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The Role of Several L-HPCs in Preventing Tablet Capping During Direct Compression of Metronidazole

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Several low-hydroxypropyl cellulose (L-HPC) derivatives (LH-11, 21, 22, 31, and 32) differing in granulometric particle size or in hydroxypropyl content were considered in the present study. The L-HPC grades were characterized as pure powders, in order to determine both compression and densification behavior, in presence or in absence of magnesium stearate as lubricant, and then, were physically mixed in different proportions with metronidazole, which was also previously characterized as pure powder. The tabletability and compressibility of these binary mixtures were then evaluated, in presence or in absence magnesium stearate as lubricant at two different compression speeds (20 and 70 mm/sec). It was observed that both binary mixture compression behavior and capping tendency were influenced by compression speed and by the presence of lubricant.

Differences in anti-capping efficiency between the L-HPCs may be related to their hydroxypropyl content. This parameter influences the interaction between the metronidazole and the polymer particles, and consequently the ability of the binary system to undergo densification under compression.

Keywords metronidazole; L-HPC; lubricant; compression speed; tablet capping; tabletability; compressibility

INTRODUCTION

"Capping" is a general term for the anomalous axial tablet rupture that can generally occur during tablet ejection or even during storage. Several studies were conducted in past decades to seek a better understanding of the phenomenon of tablet capping (Shotton & Obiorah, 1961; Train, 1956). Capping can be considered as a side effect of the compaction process and has been related to several factors.

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Among them, an important one is the build-up of elastic energy during compression, and as a consequence radial/axial elastic recovery of variable importance, when axial pressure is removed (Obiorah & Shotton, 1976). When compression pressure increases, the plastic materials permanently deform, creating a wide contact surface. On the contrary, the elastic materials restore elastic energy, separating the contact particle-particle surfaces, or even breaking established bonds. Thus, the production of intact tablets depends either on the formation of strong bonds at the particle-particle contact area (Velasco, Ruiz, Monedero, & Castellanos, 1997) or on the establishment of a great number of contacts, which can limit capping risk (Casahoursat, Lemagnen, & Larrouture, 1988). On the other side, it was suggested that some elasticity of the compact inside the die can advantageously reduce die wall pressure, hence avoiding lamination of the compact by lateral stress before or during ejection (Sugimori, Mori, & Kawashima, 1990). Because capping could depend on the increase of die wall pressure during compression, many studies have measured the pressure variation in the die during the compression process (Doelker & Shotton, 1977; Hiestand, Wells, Peot, & Ochs, 1977; Leigh, Carless, & Burt, 1967; Long, 1960; Shotton & Obiorah, 1975).

Still another factor in capping and the compaction process is lubricant addition, which can have two opposite effects. It can reduce both the friction and the work necessary for tablet expansion by increasing the plastic component of the material (De Blaey & Polderman, 1970). Also, the lubricant can interrupt interparticle interactions by coating the particles, hence reducing tablet tensile strength. The negative effect of lubricants is less significant with brittle particles (Bolhuis & Hölzer, 1996).

Some other parameters can worsen capping tendency, such as friction in the die during ejection, high compression pressure and speed, powder moisture content, the type and the amount of binder and particle size. Thus, a low compression

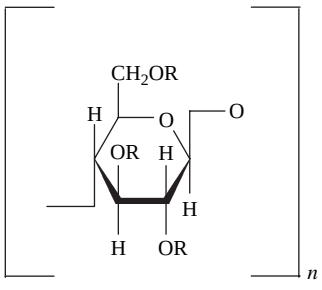
speeds and/or a precompression phase can reduce tablet capping.

Several methods have been developed to investigate and predict a powder's capping tendency, but unfortunately, most of them are the object of considerable variety of opinion (Podczeck & Newton, 2003, 2005; Uhumwangho & Okor, 2004, 2005). In addition, they call for special devices generally unavailable in industrial plant during product development (Sugimori et al., 1990).

During product development in industry, capping is a strong factor in excluding the possibility in using direct tableting processes for a large number of high dosed active drugs. In this particular case, the common excipients would have to be used in excess in order to mask the detrimental properties of the drug, and thus would yield "big tablets". The solution preferred by industry is to convert tablet production from a direct compression process to a wet granulation process, but this demands greater time, and expense, and multiplies the number of parameters to be controlled. The possibility of identifying an excipient able to counteract the capping tendency of the drug would thus prove very interesting for the pharmaceutical industry.

