ELSEVIER

International Journal of Pharmaceutics 231 (2002) 33–41

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

Compactibility of mixtures of calcium carbonate and microcrystalline cellulose

M. de Lourdes Garzón [a], Leopoldo Villafuerte [b,*]

[a] *Departamento de Sistemas Biológicos, Universidad Autónoma Metropolitana-Xochimilco, Calzada del Hueso 1100, Col. Villa Quietud C.P. 04960, Mexico*

[b] *Departamento de Farmacia, Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional, Carpio y Plan de Ayala s/n C.P. 11340, Mexico*

Received 4 January 2001; received in revised form 9 May 2001; accepted 14 August 2001

Abstract

A patented coprocessed mixture of microcrystalline cellulose (MC) and calcium carbonate (CC) is claimed to perform, as a pharmaceutical excipient, equal or better than pure MC. To investigate it, the tensile strength (T) of tablets made of mixtures of MC type 102, CC, magnesium stearate (MS) and polyvinylpyrrolidone (PVP) and formed under a compaction pressure (P_c) ranging up to 618 MPa has been determined. The compactibility of the mixtures was defined through regression parameters obtained with $\ln(-\ln(1-T/T_{max})) = \text{slope} \times \ln P_c + \text{intercept}$. MC/CC mixtures, $P_c = 618$ MPa, show a small decrease in tablet tensile strength with CC proportions up to about 20%, falling considerably thereafter. Lower compaction pressures, $P_c \leq 332$ MPa, show a continuous decrease in tensile strength as the CC proportion increases. A MC drastic fall in tablet tensile strength due to 2%-MS, $P_c = 487$ MPa, was recovered to 35% of its original value admixing about 25% CC. This maximal value of recovery showed a shift to lower proportions of CC, up to 10%, as compaction pressure decreased. This was attributed to lower CC-particles fragmentation or agglomerates spreading at lower compaction pressures. Mixtures with increased plasticity (MC/CC/PVP and MC/CC/PVP/MS) showed an increased compactibility, which was more evident at higher compaction pressures and higher CC proportions, presumably due to higher deformation and erosion of PVP particles. Inclusion of about 40% CC in a MC/PVP/MS mixture showed 60% recovery of the original MC tablet tensile strength. Lower MS proportions are expected to allow a higher recovery.

Keywords: Calcium carbonate; Microcrystalline cellulose; Mixtures compactibility; Tablet tensile strength; Lubricants; Dry agglutinants

1. Introduction

The mechanics of tableting process or compression is very complex. It can be claimed that the physics of compression is not yet understood properly (Kuentz and Leuenberger, 2000). Mix-

* Corresponding author. Fax: +52-5396-3503.
E-mail address: ivillaro@bios.encb.ipn.mx (L. Villafuerte).

0378-5173/02/$ - see front matter
PII: S0378-5173(01)00857-2

tures of powders could be considered as systems made of two phases. The component in a greater proportion and/or with the smaller particle size forms a continuous phase while other components in smaller quantities form a discontinuous or dispersed phase. The presence of a dispersed phase changes the viscoelastic behavior of the continuous phase due to localization of tensions. The compression properties of powder mixtures, although dominated by the continuous phase, are modified by the dispersed phase (Villafuerte-Robles, 1996; Castillo-Rubio and Villafuerte-Robles, 1995a,b; Wang et al., 1995).

