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International Journal of Pharmaceutics 258 (2003) 153–163
international journal of pharmaceutics
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Compactibility of agglomerated mixtures of calcium carbonate and microcrystalline cellulose

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Received 12 September 2002; received in revised form 22 January 2003; accepted 4 March 2003

Abstract

The tablet tensile strength (T) of agglomerated mixtures of microcrystalline cellulose—Avicel PH 102 (MC), calcium carbonate (CC) and polyvinylpyrrolidone (Povidone, PVP), lubricated with magnesium stearate (MS), and formed under a compaction pressure (P_c) ranging up to 618 MPa has been determined. The compactibility was defined through: $\ln(-\ln(1 - T/T_{max})) = \text{Slope} \times \ln P_c + \text{Intercept}$. MC/CC mixtures added of an agglutinant, before and after lubrication, show an important positive effect on their tablet tensile strength compared to a lineal relationship. This positive effect becomes smaller with decreasing compaction pressures. By different mixing methods, the higher the mixing efficiency the higher the compactibility, following the order: spray-dried > wet massing > tumble mixing. The compactibility of MC/CC/PVP spray-dried mixtures with calcium carbonate content from 20 to 60% was equal to or greater than that of pure microcrystalline cellulose. After lubrication with 2% MS the compactibility decreased, only the mixture with the maximal tablet tensile strength attained the tensile strength of pure microcrystalline cellulose. The presence of the binder, the lubricant and higher compaction pressures allow the accommodation of higher calcium carbonate proportions in the mixtures, at the maximal tablet tensile strength of the series. The lubricant decreases in a greater extent the compactibility of mixtures with a continuous phase of MC/PVP than that of CC/PVP. This is attributed to the plastic behavior of the MC/PVP continuous phase compared to a calcium carbonate continuous phase able to disrupt the Povidone and the possible lubricant coatings allowing a stronger interparticle interaction.

Keywords: Calcium carbonate; Microcrystalline cellulose; Compactibility; Agglomerated mixtures; Tablet tensile strength; Lubricants; Agglutinants

1. Introduction

Agglomeration is a process of size enlargement whereby small particles are gathered together into larger, permanent aggregates. The reasons for granulation include the improvement of compression characteristics of pharmaceutical formulations. Granulation improves cohesion during and after compression.

The cohesiveness and compactibility of powders get better with the addition of a binder that coats the individual powder particles causing them to adhere to each other so they can be formed into agglomerates. It is supposed that during the compaction process granules are fractured exposing fresh powder surfaces, which also contribute to improve their compactibi-

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doi:10.1016/S0378-5173(03)00185-6

lity (Bandelin, 1989). For agglomeration purposes, Povidone is a versatile polymeric binder with the advantage of being soluble in water and in alcohol. Although it is slightly hygroscopic, it is a valuable all-purpose binder.

Granulation by spray drying involves the production of small droplets from a solution or dispersion of the granule components. Thereafter, these droplets are dried by a heated gas stream. The granules obtained by this method show greater cohesiveness during compaction and low apparent densities due to a certain porosity of the granules.

Conventional wet granulation involves blending of the powders, addition of the agglomerating solution, kneading or massing of moist powders and size adjustment of density, because of the massing process.

The porosity of granules obtained by different methods is suggested to follow the order: spray drying > fluid-bed granulation > wet massing or conventional wet granulation. Thus, it is suggested that high granule porosity in combination with a homogeneous binder distribution is advantageous for the compactibility of a granulation (Wikberg and Alderborn, 1993). It has been suggested that the addition of a granulating agent to a particulate system may increase the plasticity of the system and contribute to cohesion under pressure (Armstrong et al., 1982).

Addition of a dry binder to coarse particles will affect the tensile strength of compacts in different ways, depending on such factors as the size and amount of the dry binder particles added. It has been suggested that the tensile strength of the mixture may best be increased by decreasing the size of the dry binder (Adolfsson et al., 1998).

Mehra et al. (1988) patented the production of a direct compaction excipient, coprocessed microcrystalline cellulose (MC) and calcium carbonate (CC). The composition would be useful as a pharmaceutical excipient and would exhibit low lubricant sensitivity, good flow characteristics, and good lubricity. Its compressibility would compare favorably with that of microcrystalline cellulose.

The patented coprocessed product obtained by spray drying is supposed to be superior to physical blends that do not provide the desired performance characteristics. However, physical mixtures of microcrystalline cellulose with calcium phosphate have been observed to show greater compactibility than microcrystalline cellulose alone (Castillo-Rubio and Villafuerte-Robles, 1995; Castillo and Villafuerte, 1995; Garr and Rubinstein, 1991).

In a previous paper, we have reported the compaction behavior of physical blends of microcrystalline cellulose and calcium carbonate, alone and in combination with an agglutinant and/or a lubricant (Garzón and Villafuerte, 2002). The evaluation showed that addition of calcium carbonate to microcrystalline cellulose, as physical mixtures, maintained the compaction behavior of microcrystalline cellulose with calcium carbonate proportions up to 20%. However, this occurred only at high compaction pressures (618 MPa). The beneficial effect of high compaction pressures on the compactibility of MC/CC mixtures was attributed to a better spreading of calcium carbonate agglomerates with increasing compaction pressures.

Addition of magnesium stearate (2%) to the above-mentioned MC/CC mixtures showed that under compaction the lubricant facilitates the calcium carbonate distribution in the tablet matrix, allowing a better contact with microcrystalline cellulose particles. This permits the accommodation of greater quantities of calcium carbonate in the mixtures with the maximal tablet tensile strength of the series.

