tablets, compressed

Table I. Physical Properties of Inulin Particles

Inulin	DP[a]	Moisture content (%)	Particle size (μm) $d_{25\%}$	$d_{50\%}$	$d_{75\%}$	Density (g, cm^{-3}) (mean ± SD)
Hollow particles	11	3.1	28.0	52.5	78.4	1.180 ± 0.001
Solid particles	11	3.5	26.1	42.3	61.6	1.390 ± 0.001

[a] Number average degree of polymerization.

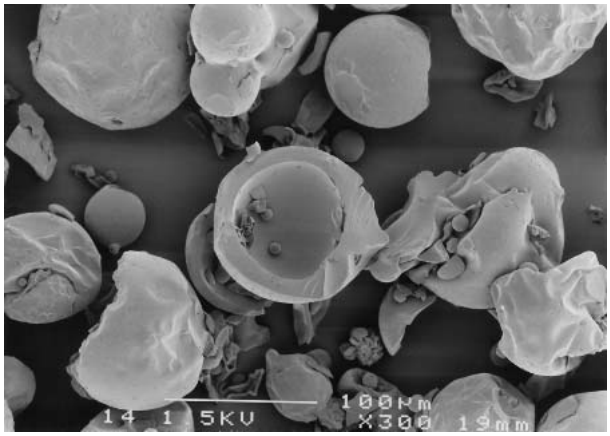

Fig. 1. Scanning electron micrograph of hollow inulin particles.

from hollow inulin particles, were higher than those of the solid particles. However, after mixing with magnesium stearate, the compactibility of the solid inulin particles decreased to a large extent. The compactibility of the hollow inulin particles was affected much less by the presence of the lubricant. The rather good compactibility of unlubricated solid inulin particles was caused by plastic deformation of the ductile particles under load (5). This plastic deformation was visible on scanning electron micrographs of the surface of fracture of tablets, compressed at two compaction pressures shown in Fig. 3. The pictures clearly show that densification involves rather plastic deformation than fragmentation. Even after compaction with a pressure of 148 MPa, the particles were more or less intact. The ductile behavior of the solid inulin particles explains the high lubricant sensitivity of the material (Fig. 2). Figure 4 shows scanning electron micrographs of the surface of fracture of unlubricated tablets compressed from hollow inulin particles. Comparing the pictures of tablets compressed at low and high force strongly suggests that the particles are broken into fragments before they start plastic deformation. The combination of fragmentation and subsequent plastic deformation is responsible for higher crushing strengths of unlubricated tablets when compared with unlubricated tablets compressed from solid inulin particles. More important, however, is the fact that the compactibility of the hollow inulin particles is much less affected by the addition of magnesium stearate (Fig. 2). This effect is caused by fragmentation of the hollow particles during early stages of the com-

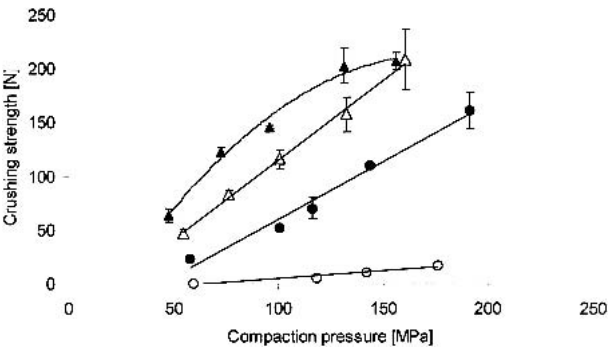

Fig. 2. Compaction profiles of hollow inulin particles (▲,△) and solid inulin particles (●,○), both unlubricated (closed symbols) and lubricated with 0.5% magnesium stearate (open symbols). (n = 3; Mean ± SD).