The aim of this study was to characterize the compression behavior of several grades of Low-Hydroxypropyl Cellulose (L-HPC) and to examine their ability to prevent the capping tendency of metronidazole (Martindale, 1996) a high dose antimicrobial drug, orally administered in the unit dose of 250 mg. Because of its very poor compression properties, tablets cannot be obtained by direct compression and a wet granulation process must therefore be used.

Different grades of LHPCs were used (Figure 1). These polymers differ from the most common used hydroxypropyl celluloses (HPCs), in their lower substitution degree. Unlike HPCs, LHPC's are practically insoluble, but swell in water and thus can be used as tablet disintegrants (Di Martino, Martelli, Wherlé, 2005; Kawashima, Takeuchi, Hino, Niwa, Lin, Sekigawa, & Ohia, 1993), as well as proposed as diluents for both conventional tablets (Kanzaki, Shimoyama, Tsukamot, Okan, Suzuki, Inoue, Tanak, Koizumi, & Watanabe, 1998; Kawashima et al., 1993) and pellets (Kleinebudde, 1994). Curiously, although



R = H; R = $CH_2CH(OH)CH_3$

FIGURE 1. Molecular structure of L-HPC.

L-HPCs are not new products, their compression behavior as pure substance has never been fully described (Alvarez-Lorenzo, Gómez-Amoza, Martínez-Pacheco, Souto, & Concheiro, 2000).

MATERIALS AND METHODS

Materials

Metronidazole USP (henceforth indicated as "MTZ") was kindly supplied by Pfizer (Ascoli, Italy). The low-hydroxypropyl celluloses (L-HCP) were kindly provided by Shin-Etsu Chemical Co. (Tokyo, Japan). The LH-11, LH-21, LH-22, LH-31, and LH-32 grades were used. Several characteristics are reported in Table 1, according the Shin-Etsu Technical Bulletin (2005). They are roughly divided into three classes, according to particle size, and in turn divided into two groups according to their hydroxypropyl content.

Powder Characterization

Granulometric distribution was determined by sieving 100 g of powder through screens of the following sizes: 850, 600, 425, 300, 180, 106, 53 μm.

The loss on drying (LOD%) was determined in triplicate by heating approximately 20 g of powders at 120°C until constant weight was reached in a thermal balance (Scaltec, SMO 01, Goettingen, Germany).

Carr's index (Carr, 1965a, 1965b) was calculated from powder volumes of 100 g of powder at the initial stage and at constant volume according to the Compressibility Index (USP 27 <616>) (Tecnogalenica, Italy). Results are the mean of three measurements.

Compression Study

The compression study was performed on a mini rotary press (Ronchi, Piccola 10, Italy) equipped with a computerized control system for detecting and analyzing force signals (pressing force and ejection force) and with 10 flat 11.28 mm-diameter punches. Samples were manually introduced in only one die. Die and punches were pre-lubricated with a 1% (w/v) magnesium stearate (MGS; A.C.E.F., Italy) suspension in ethanol 96% (v/v) (PRS, Panreac, Spain).

The L-HPCs were first compressed as pure materials in presence or absence of MGS at two different compression speeds, 20 and 70 mm/sec, expressed as vertical upper punch speed at the entry into the die. Corresponding dwell times, calculated as described by Hoblitzell and Rhodes (1990) were 196 and 56 ms, respectively. The compression pressures were progressively increased and the force at the upper punch was recorded. The powder mass was always constant in order to obtain 500 mg tablets. Results for each compression force were the mean of five measurements.

The MTZ was then mixed with several L-HPCs in different percentages (10, 30, 50, 70, and 90%), first by gently mixing

TABLE 1
Technological Properties of the Different L-HPC Grades, According to the Shin-Etsu Technical Bulletin (2005)

	Grade	Particle Size	Hydroxypropyl Content (%)	Application
LH	11	On 180 μm: ≤0.5%, passes through 150 μm: ≥98%	10.0–12.9	Direct compression
	21	On 106 μm: ≤1.0%, passes	10.0–12.9	Direct compression
	22	through 75 μm: ≥ 90%	7.0–9.9	Wet granulation Pellettization
	31	On 75 μm: ≤5.0%, passes	10.0–12.9	Wet granulation
	32	through 45 μm: ≥ 50%	7.0–9.9	Pellettization

them in a mortar with the progressive dilution method and then by mixing powders in a V-shaped mixer (Divisione Artha, Laboratori Mag, Garbagnate Milanese, Italy) for 10 minutes. When MGS was used, it was added to the V-shaped mixer during the last stage for a mixing time of 10 min. The optimal MGS mixing conditions were established by several preliminary trials. In presence of MGS the mixing in the mortar caused the sudden loss in tablet tensile strength, making it difficult to evaluate the excipient's effect on the mixture characteristics. Mixing in the V-shaped mixer was less vigorous and made it possible to evaluate the differences due to the mixing times used. The mixing time of 10 min provided satisfactory results and easy handling of results. The optimal mixing conditions were established by assessing the tablet crushing strength: mixing times lower than 10 min yielded tablets of highly variable crushing strength, while mixing times higher than 10 min gave tablets of very low crushing strength.