In the case of MC/CC/PVP physical mixtures, the effect of polyvinylpyrrolidone (Povidone, PVP), as a dry agglutinant, was increased through its better distribution in the tablet matrix. This was favored by increasing compaction pressures and increasing calcium carbonate proportions in the mixtures. The results suggested that Povidone requires a wear out or erosion of its particles during compaction to improve its distribution, improving at the same time its agglutinant effect and the cohesiveness of the tablet.

All above-mentioned effects to improve compactibility of MC/CC mixtures seem to be dependent on the possibilities of a better distribution of the agglutinant in the tablet matrix as well as a better distribution of calcium carbonate around microcrystalline cellulose particles. In this sense, it is expected that agglomeration processes like wet granulation and spray drying of the mixtures will produce a better deployment of compaction capabilities of the MC/CC mixtures. This was attempted in this work through

agglomeration by conventional wet granulation and spray drying utilizing Povidone as a binder and with and without subsequent lubrication with 2% magnesium stearate.

2. Experimental procedures

2.1. Material

The pharmaceutical excipients microcrystalline cellulose (MC), Avicel PH 102; extra light calcium carbonate (CC) (Liquid Quimica, calcite of red diamond type), with a nominal average particle size of 1.2 ± 0.3 μm; Povidone, polyvinylpyrrolidone K-30 (PVP), from Helm de Mexico, and magnesium stearate (MS), from Droguería Cosmopolita, were used without further treatment.

2.2. Methods

2.2.1. Granulation

2.2.1.1. Spray drying agglomeration. Corresponding quantities of calcium carbonate for 100 g of MC/CC mixtures were dispersed by mechanical stirring in a hydroalcoholic Povidone solution (12 g Povidone:50 ml ethanol:200 ml water). Stirring was maintained until a homogeneous dispersion was obtained. The corresponding quantity of microcrystalline cellulose was dispersed separately in 200 ml water. The two dispersions were then mixed and brought to a volume of 650 ml with water. This hydroalcoholic dispersion was fed to a pneumatic spray dryer (Niro, model Minor). The operation conditions included an inlet temperature of 210 °C and an outlet temperature of 125 °C.

2.2.1.2. Wet granulation agglomeration. Corresponding quantities of microcrystalline cellulose were moistened in a mortar with a solution containing 12 g Povidone, dissolved in 30, 20 or 15 ml water. The quantity of water used corresponded to high, medium and low proportions of microcrystalline cellulose in the mixtures. The corresponding quantities of calcium carbonate were added over the moistened microcrystalline cellulose particles and homogeneously mortar and pestle mixed. The obtained agglomerates were dried for 1 h at 60 °C.

2.2.1.3. Mixtures lubrication. Agglomerated mixtures were lubricated with magnesium stearate (2%). The lubrication was carried out by mixing in a cylindrical tumble mixer for 30 min at 35 rpm. The mixing time was fixed in 30 min to work with a well-lubricated system (Shah and Mlodozeniec, 1977; Doelker, 1993), as an extreme condition to evaluate the effect of lubrication on the compactibility of the mixtures.

The microcrystalline cellulose and calcium carbonate proportions varied in a range from 0 to 100%, with a variation unit of 10%. The batch size was fixed in 100 g. Lubricated versions of the above-mentioned mixtures were obtained adding 1 g magnesium stearate to 49 g of the corresponding mixtures.

2.2.2. Tablets

Seven hundred milligrams of the corresponding mixtures were compressed for 10 s at six different compaction pressures in a hydraulic press (Enerpac) and in a range up to 618 MPa (139, 255, 332, 487 and 618 MPa). The punches used were flat and had a diameter of 12.9 mm. The selected compaction pressures were maintained for 10 s to allow the development of most possible plastic deformation on the powders, to avoid the effect of different dwell times producing different degrees of plastic deformation and their consequent effect on tablet tensile strength.

2.2.3. Tablets tensile strength measurement

Tablet tensile strength measurement was performed on tablets prepared 24–72 h before, with three repetitions and registering the results as an average. For the purpose, a hydraulic press adapted with a pressure transducer was used. The transducer was connected to a voltmeter to determine the breaking force. The procedure was to place each tablet diametrically between two flat surfaces and to apply pressure until the tablet breaks. The results obtained were converted into tablet tensile strength (T), considering the actual tablet form of a right circular cylinder (Fell and Newton, 1970).

$$T = \frac{2P}{\pi D t} \tag{1}$$

where P is the applied pressure, D is the tablet diameter, and t is the tablet thickness.

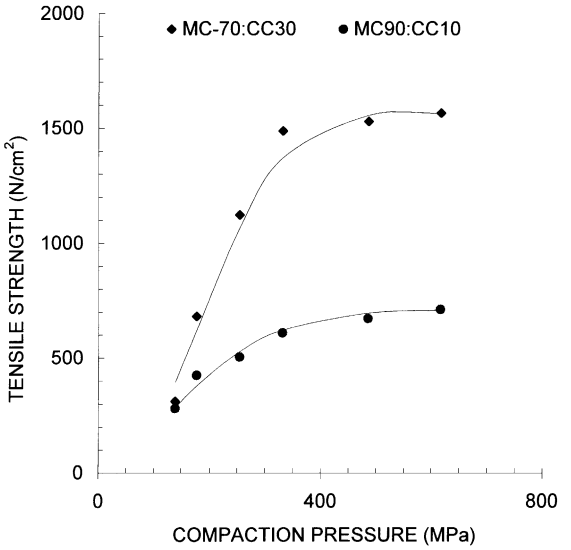

Fig. 1. Compactibility curves of spray-dried mixtures of microcrystalline cellulose (MC), calcium carbonate (CC) and 10.7% Povidone (PVP). Experimental points and regressions with: $\ln(-\ln(1 - T/T_{max})) = \text{Slope} \times \ln P_c + \text{Intercept}$.