It is claimed that most studies of compactibility of powder mixtures show complex non-linear relationships of a mechanical property like tensile strength against the mass fraction of the components (Kuentz and Leuenberger, 2000). However, many studies show clearly three different possibilities for this relationship, a positive or negative effect or a linear relationship (Panaggio et al., 1984). Cases with an increase of tensile strength or a positive effect like those between microcrystalline cellulose (MC) and fragmenting excipients like calcium phosphate (Garr and Rubinstein, 1991; Castillo-Rubio and Villafuerte-Robles, 1995a,b) and spray dried lactose (Villafuerte, 1998) and between phenacetin and dicalcium phosphate (Newton et al., 1977). Cases with a negative effect or a decreased compactibility like those between cellulose and a more elastic component as carragenan (Picker, 1999) and lactose monohydrate mixed with the more elastic corn starch (Villafuerte Robles, 1990). In some other cases, a linear relationship has been observed as by mixtures between MC type 101 and Pharmatose 100M (Pacheco et al., 1997) or by mixtures of MC 102 and calcium phosphate dihydrate (Villafuerte-Robles, 1996). These results were attributed to a certain degree of compatibility or incompatibility between particles of different materials to increase or decrease the interparticle surface of contact after compression.

The addition of a dry binder to compaction mixtures has the purpose to give them cohesion and certain elastic–plastic properties that increase the permanent deformation and decrease the elastic recovery (Armstrong et al., 1982). Addition of a dry binder to coarse particles will affect the tensile strength of compacts in different ways, depending on factors such as the size and amount of the dry binder particles added. An agglutinant normally increases and changes the nature of the surface area available for interparticulate bonds. 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).

Many authors have studied the deteriorating effect of magnesium stearate (MS) on the mechanical resistance of tablets (Jarozs and Parrott, 1984; Leinonen et al., 1992; Johansson and Nicklasson, 1995; Riepma et al., 1993; Castillo-Rubio and Villafuerte-Robles, 1995a). It has been shown that materials that compact predominantly by fragmentation are little sensitive to addition of lubricants while materials that behave plastically show an important loss in their capacity to form links.

Riepma et al. (1993) reported that MS sensitivity of brittle materials is not related directly to the degree of fragmentation during compression. They suggest that a coherent matrix of MS is highly sustained during consolidation and compaction of the particulate system. Failure of the tablets would happen, therefore, principally along the interfaces of the original excipient crystals. Fragmentation of the excipient particles would contribute, therefore, little to the crushing strength of the tablets. Independent of this mechanism, it is recognized that addition of brittle materials decreases the lubricant sensitivity of MC (Castillo-Rubio and Villafuerte-Robles, 1995b).

Mehra et al. (1988) patented the production of a direct compaction excipient, coprocessed 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 MC.

The patented coprocessed product obtained by spray drying is supposed to be superior to physical blends that do not provide the desired performance characteristics. In spite of this, physical

mixtures of MC with calcium phosphate have been observed to show greater compactibility than MC alone (Castillo-Rubio and Villafuerte-Robles, 1995a,b; Garr and Rubinstein, 1991). Under these circumstances the aim of this work was to study the compactibility properties of physical blends of MC and CC, alone and added of an agglutinant and/or a lubricant to evaluate a possible improvement in MC performance as a pharmaceutical excipient.

2. Materials and methods

2.1. Material

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

2.2. Methods

2.2.1. Mixtures

Corresponding quantities of MC and CC for each mixture were mixed in a cylindrical tumbling mixer at 35 rpm and for 30 min. The proportion of both components varied in a range from 0 to 100%, with a variation unit of 10%. The batch size was fixed in 100 g. For mixtures with PVP, corresponding proportions of MC and CC to make a total quantity of 100 g were mixed with 12 g of the agglutinant during 30 min. The agglutinant final concentration was calculated as 10.7%. Lubricated versions of the above-mentioned mixtures were obtained adding 1 g MS to 49 g of the corresponding mixtures. The mixing time was fixed as well in 30 min to work with a well-lubricated system (Shah and Mlodozeniec, 1977; Doelker, 1993). Although this high concentration of MS could be considered to be excessive, it was included as an extreme case to show more clearly the possibilities of CC to improve, protect or recover the compactibility of MC.

2.2.2. Tablets

Seven hundred milligrams of the corresponding mixtures were compressed at six different compaction pressures in a hydraulic press (Enerpac), 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 denotes applied pressure; D is tablet diameter; t is tablet thickness.