The physical mixes were manually added into the die. The compression force was adjusted in order to maintain a constant compression pressure of 120 ± 0.2 MPa. Two different compression speeds, 20 and 70 mm/sec, were used.

Thickness and diameter of intact ejected tablets were measured with a manual micrometer (Mitutoyo, Japan) immediately after ejection. Some tablets were then stored in closed containers and the increase in tablet thickness was periodically checked during the next 2 weeks. Tablet porosity was calculated from tablet dimensions, mass, and apparent particle density. This parameter was determined by using a helium pycnometer (Accupyc 1330, Micromeritics, England) with a cell of 10 cm^3. Results are the mean of 10 measurements. Crushing strength was measured immediately after compression with a tablet strength tester (Erweka, type TBH30, Germany). Tensile strength Q (Fell & Newton, 1970) was calculated according to Eq. 1:

$$Q = \frac{2H}{\pi dt} \quad (1)$$

where H is the tablet crushing strength, d the diameter and t the thickness of the tablet.

Compression results were expressed in the form of three different but complementary relationships as previously described (Joiris, Martino, Berneron, Guyot-Hermann, & Guyot, 1998). Compressibility is the ability of a material to undergo a reduction in volume as a result of an applied pressure. Compactibility is the capacity of a material to be transformed into tablets of specified strength as a result of volume reduction. Both relationships used together afford a basic understanding of product compression behavior. The former express particle closeness, and the latter interparticle bonding. Finally, tabletability is the capacity of different materials to be transformed into tablets of specified strength under the effect of compression pressure. In industrial practice, tabletability is the most important compression relationship.

Densification Study

For the densification study, powders were compressed with an instrumented Frogerais OA single punch tablet machine (Frogerais, Vitry, France) equipped with 11.3 mm flat-faced punches, by introducing samples manually into the prelubricated die. Powder mass was varied to obtain 3 mm thick compacts at each compression pressure. For each mass five cycles were performed, corresponding to maximal punch pressure of about 120 MPa. For a single compression cycle, the compression pressures on the upper and lower punches and the displacement of the upper punch were measured and recorded at a frequency of 4000 Hz. Correction of displacement transducer data for machine looseness and punch deformation were carried out according to Juslin and Paronen (1980). The compression speed, which is fixed in this machine, corresponds to a vertical upper punch speed of 70 mm/s when the punch enter the die.

Pressure transmission through powder bed in the die was estimated by comparing the maximal compression pressures on the upper and lower punches. The transmission coefficient corresponds to the ratio of lower and upper punch values.

The displacement profile used to generate Heckel data is sinusoidal, with a total compression-decompression time of approximately 150 msec.

The densification behavior of powders was studied using Heckel equation (1961)

$$\ln \frac{1}{1-D} = KP + A \tag{2}$$

where D is the relative density of the compressed powder bed at applied pressure P and K is the slope of the straight linear portion of the Heckel plot, while the reciprocal of K is the mean yield pressure (P_Y). The constant A is the sum of two densification terms:

$$A = \ln\left(\frac{1}{1-D_0'}\right) + B'. \tag{3}$$

According to Doelker (1994), D_0' corresponds to the relative density of the powder at the moment when the last recorded applied pressure is still nil, and B' is the densification due to particle fragmentation. Constants A and B' can be expressed as relative densities using:

$$D_A = 1 - e^{-A} \tag{4}$$

$$D_B' = D_A - D_0'. \tag{5}$$

Heckel profiles were established from single compression cycles of tablets compressed at 120 MPa. Parameters P_Y, D_A, D_0', D_B' were calculated using a precompression pressure value of 2.0 MPa. There are several methods for selecting a linear region of the Heckel function in order to determine Heckel constants. Using that of Paronen and Ilkka (1996), we selected a range of measurement points at which the linear regression coefficient was as high as possible. This corresponds for all the samples to the 50 to 90 MPa range, with coefficient values superior to 0.998. Each value is a mean of five measurements.