3. Results and discussion

3.1. Compactibility of powder mixtures

Compactibility curves defining the relationship between tablet tensile strength and compaction pressure were calculated for each mixture. Fig. 1 shows two of these curves. In this figure, the points are experimental for two spray-dried mixtures of different proportions of microcrystalline cellulose and calcium carbonate, with a constant proportion of Povidone (10.7%). The lines are the calculated regressions using Eq. (2). This equation, in a similar version, has been used successfully to describe compactibility curves (Castillo-Rubio and Villafuerte-Robles, 1995; Castillo and Villafuerte, 1995; Villafuerte-Robles, 1996).

$$\ln\left(-\ln\left(1 - \frac{T}{T_{max}}\right)\right) = n \ln P_c + I \qquad (2)$$

In this equation T denotes the tablet tensile strength at a given compaction pressure, T_{max} the maximal tablet tensile strength obtained, P_c is the compaction pressure, n is the slope of the curve and I is its intercept.

Following this procedure, the compactibility of each mixture was defined through the regression parameters, i.e. the maximal tablet tensile strength, the slope and the intercept of the curve. These parameters allow the calculation of the tablet tensile strength at every compaction pressure with the support of all experimental points of each curve.

3.2. Compactibility of the MC/CC/PVP spray-dried excipient system

A further analysis of the compaction behavior of the mixtures allows the estimation of the effect of the excipient ratio on the tablet tensile strength. Fig. 2 shows the effect of the calcium carbonate content on the maximal tablet tensile strength attained by mixtures with microcrystalline cellulose. The points are experimental values from compactibility curves. Complete regression parameters of compactibility curves corresponding to this series are summarized in Table 1. The first part of the relationship depicted in Fig. 2 corresponds to tablets with a matrix with a continuous phase of a MC/PVP mixture with the inclusion of disperse particles of calcium carbonate. Increas-

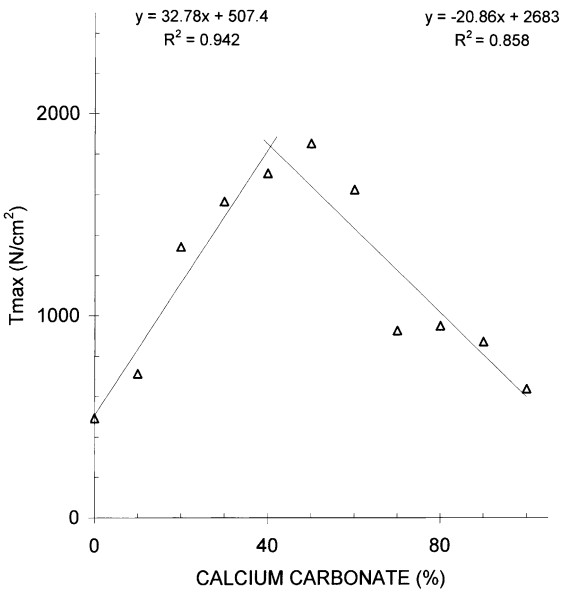

Fig. 2. Effect of the calcium carbonate proportion on the maximal tablet tensile strength (T_{max}) of spray-dried mixtures with microcrystalline cellulose (MC) and 10.7% Povidone (PVP).

Table 1
Regression parameters for compactibility curves of spray-dried mixtures of microcrystalline cellulose (MC), calcium carbonate (CC) and 10.7% Povidone (PVP)

$CaCO_3$ (%)	T_{max} (N/cm^2)[a]	Slope	Intercept	r^2
0	492	1.410	−7.673	0.79
10	712	1.591	−8.518	0.96
20	1341	2.155	−12.670	0.80
30	1566	2.266	−12.420	0.97
40	1704	2.491	−14.470	0.93
50	1851	2.256	−12.418	0.97
60	1624	2.352	−13.478	0.94
70	925	2.208	−12.697	0.93
80	948	2.047	−11.755	0.90
90	870	2.053	−11.704	0.94
100	636	1.842	−10.575	0.71

[a] T_{max}: maximal experimental tablet tensile strength obtained.

ing concentrations of calcium carbonate produce a change in the microcrystalline cellulose particles distribution. Microcrystalline cellulose particles turn out to be the disperse phase while a mixture of Povidone and calcium carbonate particles becomes the continuous phase. Tablets with an MC/PVP continuous phase increase their maximal tensile strength as the calcium carbonate content increases. After the phase inversion, at a calcium carbonate proportion of about 40%, the tensile strength of the tablets begins to decline.

In our previous report (Garzón and Villafuerte, 2002), the compactibility of physical mixtures of MC/PVP was maintained in the range of that of pure microcrystalline cellulose after addition up to 20–30% calcium carbonate, declining thereafter. After spray drying mixtures of MC/CC, dispersed in a Povidone solution, the Povidone distribution around the dispersed particles was the best possible. As a result of the coating of microcrystalline cellulose particles with Povidone the compactibility of microcrystalline cellulose decreased considerably. The tablet tensile strength decreased from 1265 to 492 N/cm^2.