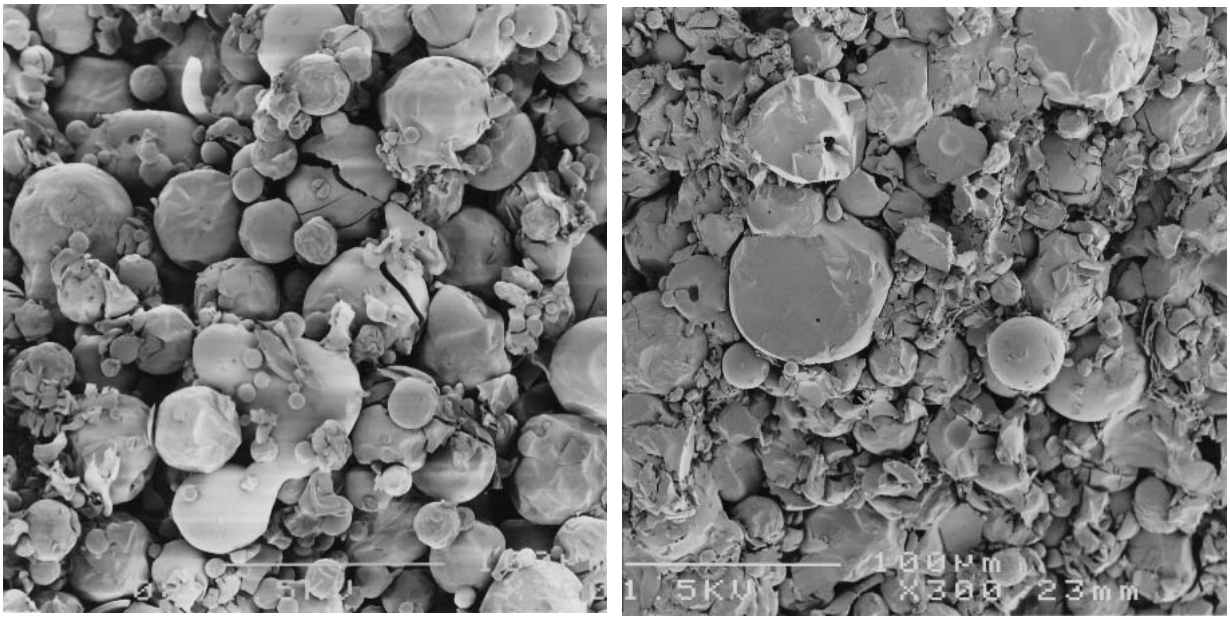

Fig. 3. Scanning electron micrographs of the surface of fracture of tablets compressed from solid inulin particles, compressed at 37 MPa (left side) and 148 MPa (right side), respectively.

paction process, which will destroy the lubricant film to a large extent.

In previous work, it was shown that particle fragmentation during compaction can be illustrated by measuring the tablet's specific surface area as a function of the compaction pressure (10). Figure 5 shows the specific surface area of tablets compressed from both inulin types, as a function of the compaction pressure. It can be seen that with increasing compaction pressures the specific surface area increases much more for tablets compressed from hollow inulin particles than for tablets compressed from solid inulin particles.

Hollow particles fragment by buckling (11–13). The buckling strength is the critical force, necessary for a sudden collapse of a hollow object exposed to an increasing stress. Von Kármán and Tsien, in (12) describe the theoretical buckling strength of shells by the following equation:

$$p_{cr} = \frac{2 \cdot E}{\frac{1}{4}\sqrt{3 \cdot (1 - \nu^2)}} \cdot \frac{d_s^2}{d_p^2} \tag{1}$$

with p_{cr} = critical pressure, E = elastic modulus, ν = Poisson ratio, d_s = thickness of the shell, and d_p = diameter of the sphere. In practice, the critical pressure is lower and an empirical equation for practical use was derived (13):