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 mixtures of different proportions of MC type 102 and CC, added of 10.7% PVP. 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, 1995a,b; Villafuerte-Robles, 1996).

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

In this equation, T denotes the tablet tensile strength at a given compaction pressure; $T_{\max}$ is the maximal tablet tensile strength obtained; P_c is the compaction pressure; n stands for the slope of the curve and I 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 excipient system

A further analysis of the mixtures compaction behavior allows the estimation of the effect of the excipient ratio on the tablet tensile strength. Fig. 2 shows the effect of the CC content on the tablet tensile strength of mixtures with MC, at different compaction pressures. The points are calculated values from compactibility curves (Eq. (2)). The first part of the curves corresponds to tablets with a continuous phase of MC with the inclusion of a disperse phase of CC. Increasing concentrations of CC produce a change in the MC particles distribution. MC particles turn out to be the disperse phase while CC particles become the continuous phase. Tablets with an MC continuous phase decrease their tensile strength as the CC content increases, as can be seen in the calculated response surface shown in Fig. 3. Tablets with a CC continuous phase practically maintain the same tensile strength (Fig. 2).

Although it is known that MC forms stronger compacts than CC, it is the aim of this part of the study to know if the positive effect on compactibility observed with other similar mixtures (Garr and Rubinstein, 1991; Castillo-Rubio and Villafuerte-Robles, 1995a,b) occurs also with MC/CC mixtures.

At high compaction pressures, i.e. 618 MPa, MC/CC mixtures show a small decrease in tablet

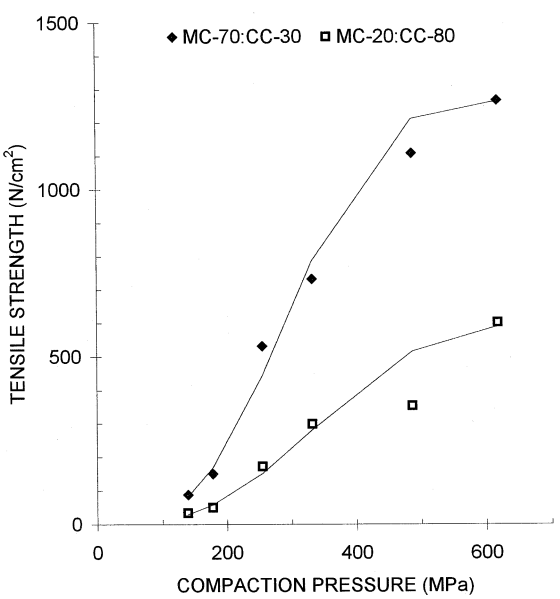

Fig. 1. Compactibility curves of mixtures of MC and CC, added of 10.7% PVP. Experimental points and regressions with $\ln(-\ln(1-T/T_{\max})) = \text{slope} \times \ln P_c + \text{intercept}$.

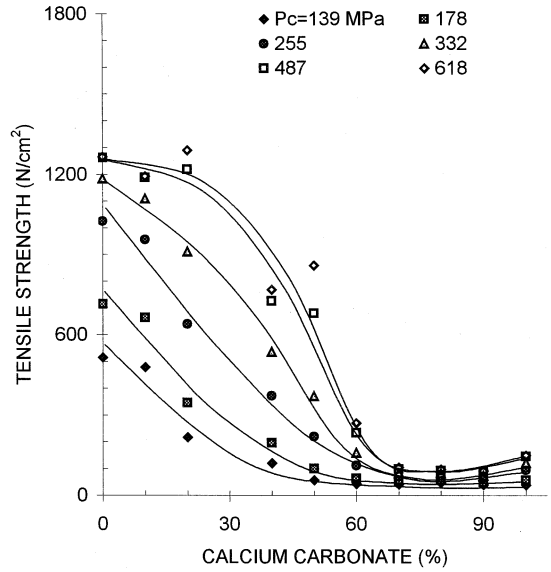

Fig. 2. Effect of compact pressure and the proportion of CC on the tablet tensile strength of mixtures with MC.

tensile strength with increasing CC proportions up to about 20%, falling considerably thereafter (Fig. 2). Decreasing compaction pressures show a more pronounced fall in mixtures compactibility as the CC proportion increases. As can be seen in Fig. 3, most of the curves show a negative effect on compactibility. This means lower compactibility than that expected from a linear relationship.