It has been suggested that the effect of a dry binder will depend on the amount added and the particle size of the dry binder. If the amount added is large enough, the surface properties of the core material become identical with those of the pure binder material (Adolfsson et al., 1998). The compactibility of Povidone has been found to be about one third of that of microcrystalline cellulose, when the moisture content of the samples is <6% (Torres and Villafuerte, 1993). Actually, microcrystalline cellulose coating with Povidone in the course of spray drying deteriorates instead of improving the compactibility properties. Therefore, it can be inferred that coating with Povidone will deteriorate the compactiblity of every predominantly plastic pure excipient with higher compactibility than that of Povidone. It seems that only predominantly plastic excipients with lower compactibility than Povidone could be improved by the agglutinant, when its surface is completely coated by the agglutinant.

The inclusion of calcium carbonate in the spray-dried mixtures, most probably disrupted the Povidone coating of microcrystalline cellulose particles from the very beginning and during compaction, allowing a stronger interaction between calcium carbonate and microcrystalline cellulose. Moreover, the previous dispersion in water of calcium carbonate particles and the improved plasticity created by the agglutinant allowed a better spreading of calcium carbonate particles around the microcrystalline cellulose particles, maximizing their interaction. As a result, the mixtures attained a maximal tablet tensile strength of 1851 N/cm^2 which is about 50% greater than that of pure microcrystalline cellulose (1265 N/cm^2). The same circumstances allowed the accommodation of greater quantities of calcium carbonate (40%) in the spray-dried mixtures showing the maximal tablet tensile strength, compared to physical mixtures showing a maximal tablet tensile strength at a calcium carbonate content of 20–30%. The compactibility of spray-dried MC/CC mixtures with 10.7% Povidone was equal to or greater than that of pure microcrystalline cellulose in a range from about 20 to 60% calcium carbonate.

By physical mixtures the maximum in compactibility experienced a shift to lower calcium carbonate proportions with lower compaction pressures. The spray-dried mixtures showed no-shift of the maximum in compactibility with decreasing compaction pressures because of the better and fixed Povidone and calcium carbonate particles distribution from the very beginning.

Further regression parameters of compactibility curves, i.e. the slope and the intercept (Table 1) show similar relationships with the calcium carbonate proportion in the spray-dried mixtures (Figs. 3 and 4). Calculated values of regression parameters allowed

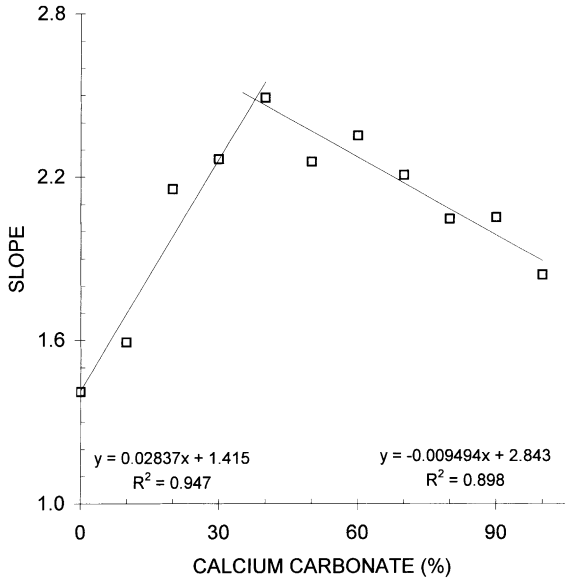

Fig. 3. Effect of the calcium carbonate proportion on the slope of compactibility curves calculated for spray-dried mixtures with microcrystalline cellulose (MC) and 10.7% Povidone (PVP).

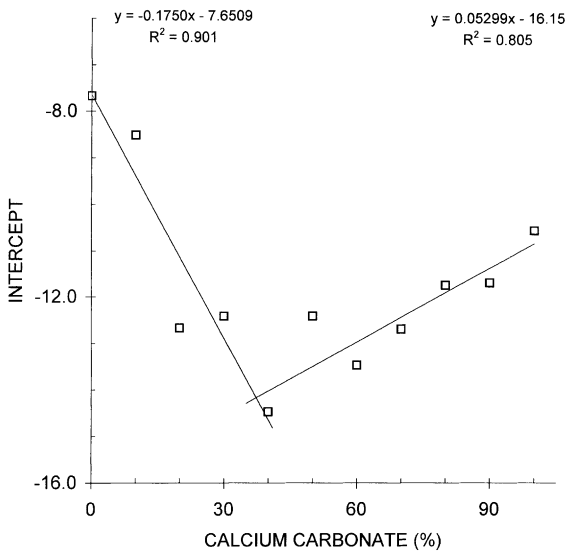

Fig. 4. Effect of the calcium carbonate proportion on the intercept of compactibility curves calculated for spray-dried mixtures with microcrystalline cellulose (MC) and 10.7% Povidone (PVP).