Elastic recovery (ER) at different stage of the compression cycle was calculated according to Armstrong and Haines-Nutt (1974):

$$ER = \left(\frac{t - t_{\min}}{t_{\min}}\right) \tag{6}$$

where t_{min} is the minimal thickness of the powder bed in the die and t is the tablet thickness at a given time.

For Immediate Elastic Recovery (IER), t is the tablet thickness at the end of compression, when upper punch has just left tablet, before its ejection.

For Total Elastic Recovery (TER), t is the tablet thickness after 15 days storage in closed containers.

RESULTS AND DISCUSSION

Powder Properties

L-HPC particle size distribution, determined by the sieving method, is reported in Figure 2. With all the L-HPCs, about 95% of their particles are smaller than 100 μm; the largest fraction measures less than 53 μm. Distribution results clearly show that the dimensions of LH-11 particles are greater than those of other samples. Unfortunately, it was impossible to calculate mean particle size from distribution data. Similarly, SEM micrographs could not be properly analyzed due to the chaotic aspect of the powdered L-HPC. So, finally, the *Handbook of Pharmaceutical Excipients* (Harwood, 2000) had to suffice for obtaining an estimation of the particle size of samples: 50 μm for LH-11, 40 μm for LH-21 and LH-22, and 25 μm for LH-31 and LH-32. These values are not used quantitatively in the present work. Also, the hydroxypropyl content of LHPC samples was not determined. The authors refer to Handbook values, i.e., 11% for LH-11, LH-21, and LH-31, and 8% for LH-22 and LH-32, considering them as "high" or "low" hydroxypropyl content.

MTZ particle size distribution could not be determined by the sieving procedure, because particles agglomerated and rolled up on the sieve. The mean particle size (35.7 ± 1.2 μm) was thus determined by SEM analysis, by counting the Ferret's diameter of 500 particles. Due to the very small particle size of L-HPCs, the flow as indicated by the Carr's Index is quite poor (Table 2). L-HPC water content, determined by the loss on drying, was rather similar, ranging approximately between 5 and 7% w/w. It was somewhat less for MTZ.

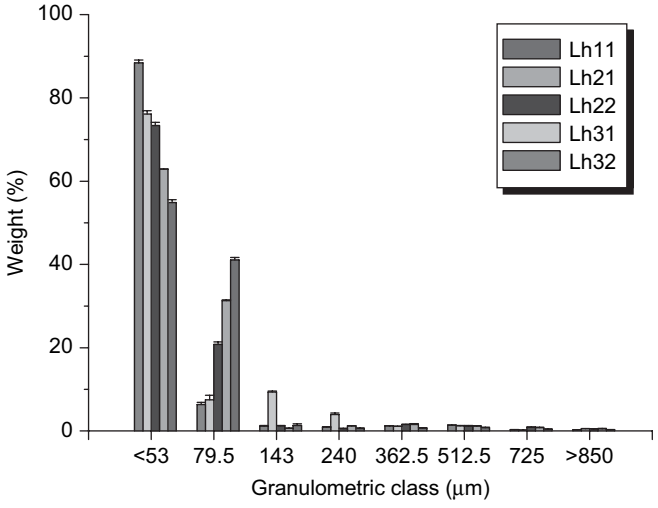


FIGURE 2. Granulometric distribution of the L-HPC samples, determined by the sieving method.

TABLE 2
Technological Characteristics of Pure Powders

	Apparent Powder Density (g/cm^3)	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Carr Index	Loss on Drying (%)
Lh-11	$1.4687 \pm 7.6E10^{-4}$	$0.344 \pm 9.19E10^{-3}$	$0.507 \pm 1.20E10^{-2}$	32.16	6.27 ± 0.48
Lh-21	$1.4671 \pm 3.8E10^{-4}$	$0.402 \pm 2.83E10^{-3}$	$0.589 \pm 7.07E10^{-4}$	31.67	4.99 ± 0.64
Lh-22	$1.4795 \pm 6.5E10^{-4}$	$0.366 \pm 4.24E10^{-3}$	$0.560 \pm 4.95E10^{-3}$	34.57	5.16 ± 0.92
Lh-31	$1.4661 \pm 1.3E10^{-3}$	$0.308 \pm 1.13E10^{-2}$	$0.426 \pm 4.24E10^{-3}$	27.69	7.35 ± 0.07
Lh-32	$1.5001 \pm 4.7E10^{-4}$	$0.236 \pm 3.54E10^{-3}$	$0.383 \pm 5.66E10^{-3}$	31.41	6.68 ± 0.01
MTZ	$1.4501 \pm 1.0E10^{-3}$	$0.239 \pm 8.49E10^{-3}$	$0.332 \pm 7.78E10^{-3}$	27.89	3.43 ± 0.01

Compression Properties of Pure Compounds

All L-HPC powders were compressed alone to determine their compression properties, in the presence or absence of MGS as lubricant. The study was carried out at two different compression speeds (20 and 70 mm/sec). Because no significant differences were observed, only the results obtained at the high compression speed are indicated and evaluated here. The lack of differences shows that the compression behavior of these materials, when pure, is uninfluenced by moderate variations in compression speed.