The tablet tensile strength or compactibility of powder mixtures is determined by the cohesive forces between particles of the continuous phase, by adhesive forces between particles of both phases and by the effective surface of contact between particles. The surface of contact between the particles is determined by deformation, fragmentation and the elastic behavior of the particles under pressure, the compaction pressure producing a heterogeneous stress transmission through a great number of particles in the powder bed. The surface of contact is not only determined by the applied compression force but also by the bond-destructive effects of elastic recovery of the particles after compression (Villafuerte, 1998; Wang et al., 1995).

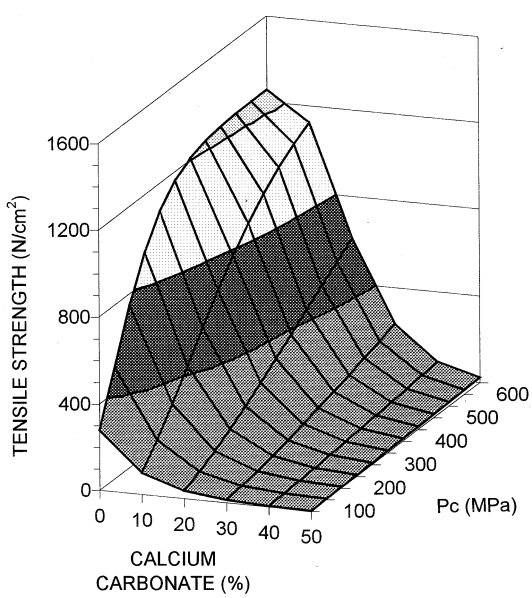

Fig. 3. Calculated response surface for the effect of compaction pressure and proportion of CC on the tablet tensile strength of mixtures with MC.

The different compaction behavior of the mixtures, at different compaction pressures, may be attributed to a higher fragmentation or better spreading of CC agglomerates with increasing compaction pressures. This circumstance facilitates a better distribution of CC particles around those of MC as compaction pressure increases. The better distribution of CC particles allows the formation of additional stronger MC–CC bonds and, at the same time, decreases the CC–CC weaker bonds. Decreasing compaction pressures reduce fragmentation or spreading of CC agglomerates, and with this, increase the weak spots created by CC–CC bonds. The curves corresponding to lower compaction pressures resemble the behavior of curves obtained at higher compaction pressures but with higher CC proportions.

It is considered that the total coverage of MC with CC particles would produce tablets of maximal tensile strength due to formation of CC–MC bonds, which are stronger or with greater surface of contact. Exceeding the total coverage or with a bad distribution of CC particles, the excess of CC, between MC particles, would produce a greater proportion of the weaker CC–CC bonds. MC particles slip better under higher compaction pressures, dragging and redistributing CC particles. The highest tablet tensile strength could be expected with a CC proportion just enough to cover MC particles with a monoparticulate coat.

The compaction profile of MC/CC mixtures, at high compaction pressures (487–618 MPa, Fig. 2), shows a similar but less pronounced positive effect on compactibility as that obtained from mixtures of MC and calcium phosphate (Garr and Rubinstein, 1991; Castillo-Rubio and Villafuerte-Robles, 1995a,b). In that study, a concentration of about 20% calcium phosphate produced a maximum in compactibility. Actually, the reduced positive effect in compactibility could be attributed to a much lower compactibility of CC, about 10% of that of MC (Fig. 2), compared with the calcium phosphate compactibility, about 40% of that of MC (Garr and Rubinstein, 1991; Castillo-Rubio and Villafuerte-Robles, 1995a).