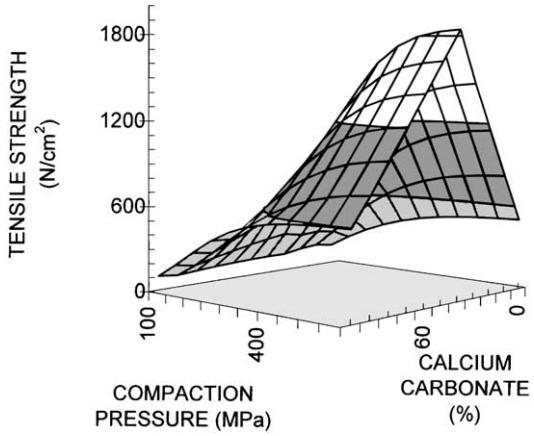

Fig. 5. Calculated response surface for the compactibility of spray-dried mixtures of microcrystalline cellulose (MC) and calcium carbonate (CC) with 10.7% Povidone (PVP), at different compaction pressures.

the calculation of a compactibility response surface (Fig. 5).

Fig. 5 shows a positive effect on compactibility of the MC/CC/PVP spray-dried mixtures. Tablets obtained at high compaction pressures (i.e. 600 MPa) attain a maximum in tablet tensile strength at about 40% calcium carbonate. The positive effect on compactibility decreases with decreasing compaction pressures. At a compaction pressure of 100 MPa, the calculated tablet tensile strength is described with a linear relationship that declines to some extent with increasing proportions of calcium carbonate, showing basically the compactibility of the Povidone outer coat, modified in a certain degree by the compaction behavior of calcium carbonate. The reduction of the positive effect is attributed to decreased abrasion or disruption of the Povidone coat on the microcrystalline cellulose particles by calcium carbonate, during compaction. This circumstance reduces the interaction between microcrystalline cellulose and calcium carbonate and therefore, reduces the tablet tensile strength.

3.2.1. Compactibility of the lubricated spray-dried MC/CC/PVP excipient system

Fig. 6 shows the compactibility of the spray-dried MC/CC/PVP system lubricated with 2% magnesium stearate (MS), calculated from data registered in Table 2. It is reported in literature that the compactibility of microcrystalline cellulose decreases drastically

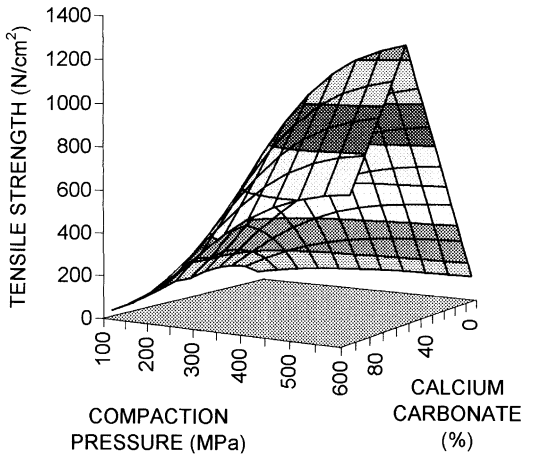

Fig. 6. Calculated response surface for the compactibility of spray-dried mixtures of microcrystalline cellulose (MC) and calcium carbonate (CC) with 10.7% Povidone (PVP) and 2% magnesium stearate at different compaction pressures.

after addition of this type of lubricants (Riepma et al., 1993; Castillo-Rubio and Villafuerte-Robles, 1995). A physical mixture of microcrystalline cellulose with 2% MS reduces the compactibility of microcrystalline cellulose to about one-tenth of its original value (Garzón and Villafuerte, 2002). Spray-dried microcrystalline cellulose, with 10.7% Povidone, lubricated with 2% MS behaves very similar; its compactibility ($T_{max} = 90\,N/cm^2$) is about one-tenth of that of pure microcrystalline cellulose ($T_{max} = 1265\,N/cm^2$) and about one-fifth of that of the spray-dried MC/PVP mixture without lubrication ($492\,N/cm^2$). This lubricant negative effect on the microcrystalline cellulose compactibility was lesser with the addition of increasing calcium carbonate proportions.

Table 2
Regression parameters for compactibility curves of spray-dried mixtures of microcrystalline cellulose (MC), calcium carbonate (CC), 10.7% Povidone (PVP) and 2% magnesium stearate

$CaCO_3$ (%)	T_{max} (N/cm^2)[a]	Slope	Intercept	r^2
0	90	1.154	−5.932	0.88
10	363	1.372	−7.437	0.85
20	313	1.911	−10.415	0.97
30	933	1.674	−9.283	0.88
40	887	2.070	−11.410	0.94
50	939	2.212	−12.839	0.80
60	1231	2.155	−12.321	0.91
70	1145	2.189	−12.406	0.93
80	1040	2.292	−13.544	0.84
90	839	2.530	−14.812	0.93
100	578	2.651	−15.357	0.96

[a] T_{max}: maximal experimental tablet tensile strength obtained.

The better distribution of calcium carbonate particles obtained through spray drying was further improved after compaction of the lubricated mixtures. The tablet tensile strength of the spray-dried MC/CC/PVP mixtures lubricated with 2% MS shows a maximum at about 60% calcium carbonate, at a compaction pressure of 350 MPa. This means the accommodation of a greater quantity of calcium carbonate particles, at the maximum of compactibility, than by physical mixtures (about 20%) and than by spray-dried mixtures without lubrication (about 40%).

Although the compactibility of spray-dried MC/CC/PVP mixtures maintain their maximum at the same calcium carbonate proportion with decreasing compaction pressures, the lubricated mixtures show a shift to lower calcium carbonate proportions as the compaction pressure decreases. This is attributed to the extragranular position of the lubricant. In this position, the lubricant improves its slipping effect, by wear out or abrasion, as the compaction pressure increases. This occurs in the same way observed before by physical mixtures (Garzón and Villafuerte, 2002).