L-HPC compression behavior without lubricant is depicted in Figure 3. Numerical values for tablets compressed at 120

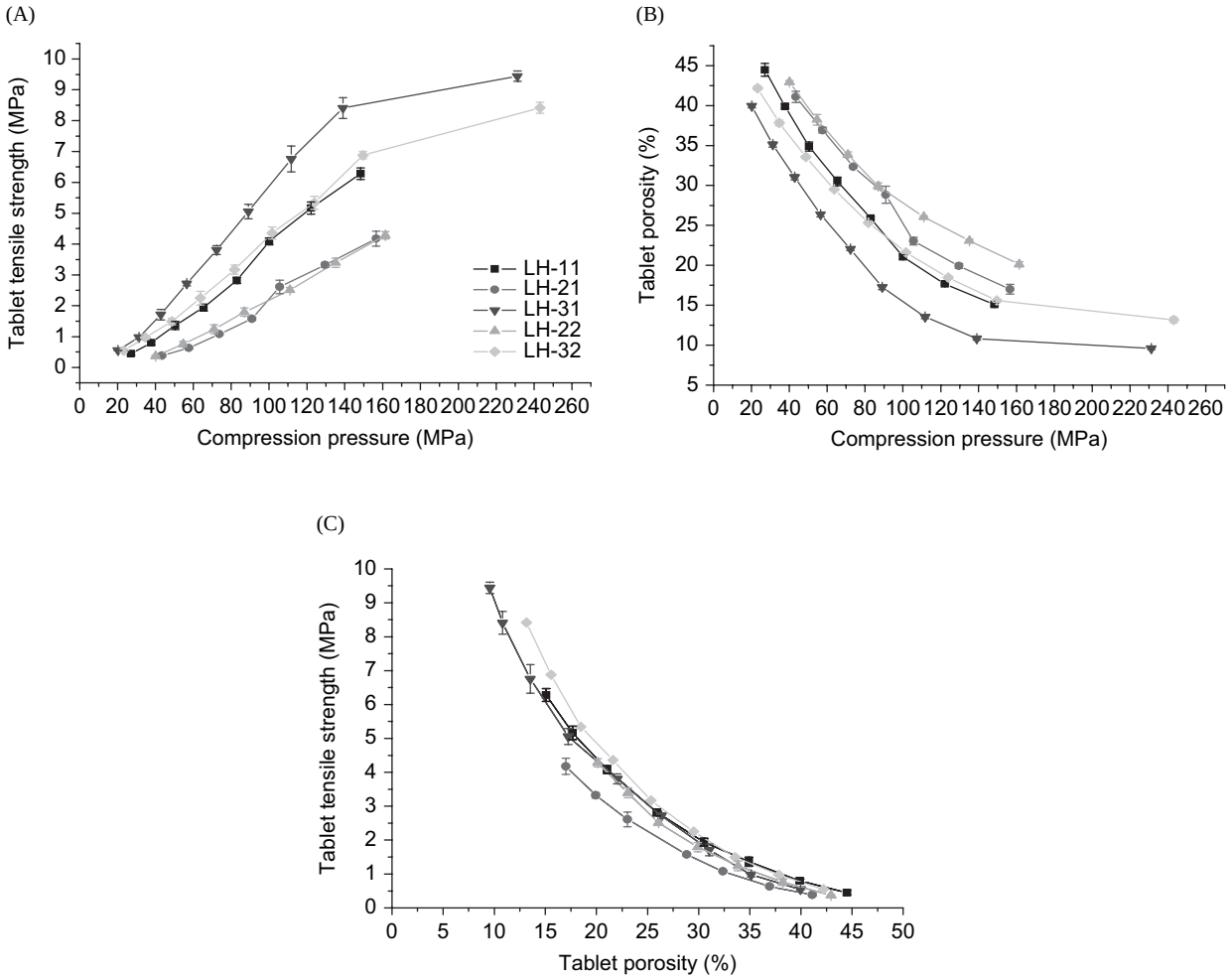


FIGURE 3. Compression behavior of L-HPCs either without lubricant. Values are the mean of five experiments. (A) Tabletability. (B) Compressibility. (C) Compactibility.