In the case of mixtures with calcium phosphate, the maximal tablet hardness was attributed to a maximal surface of contact between the compo-

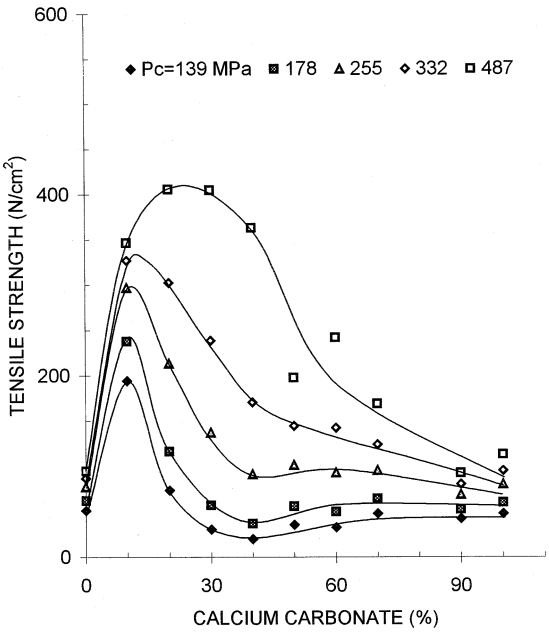

Fig. 4. Effect of compact pressure and the proportion of CC on the tablet tensile strength of mixtures with MC, lubricated with 2% MS.

nents. The differences in compaction properties of calcium phosphate and CC might be due to the water of crystallization present in calcium phosphate. Jaffe and Fosse showed that substances with water of crystallization, which formed good tablets, could not be tableted when this water was removed, considering that the water of crystallization acted as 'built in' binding agent (Haines-Nutt, 1976).

Another factor contributing to the lower positive effect in compactibility showed by the MC/CC mixtures, compared with MC/calcium phosphate mixtures, could be the particle size. Calcium phosphate has been used with a particle size of 45–125 μm (Garr and Rubinstein, 1991) while CC shows actually a nominal average particle size of 1.2 ± 0.3 μm.

3.3. Compactibility of the MC/CC/MS excipient system

Fig. 4 shows the compactibility of the MC/CC system lubricated with 2% MS. As registered in literature the compactibility of MC decreases drastically after addition of this type of lubricants (Riepma et al., 1993; Castillo-Rubio and Villafuerte-Robles, 1995a). However, the lubricant negative effect on the MC compactibility decreased with the addition of increasing proportions of CC in the mixtures. The tablet tensile strength of the MC/CC lubricated mixtures shows a maximum at about 25% CC, at a compaction pressure of 487 MPa (Fig. 4). However, there is a shift of the curves showing compactibility profiles with a maximum at decreasing CC proportions, up to 10% CC, as compaction pressure decreases. The shift of the maximal tablet tensile strength, to lower CC proportions, can be better seen in Fig. 5. The calculated response surface depicted in Fig. 5 shows the progressive movement of the maximum in tablet tensile strength from about 10% CC, at a compaction pressure of 100 MPa, to about 35% CC at 650 MPa.

A comparison of Fig. 2 with Fig. 4 shows that the lubricant facilitates the CC distribution in the tablet matrix, allowing a better contact with the MC particles. This circumstance permits the observation of a clear positive effect at higher CC proportions. Although high compaction pressures are still necessary to achieve a better distribution