A comparison of Fig. 5 with Fig. 6 shows that the under pressure slipping effect of the lubricant facilitates the calcium carbonate distribution in the tablet matrix, allowing a better contact with the microcrystalline cellulose particles. This circumstance permits the observation of a compactibility positive effect at higher calcium carbonate proportions by lubricated spray-dried mixtures, compared to the mixtures without lubrication. The better distribution of the particles of a second excipient, with the aid of a lubricant, was observed before in the microcrystalline cellulose/calcium phosphate excipient system, utilizing sodium laurylsulfate as a lubricant (Castillo and Villafuerte, 1995).

Regardless of an increased accommodation of calcium carbonate particles in the lubricated MC/CC/PVP spray-dried mixtures, the maximal tablet tensile strength is only two thirds of that without lubrication. Although the negative effect of the lubricant, the maximal tablet tensile strength of the lubricated

MC/CC/PVP spray-dried mixtures (1231 N/cm^2) is similar to that of pure microcrystalline cellulose (1265 N/cm^2). Compared to physical mixtures with the same composition, the compactibility of spray-dried mixtures show an increase of about 40% in the tablet tensile strength. This is attributed to the better distribution of Povidone and the calcium carbonate particles after spray drying. The observed positive effect on compactibility is maximized at high compaction pressures. By decreasing compaction pressures, this positive effect decreases considerably.

3.3. Compactibility of the wet granulated MC/CC/PVP excipient system

Fig. 7 shows the compactibility of the MC/CC/PVP mixtures obtained by wet massing. The compactibility response surface was calculated from data in Table 3. The pattern of the tablet tensile strength is similar to that of spray-dried mixtures (Fig. 5), changing only in the magnitude and position of the maximum in tensile strength.

The compactibility of wet massed mixtures, expressed as the maximum in tablet tensile strength, lies in between of that of physical mixtures and spray-dried mixtures (Fig. 8). This is attributed to a lesser capability to distribute Povidone and calcium carbonate particles by tumble mixing (physical mixture), compared to wet massing as well as lesser capability of wet massing compared to spray drying. The higher capability to distribute Povidone and calcium carbonate particles and the higher compactibility follow the order: spray drying > wet massing > tumble mixing of the powders.

Table 3
Regression parameters for compactibility curves of wet granulated mixtures of microcrystalline cellulose (MC), calcium carbonate (CC) and 10.7% Povidone (PVP)

$CaCO_3$ (%)	T_{max} (N/cm^2)[a]	Slope	Intercept	r^2
0	583	2.342	−13.437	0.96
10	869	2.456	−13.873	0.99
20	1562	2.799	−15.781	1.00
30	1259	2.913	−17.039	0.96
40	1328	3.256	−19.061	0.98
50	1211	2.662	−15.281	0.98
60	1145	2.424	−14.038	0.95
70	1086	2.313	−13.458	0.89
80	466	2.221	−13.284	0.83
90	646	2.402	−14.299	0.75
100	344	1.820	−10.110	0.93

[a] T_{max}: maximal experimental tablet tensile strength obtained.

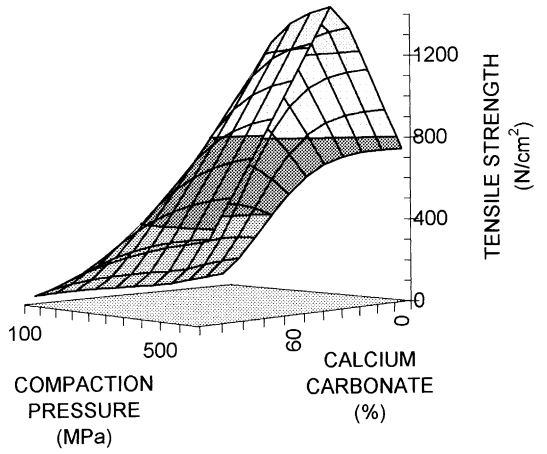

Fig. 7. Calculated response surface for the compactibility of wet granulated mixtures of microcrystalline cellulose (MC) and calcium carbonate (CC), with 10.7% Povidone (PVP), at different compaction pressures.

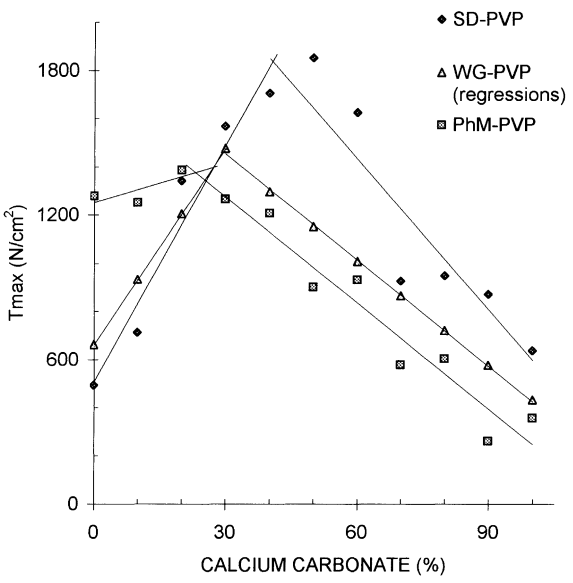

Fig. 8. Comparative effect of calcium carbonate on the maximal tensile strength of tablets made of spray-dried (SD), wet granulated (WG) and physical mixtures (PhM) of microcrystalline cellulose (MC) and calcium carbonate (CC) with 10.7% Povidone (PVP).