MPa (for comparison of tabletability and compressibility) or at a final porosity of 25% (for comparison of compactibility) are shown in Table 3.

Tabletability (the relationship between compression pressure and tablet tensile strength) of various L-HPC grades varied considerably: the lowest value/highest value quotient (Table 3) was 0.4. LH-31 showed the best tabletability (Figure 3a): the tablet tensile strength proportionally increased with increase in compression pressure. A slope deflection can be observed for compression values above 140 MPa. LH-32 displayed similar behaviour, the though it exhibited lower tabletability. LH-11 exhibited the same tabletability as LH-32. It was impossible to recover tablets of LH-11 over 150 MPa, because excessive friction force in the powder bed or at the die wall, caused the machine to jam during compression. Far lower tabletability was exhibited in both LH-21 and LH-22, the tabletability profiles of which practically overlap.

From values of Table 3, L-HPCs can be classified as binders with "high" (LH-31), "moderate" (LH-32 and LH-11), or "low" (L-HPC-21 and LH-22) tensile strength. Comparing results for LH-11 (50 μm), LH-21 (40 μm), and LH-31 (25 μm), it can be concluded that particle size is not the most important factor in understanding L-HPC tabletability.

TABLE 3
Compression Behavior of Pure L-HPCs

	Without Lubricant	With Lubricant	
Tabletability[a]	Q_u (MPa)	Q_l (MPa)	*LSR*
LH-11	5.17 ± 0.19	4.30 ± 0.21	0.17
LH-21	3.04 ± 0.15	2.82 ± 0.06	0.07
LH-22	2.84 ± 0.11	2.55 ± 0.06	0.10
LH-31	7.07 ± 0.38	7.06 ± 0.27	0.00
LH-32	4.89 ± 0.21	4.73 ± 0.12	0.03
Compressibility[a]	Porosity (%)	Porosity (%)	
LH-11	17.48 ± 0.22	16.60 ± 0.24	
LH-21	22.08 ± 0.35	19.37 ± 0.26	
LH-22	25.28 ± 0.22	24.91 ± 0.34	
LH-31	12.84 ± 0.22	12.09 ± 0.31	
LH-32	19.10 ± 0.16	20.01 ± 0.30	
Compactibility[b]	Q_u (MPa)	Q_l (MPa)	*LSR*
LH-11	2.80 ± 0.11	2.12 ± 0.09	0.24
LH-21	2.07 ± 0.17	1.88 ± 0.09	0.09
LH-22	2.81 ± 0.17	2.46 ± 0.15	0.12
LH-31	2.63 ± 0.15	2.55 ± 0.12	0.03
LH-32	3.12 ± 0.14	3.05 ± 0.14	0.02

[a]tablets compressed at 120 MPa.
[b]tablets of 25% porosity.

Kawashima et al. (1993) found that tabletability of L-HPC increased with decreased particle size; however, their paper described the behaviour of LHPC-paracetamol mixtures, relating the geometrical layout of particles of both components in the tablets. Comparing LH-21 to LH-22, and LH-31 to LH-32, it appears that a decrease in hydroxypropyl content leads to a decrease in tabletability. However, a difference between LH-31 and LH-32 is noticeable, while LH-21 and LH-22 are relatively similar.

Finally, it appears that L-HPC tabletability cannot explained solely in terms of particle size and degree of substitution. It should kept in mind that tabletability is a complicated property involving both interparticle bonding and the effect of particle closeness. These two phenomena can be examined separately by analyzing compressibility and then compactibility.

It seems that variation in compressibility (the decrease in tablet porosity as a function of the increase in compression pressure), provides the primary explanation for the variability in L-HPC tabletability (Figure 3b). A very good inverse correlation is found by Pearson's test between tensile strength and porosity (data of unlubricated tablets compressed at 120 MPa, displayed in Table 3; $r = -0.97$, $p < 0.005$). Also, from the data of Table 3, it appears that there is no clear relationship between compressibility and particle size, and that a decrease in hydroxypropyl content leads to a decrease in compressibility.

Compactibility (the relationship between tablet tensile strength and porosity) appears relatively similar for all the samples (Figure 3c), an observation that is corroborated by values in Table 3. Interestingly, compactibility makes it possible to compare the strength of interparticle bonds for each sample, since the distance between particles is similar in all tablets. So, it appears that the type of bond is probably similar for all the samples, with little advantage in the number and/or the strength of bonds for L-HPC of low degree of substitution (LH-22 and 32).