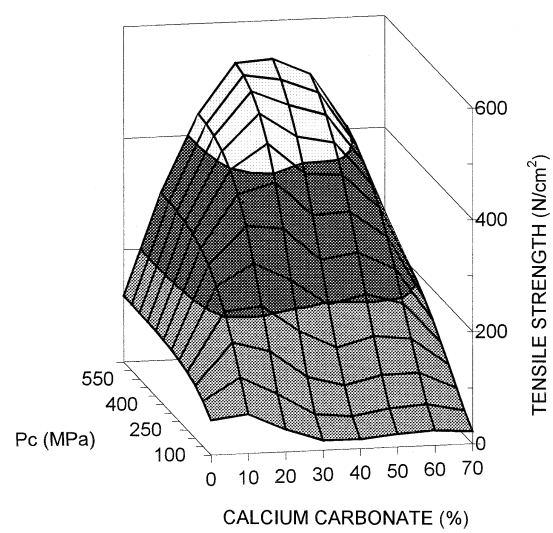

Fig. 5. Calculated response surface for the effect of compaction pressure and proportion of CC on the tablet tensile strength of mixtures with MC lubricated with 2% MS.

of CC particles in the tablet matrix, it is still possible to see this positive effect at lower compaction pressures. The better distribution of the particles of a second excipient, with the aid of a lubricant, was observed before in the MC/calcium phosphate excipient system, when lubricated with sodium laurylsulfate (Castillo-Rubio and Villafuerte-Robles, 1995b).

The strong decrease of tablet tensile strength showed by plastic deforming materials such as MC, after lubrication, has been attributed to the obstruction of the CM–CM interparticle bonds. Particularly by lubrication with fatty acids derivatives like MS, which produce easy rupturing CM–MS interfaces (Riepma et al., 1993). Although an increase in densification is favored by the lubricant, its contribution to tablet tensile strength of plastic deforming materials is unimportant, because of the loss of contact between the CM particles. On the other hand, the effect of lubricants derived from fatty acids on the tablet tensile strength of hard and fragmenting materials is quite different. The addition of this type of lubricants facilitates the densification of the particles under compression. This increased densification is associated to a decrease of void space in the tablets and to an increased surface of contact between the particles being compressed, and as a consequence, to a greater tensile strength of the tablets. In a second part, the interparticle bonding of hard and fragmenting materials can be obstructed by the lubricant, decreasing the tablet tensile strength. However, fragmenting materials overcome partially this circumstance through creation of new clean surfaces or through penetration of the lubricant film. The obstruction of interparticle bonds would take place only with higher lubricant concentrations. The sum of these effects on the compactibility of hard and fragmenting materials, at low lubricant proportions, is small or not noticeable.

The results observed in Figs. 4 and 5 could be attributed to the stronger MC–CC bonds or to a higher surface of contact between these particles. A contribution of both circumstances seems to be more probable. The effect of the lubricant seems to be facilitation of the CC particles distribution in the tablet matrix, an increased densification of

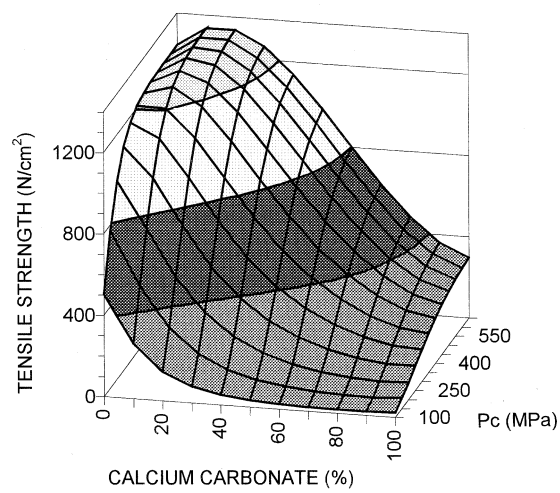

Fig. 6. Calculated response surface for the effect of compaction pressure and proportion of CC on the tablet tensile strength of mixtures with MC and 10.7% PVP.

powders and a certain obstruction of the effective MC–CC bonds. The sum of these contrasting contributions to tablet tensile strength produces a maximum where the positive and negative effects are in equilibrium. Higher compaction pressures allow a better distribution and an easier penetration of the lubricant film by CC particles, increasing the tablet tensile strength. After the limit of a maximal surface of interaction between MC and CC, higher concentrations of CC decrease the tablet tensile strength because of the lower tensile strength of the increasing CC–CC bonds.