The lesser mixing efficiency is also observed as a lower capability to distribute greater quantities of calcium carbonate particles around microcrystalline cellulose, at the maximal tablet tensile strength. The calcium carbonate proportion corresponding to the maximum in compactibility, obtained by wet massing, lies in between of those of tumble mixing and spray drying (Fig. 8). The better the homogeneity of calcium carbonate and Povidone, the higher the calcium carbonate proportion that can be accommodated at the maximal tablet tensile strength and the higher the compactibility. Furthermore, Fig. 8 shows that by low calcium carbonate proportions, tablets with a continuous phase of MC/PVP, the tablet tensile strength of the mixtures declines as the efficiency of the mixing process increases. The compactibility follows the order: physical mixtures > wet massed mixtures > spray-dried mixtures. After inversion to a continuous phase of CC/PVP, subsequent to the maximum in tensile strength, the opposite occurs.

As mentioned above, the results observed in the first part of the curves in Fig. 8 are attributed to obstruction of the microcrystalline cellulose interparticle interaction through Povidone particles or a Povidone coating. The greater the obstruction achieved by Povidone the greater the reduction in compactibility of tablets with a MC/PVP continuous phase. In the second part of the curves of Fig. 8, with a continuous phase of CC/PVP, the opposite occurs. The greater the efficiency to distribute Povidone and accommodate calcium carbonate particles around microcrystalline cellulose particles, the greater the compactibility of tablets with a CC/PVP continuous phase.

3.3.1. Compactibility of the lubricated wet massed MC/CC/PVP excipient system

The compactibility of wet massed mixtures of MC/CC/PVP, lubricated with 2% MS, is summarized in Table 4 and depicted in Fig. 9. Lubricated wet massed mixtures show a higher capability to distribute calcium carbonate particles, at the maximal tablet tensile strength, than mixtures without lubrication (Tables 3 and 4). However, the compactibility expressed as the maximum in tablet tensile strength is lesser (Figs. 8 and 10).This behavior is similar to that of lubricated spray-dried mixtures (Tables 1 and 2).

The presence of the lubricant in the wet massed mixtures affects in a greater extent the compactibility of mixtures with a continuous phase of MC/PVP than those with a continuous phase of CC/PVP. While tablets obtained from the unlubricated wet massed MC/PVP mixture show higher tensile strength than those obtained from the CC/PVP mixture (Fig. 8), after lubrication the compactibility of the two mixtures is comparable (Fig. 10). A similar effect is observed by MC/CC/PVP spray-dried mixtures (Figs. 8 and 10).

Table 4
Regression parameters for compactibility curves of wet granulated mixtures of microcrystalline cellulose (MC), calcium carbonate (CC), 10.7% Povidone (PVP) and 2% magnesium stearate

$CaCO_3$ (%)	T_{max} (N/cm^2)[a]	Slope	Intercept	r^2
0	91	1.441	−7.930	0.88
10	369	1.837	−10.318	0.95
20	429	2.034	−11.593	0.83
30	675	2.785	−16.033	0.95
40	850	2.555	−14.917	0.92
50	819	2.293	−13.760	0.81
60	391	2.283	−13.677	0.83
70	316	1.941	−11.416	0.83
80	185	1.687	−9.347	0.91
90	121	1.480	−8.235	0.83
100	168	1.651	−9.378	0.87

[a] T_{max}: maximal experimental tablet tensile strength obtained.

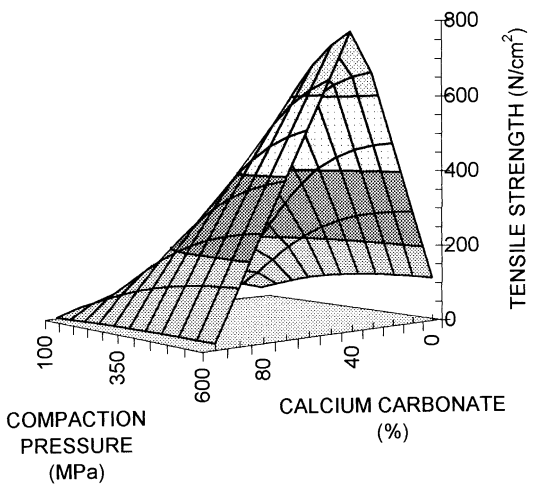

Fig. 9. Calculated response surface for the compactibility of wet granulated mixtures of microcrystalline cellulose (MC) and calcium carbonate (CC) with 10.7% Povidone (PVP) and 2% magnesium stearate, at different compaction pressures.

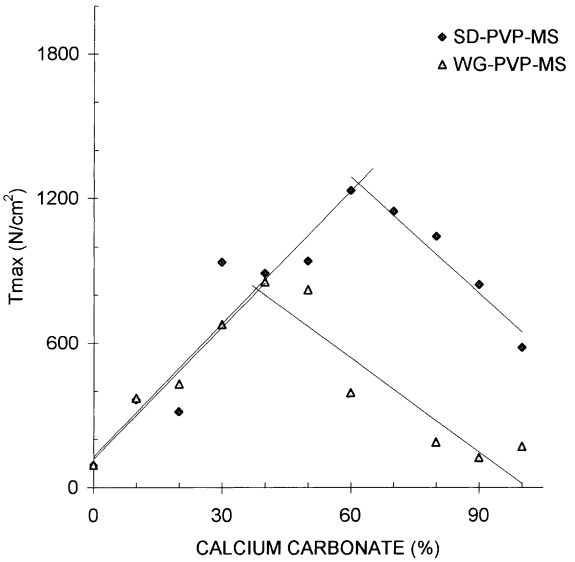

Fig. 10. Effect of calcium carbonate on the maximal tensile strength of tablets made of spray-dried (SD) and wet granulated (WG) mixtures of microcrystalline cellulose (MC) and calcium carbonate (CC) with 10.7% Povidone (PVP) and 2% magnesium stearate.