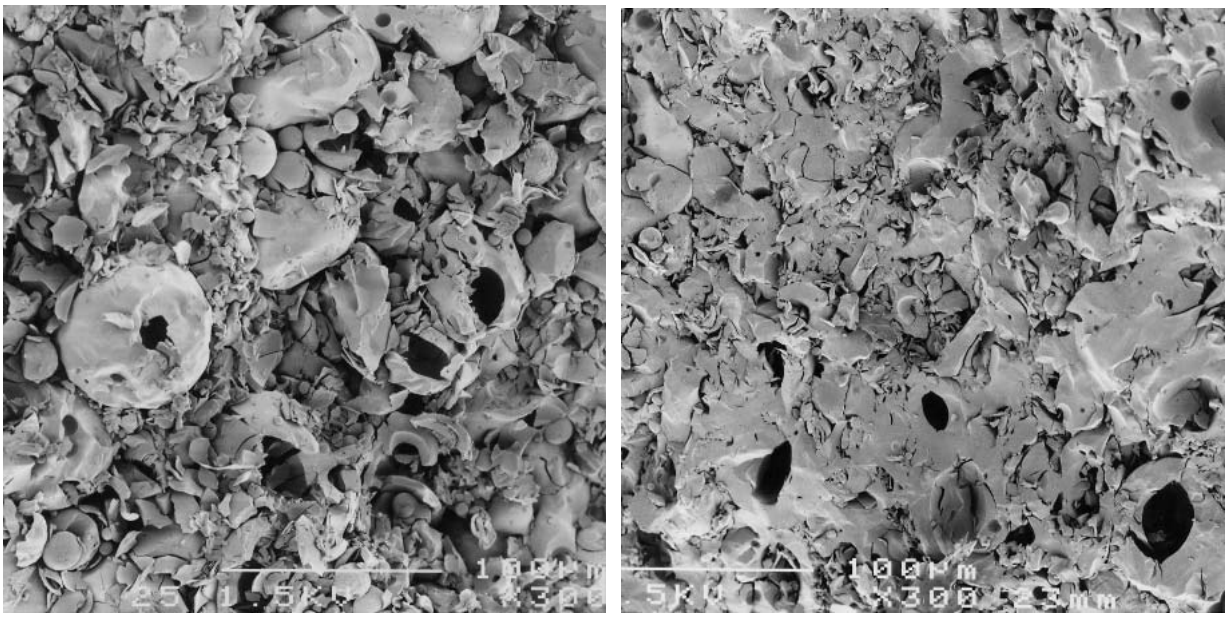

Fig. 4. Scanning electron micrographs of the surface of fracture of tablets compressed from hollow inulin particles, compressed at 37 MPa (left side) and 148 MPa (right side), respectively.

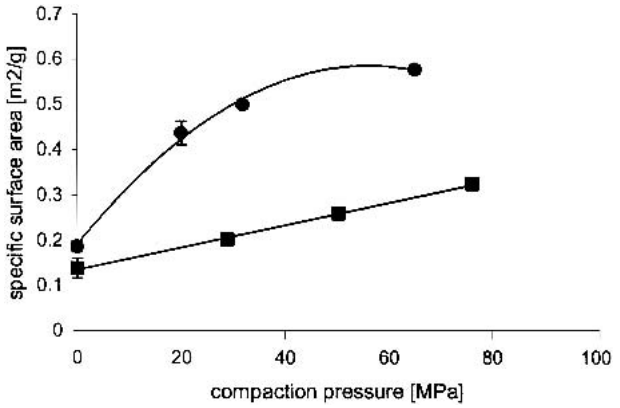

Fig. 5. Specific surface area of tablets compressed from (■) unlubricated solid inulin particles and (●) unlubricated hollow inulin particles as a function of the compaction pressure. Mean ± SD.

$$p_{cr} = \frac{0.312 \cdot E}{\frac{1}{4}} \cdot \frac{d_s^2}{d_p^2} \quad (2)$$

For spherical particles, the quotient of the thickness of the shell and the particle diameter can easily be expressed in the material density by Eq. (3):

$$\frac{d_s}{d_p} = \frac{1 - \left(\frac{\rho_m - \rho}{\rho}\right)^{\frac{1}{3}}}{2} \quad (3)$$

with ρ_m = density of milled material and ρ = density of material consisting of hollow particles.

Combining Eq. (2) and Eq. (3) gives the following:

$$p_{cr} = 0.312 \cdot E \cdot \left[1 - \left(\frac{\rho_m - \rho}{\rho}\right)^{\frac{1}{3}}\right]^2 \quad (4)$$

Eq. (4) shows that pressure under which spheres buckle only depends on the elastic modulus and intraparticule porosity of the powder. For both inulin powders, the elastic modulus, calculated from dynamic mechanical analysis measurements, has the same value of 5 Gpa, so the difference in buckling strength is determined by the difference in intraparticle porosity only. This can be varied via the conditions used in the spray dryer for producing the particles.

Eq. (4) is valid for a uniform hollow sphere under uniform pressure. It predicts that buckling should occur at a pressure of about 200 MPa. In the powder, the particles have different sizes (see Fig. 1) and varying wall thickness. Also the pressure distribution will not be uniform. So it is not surprising that substantial fracturing already occurs at pressures much lower than this value, as was seen in Figs. 3 and 4.

CONCLUSIONS

Hollow particles of ductile excipients have an increased compactibility as compared with solid particles of the same excipient. The hollow particles collapse when the applied force exceeds the critical buckling force. The fragmented particles not only have an increased compactibility but also a strongly reduced lubricant sensitivity. The decreased lubricant sensitivity is caused by a destruction of the lubricant film during fragmentation of the hollow particles.

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