In spite of an increased compactibility of the lubricated MC by admixture of different proportions of CC, the maximal tablet tensile strength of these mixtures is only about 35% of that of MC without lubrication.

3.4. Compactibility of the MC/CC/PVP excipient system

The calculated response surface in Fig. 6 shows the compactibility of the MC/CC/PVP mixtures. In this figure, the increased plasticity of the MC/CC mixtures shows better the positive effect on compactibility of a greater proportion of the MC–CC bonds. This increased plasticity obtained after addition of the dry agglutinant. Compared

with MC/CC mixtures (Fig. 2), the presence of PVP allows a better CC distribution or the possibility of accommodation of a greater quantity of CC particles before a decrease in tensile strength can be observed. Although every addition of PVP could be expected to increase the tensile strength of every tablet, this occurs only in presence of CC. PVP do not contribute to increase the plasticity and compactibility of the plastic deforming MC.

The MC/PVP excipient system increases its compactibility with increasing CC concentrations up to about 15%, at compaction pressures of 350 MPa and higher (Fig. 6). At lower compaction pressures, the interparticle movement under compaction is not enough to allow the total deployment of the binding properties of PVP. At lower compaction pressures, there is no positive effect on compactibility but a negative one. A positive or negative effect on compactibility of this excipient system is dependent on compaction pressure. This suggests that PVP requires a wear out or erosion of its particles to improve its distribution, improving at the same time its agglutinant effectiveness and the cohesiveness of the tablet. The presence of PVP, as well as that of MS, promotes a better distribution of the CC particles in the tablet matrix but without the negative effect on compactibility showed by MS. The increase in compactibility produced by PVP is more evident at higher CC proportions. The PVP effectiveness as agglutinant is high in presence of hard materials like CC and practically inexistent with soft-plastic materials like MC.

3.5. Compactibility of the MC/CC/PVP/MS excipient system

The compactibility of the MC/CC/PVP/MS mixtures can be seen in Fig. 7. As well as by above-mentioned mixtures, the addition of PVP and MS makes possible the accommodation of greater quantities of CC. The maximum value of tensile strength is obtained at CC proportions around 40%. Although the addition of PVP increases the tensile strength of the MC/CC/MS mixtures, the tensile strength of these tablets is always smaller than that of pure MC tablets. Addition of PVP and MS to MC/CC mixtures produces a sum of the above-mentioned individual effects.

Concluding, MC/CC mixtures admixed of a dry agglutinant and/or a lubricant produce a positive effect of increased tablet tensile strength from that expected from a linear relationship, which becomes more important as compaction pressure increases. This occurs in a similar way as that of MC mixtures with fragmenting materials like calcium phosphate and spray dried lactose. The magnitude of this effect seems to be dependent on the surface of contact between MC and CC. This surface of contact depends, at the same time, on a localized fragmentation of CC particles or spreading of their agglomerates, covering the obtained fragments only a small area around the position of the original CC particle or agglomerate. Thus, the MC–CC surface of contact increases only in a certain degree with increasing compaction pressures.

The addition of a lubricant allows the spreading or better distribution of the hardly gliding CC particles increasing the MC–CC surface of contact, and in this way, increasing also the compactibility of the lubricated MC.

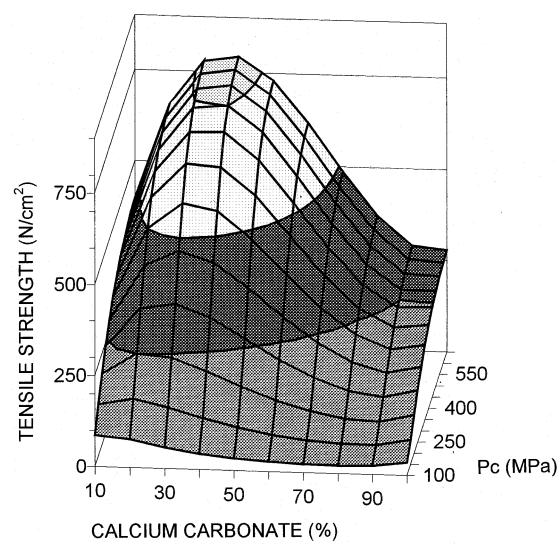

Fig. 7. Calculated response surface for the effect of compaction pressure and proportion of CC on the tablet tensile strength of mixtures with MC with 10.7% PVP and 2% MS.