4. Conclusion

The presence of an agglutinant and a lubricant in agglomerated MC/CC mixtures show an important positive effect on their tablet tensile strength. The tensile strength of the tablets is higher than that of the pure agglomerated microcrystalline cellulose or calcium carbonate. This positive effect becomes smaller and finally disappears with decreasing compaction pressures. The magnitude of the positive effect depends on the mixing process efficiency to distribute the agglutinant and the calcium carbonate particles around microcrystalline cellulose particles. The higher the mixing efficiency the higher the compactibility of the mixtures, following the order: spray-dried > wet massing > tumble mixing of dry powders. Tablets with a MC/PVP continuous phase show greater compactibility with the less efficient mixing method while those with a CC/PVP continuous phase attain higher tablet tensile strengths with the more efficient mixing method. The compactibility of MC/CC/PVP spray-dried mixtures was equal to or greater than that of pure microcrystalline cellulose in a range from about 20 to 60% calcium carbonate.

After lubrication of spray-dried mixtures with 2% MS, as an extreme case, decreased the compactibility; only at the maximum the tablet tensile strength attains a similar value as that of pure microcrystalline cellulose. By smaller proportions of the lubricant, the loss in compactibility is expected to be lesser.

As suggested by Adolfsson (Adolfsson et al., 1998), the coating of microcrystalline cellulose particles with a binder (PVP) cancels the microcrystalline cellulose compaction properties, remaining those of the pure binder. Microcrystalline cellulose keeps its Povidone coating during compaction, deteriorating its compactibility. However, not plastically deforming excipients like calcium carbonate are capable to disrupt the Povidone coating, improving its compactibility.

The presence of the binder and the lubricant as well as high compaction pressures allow the accommodation of higher calcium carbonate proportions, at the maximal tablet tensile strength, reducing the cost of the excipient system.

References

Adolfsson, A., Caramella, C., Nyström, C., 1998. The effect of milling and addition of dry binder on the interparticulate bonding mechanisms in sodium chloride tablets. Int. J. Pharm. 160, 187–195.

Armstrong, N.A., Abourida, N.M.A.H., Gough, A.M., 1982. Introduction of plastic behavior into a particulate mass by addition of a granulating agent. Pharm. Tech. October, 66–72.

Bandelin, F.J., 1989. Compressed tablets by wet granulation. In: Lieberman, H.A., Lachman, L., Schwartz, J.B. (Eds.), Pharmaceutical Dosage Forms: Tablets, vol. 1. Marcel Dekker, New York, pp. 131–193.

Castillo, S., Villafuerte, L., 1995. Compactibility of ternary mixtures of pharmaceutical powders. Pharm. Acta Helv. 70, 329–337.

Castillo-Rubio, S., Villafuerte-Robles, L., 1995. Compactibility of binary mixtures of pharmaceutical powders. Eur. J. Pharm. Biopharm. 41, 309–314.

Doelker, E., 1993. Comparative compaction properties of various microcrystalline cellulose types and generic products. Drug Dev. Ind. Pharm. 19, 2399–2471.

Fell, T.T., Newton, J.M., 1970. Determination of the tensile strength of tablets by the diametral-compression test. J. Pharm. Sci. 59, 688–691.

Garzón, M.L., Villafuerte, L., 2002. Compactibility of mixtures of calcium carbonate and microcrystalline cellulose. Int. J. Pharm. 2312, 33–41.

Garr, J.S.M., Rubinstein, M.H., 1991. The effect of rate of force application on the properties of microcrystalline cellulose and dibasic calcium phosphate mixtures. Int. J. Pharm. 73, 75–80.

Mehra, K.D., West, K.P., Wiggins, J.D., 1988. Coprocessed microcrystalline cellulose and calcium carbonate composition and its preparation. United States Patent No. 4,744,987.

Riepma, K.A., Vromans, H., Lerk, C.F., 1993. A coherent matrix model for the consolidation and compaction of an excipient with magnesium stearate. Int. J. Pharm. 97, 195–203.

Shah, A.C., Mlodozeniec, A.R., 1977. Mechanism of surface lubrication: influence of duration of lubricant-excipient mixing on processing characteristics of powders and properties of compressed tablets. J. Pharm. Sci. 66, 1377–1382.

Torres, J.J., Villafuerte, L., 1993. Efecto de la humedad sobre las características de compactación de polvos farmacéuticos puros. Efecto de la humedad sobre la dureza de las tabletas. Rev. Mex. C. Farm. 23, 8–16.

Villafuerte-Robles, L., 1996. Compactibility of the microcrystalline cellulose type 102-calcium phosphate dihydrate system. J. Pharm. Belg. 51, 19–22.

Wikberg, M., Alderborn, G., 1993. Compression characteristics of granulated materials. VII. The effect of intragranular binder distribution on the compactibility of some lactose granulations. Pharm. Res. 10, 88–94.