L-HPC compression behavior was then evaluated in presence of magnesium stearate as lubricant. From the data in Table 3, it can be observed that lubrication exerts little effect on tabletability. In order to quantify lubricant effect, the Lubricant Sensitivity Ratio *(LSR)* was used (Bolhuis & Hölzer, 1996):

$$LSR = \frac{Q_u - Q_l}{Q_u} \tag{7}$$

where Q_u and Q_l are the tensile strength of tablets prepared without and with lubricant, respectively. An *LSR* of 0 indicates complete insensitivity to lubricant, while a value of 1 corresponds to complete disappearance of tablet strength due to lubrication. From the data reported in Table 3, it can be seen that only for LH-11 (the sample with the greatest particle size) does *LSR* differ significantly from 0, while it differs a little less for intermediate particle size grades (LH-21 and 22), and is

close to 0 for small particle size grades (LH-31 and 32). *LSR* calculated from compactibility data are somewhat higher. So, compactibility is a little more affected by lubrication than tabletability, because the discrete increase in compressibility of lubricated samples enhances tabletability. Previous studies have reported lubricant insensitivity in small sized powders of plastic deforming materials was already reported, for microcrystalline cellulose (Di Martino et al., 2005) and rice starch (Bolhuis & Hölzer, 1996). Interestingly, these authors attributed this insensitivity to the fact that, when the flow properties of the host particle are extremely poor, the delamination of the lubricant particles and the consequent formation of a lubricant film during mixing will be a very slow process. To test their assertion, we measured the effect of long mixing times on MGS and L-HPC samples in the V-shaped mixer. An *LSR* value of 1 was reached after 1 hr of mixing for LH-11, and 2 hr for LH-21 and 22, while an *LRS* value of 0.9 was attained after 8 hr of mixing for LH-31 and 32. This behavior correlates well with the particle size of the samples. These results enable us to conclude that the dominant bond type for all L-HPC samples is intermolecular force, as is the case for the majority of powders, since it is completely abolished by the lubricant film (Nyström & Karehill, 1996).

Densification Behavior

MTZ cannot be characterized by direct compression, because tablets cap at any compression pressure. Consequently, the only way to characterize its densification mechanism is by using the "in die" method of Heckel's analysis. This method makes it possible to obtain data during a single compression cycle without the need to recover tablets. For this reason, only immediate elastic recovery (IER) was considered for MTZ. Results are given in Table 4.

The value corresponding to the densification of MTZ by particle slippage (D_0' = 0.574) was relatively low, corresponding to an inadequate volume reduction by particle slippage and rearrangement before compression. This is compatible with small particle size and poor flow as indicated by the Carr's Index. The value corresponding to the densification by particle brittle fracture (D_B' = 0.111) was rather high, indicating that particle fragmentation occurs at the beginning of the compression phase. The mean yield pressure (104.5 MPa) is indicative of MTZ's moderate densification attitude, by either plastic or elastic deformation when pressure is further increased. Consequently, minimal porosity at the end of compression phase remained relatively high (10%). The IER value (2.74%) was relatively low, even if it must be supposed that after the complete removal of the upper punch from the compact surface, the tablets are completely free to expand axially and to cap. Moreover, MTZ shows inadequate compactibility, limiting the ability of particles to interact and form strong bonds. The poor deformability and inadequate compactibility can explain the material's strong capping tendency.

Heckel cycles obtained for the five L-HPC grades displayed the typical shape of visco-plastic compression behavior, with a straight line for compression phase, and a curved return line indicating elastic recovery during decompression phase. Numerical values of Heckel parameters are given in Table 4.

D_0' were relatively low and more or less identical for all samples, corresponding to poor flow properties related to low particle size. Also, D_B' values were comparable and small, indicating that no fragmentation occurred at early compression stage. P_y values make it possible to discriminate the five L-HPC grades, with extreme values of 75 and 107 MPa for LH-31 and LH-22, respectively. P_y values correlated well with minimal porosity during compression (r = 0.997, P < 0.0003, porosity data not shown) and to a lower extend with final tablet porosity (r = 0.869, P = 0.0056). There is no clear relationship of P_y with particle size, but, comparing LH-21 to LH-22 and LH-31 to LH-32, it appears that a decrease in hydroxypropyl content leads to an increase in P_y. A similar trend was reported for HPMC polymers (Malamataris, Karidas, & Goidas, 1994).