Addition of CC, PVP and MS to MC produce well-lubricated mixtures with compactibilities up to 60% of the original MC compactibility. Lower concentrations of the lubricant are expected to increase the compactibility without a big loss of lubricity.

Although the effect of addition of specific drugs on the mixtures compactibility depends on the particular drug compaction properties, it could be expected that addition of drugs with poor compactibility reduce the compactibility of the mixtures, probably to a certain still pharmaceutically acceptable degree.

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. Induction of plastic behavior into a particulate mass by addition of a granulating agent. Pharm. Tech., October 66–72.

Castillo-Rubio, S., Villafuerte-Robles, L., 1995a. Compactibility of binary mixtures of pharmaceutical powders. Eur. J. Pharm. Biopharm. 41 (5), 309–314.

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

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

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.

Haines-Nutt, R.F., 1976. The compression properties of magnesium and calcium carbonates, Communications. J. Pharm. Pharmacol. 28, 468–470.

Jarozs, P.J., Parrott, E.L., 1984. Effect of lubricants on tensile strengths of tablets. Drug Dev. Ind. Pharm 10 (2), 259–273.

Johansson, M.E., Nicklasson, M., 1995. Investigation of the film formation of magnesium stearate by applying a flow through dissolution technique. J. Pharm. Pharmacol. 38, 51–54.

Kuentz, M., Leuenberger, H., 2000. A new theoretical approach to tablet strength of a binary mixture consisting of a well and a poorly compactable substance. Eur. J. Pharm. Biopharm. 49, 151–159.

Leinonen, U.I., Jalonen, H.U., Vihervaara, P.A., Laina, E.S.U., 1992. Physical lubrication properties of magnesiun stearate. J. Pharm. Sci. 81 (12), 1194–1198.

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.

Newton, J.M., Cook, D.T., Hollebon, C.E., 1977. The strength of tablets of mixed components. J. Pharm. Pharmacol. 29, 247–249.

Pacheco, J.F., Barajas, I., Villafuerte, L., 1997. Propiedades tecnológicas del sistema de excipientes Pharmatose 100M-Helmcel 100. Rev. Mex. C. Farm. 28 (3), 13–21.

Panaggio, A., Rhodes, C.T., Schwartz, J.B., 1984. Properties of mixtures of two tablet matrices. Pharm. Acta Helv. 59 (2), 37–39.

Picker, K.M., 1999. The use of carragenan in mixture with microcrystalline cellulose and its functionality for making tablets. Eur. J. Pharm. Biopharm. 48, 27–36.

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 (19), 1377–1382.

Villafuerte Robles, L., 1990. Compactabilidad de tabletas de una mezcla de dos componentes: almidón de maíz-lactosa. Rev. Mex. C. Farm. 21 (3), 20–27.

Villafuerte-Robles, L., 1996. Compactibility of the microcrystalline cellulose type 102–calcium phosphate dihydrate system. J. Pharm. Belg. 51 (1), 19–22.

Villafuerte, L., 1998. Optimización de las propiedades de tableteo de mezclas de lactosa secada por aspersión y celulosa. An. Esc. Nac. Cienc. Biol. Méx. 44, 57–69.

Wang, C., Zhang, G., Shah, N.H., Infeld, M.H., Malick, A.W., McGinity, J.W., 1995. Compaction properties of spheronized binary granular mixtures. Drug Dev. Ind. Pharm. 21, 753–779.