In order to characterize decompression phase, *IER* values were calculated, making it possible to discriminate the five L-HPC grades, with extreme values of 3.8 and 6.69% for LH-31 and LH-22, respectively. It can be pointed out that the least compressible grade (LH-22) was also characterized by the highest *IER*. On the contrary, the most compressible grade (LH-31) corresponded to the lowest *IER*. In other words,

TABLE 4
Heckel's Parameters of Pure Powders. The Values are the Mean of Five Experiments. The 95% Confidence Interval is Given

	P_Y (MPa)	D_0'	D_A	D_B'	Immediate Elastic Recovery (%) (*IER*)	Total Elastic Recovery (%) (*TER*)
LH-11	79.4 ± 0.2	0.404 ± 0.002	0.484 ± 0.001	0.080 ± 0.002	4.88 ± 0.19	15.01 ± 0.19
LH-21	90.6 ± 0.2	0.433 ± 0.005	0.495 ± 0.001	0.061 ± 0.005	5.66 ± 0.14	17.43 ± 0.25
LH-22	107.0 ± 0.5	0.426 ± 0.002	0.499 ± 0.001	0.073 ± 0.002	6.69 ± 0.12	20.33 ± 0.21
LH-31	75.0 ± 0.4	0.463 ± 0.002	0.510 ± 0.002	0.046 ± 0.004	3.80 ± 0.16	11.05 ± 0.15
LH-32	99.1 ± 0.2	0.439 ± 0.002	0.505 ± 0.001	0.066 ± 0.002	4.60 ± 0.07	12.34 ± 0.21
MTZ	104.5 ± 2.5	0.574 ± 0.002	0.685 ± 0.001	0.111 ± 0.003	2.74 ± 0.12	–

differences in compressibility that are observed at the end of the compression phase continue to rise during decompression. As previously noted for *Py* values, particle size seems to have no effect on *IER* while a decrease in hydroxypropyl content leads to an increase in *IER*.

L-HPC tablets continue to expand significantly during ejection and the first day of storage, with tablet thickness remaining unmodified during the following two weeks. Final values of elastic recovery (*TER*) are displayed in Table 4. *IER* correlates well with *TER* ($r = 0.983$, $P < 0.003$).

Compression behavior of some L-HPCs (LH-11, LH-20, LH-21, LH-22, and LH-31) was characterized by Alvarez-Lorenzo et al. (2000). Given small yield pressures calculated by the Heckel analysis, they suggested that a plastic deformation mechanism is involved in L-HPC. In this work, P_y values were higher than those obtained by Alvarez-Lorenzo et al., and the *ER* were lower. However, it is well known that the various Heckel parameters are highly dependent on both material related factors and experimental conditions (Doelker, 1994).

For this reason, it seemed more useful to compare our results for Heckel's analysis of L-HPCs with previous data obtained for various grades of microcrystalline cellulose with similar operating conditions (Di Martino et al., 2005). Microcrystalline cellulose has been characterized (Mattsson and Nyström, 2001) as a binder with a high tensile strength and a moderate degree of deformability (i.e., relatively high apparent mean yield pressure and intermediate elastic recovery). This description can partially apply to L-HPC. Indeed, P_y values are similar for both substances and tablet tensile strength for some L-HPC grades (LH-11, LH-31, and LH-32) is high. However, in the present work, both *IER* and *TER* values were far higher than those previously found for microcrystalline cellulose. This is of note as some authors (Sugimori et al., 1990) assert that elastic recovery of the material in the die could reduce residual die wall pressure, hence avoiding capping and lamination of the compact. Consequently, the high *IER* measured for all L-HPC might contribute to their anti-capping properties.

Compression Behavior of Physical Mixes

Each grade of L-HPC was mixed in various amounts with MTZ, in absence or presence of lubricant, and compressed at 120 MPa at "low" or "high" compression speeds. Results of tabletability (charts on the left) and compressibility (charts on the right) are displayed in Figure 4.

The general shape of tabletability was similar, regardless of lubricant of speed. For LH-21 and LH-22, tablet tensile strength increased regularly with the L-HPC amount, giving a more or less linear profile. For LH-11, LH-31, and LH-32, tensile strength also increased progressively with L-HPC amount, but less than would be expected on a mathematical basis, giving a curved profile. Consequently, for the low L-HPC proportion, the tabletability was relatively similar for all L-HPC samples, regardless on how they behave when compressed alone. The advantage of the good compression properties of LH-11, LH-31, and LH-32 clearly appeared only when their proportion in the mixture was above 50%.

Another parameter that could be useful in discerning the efficiency of different grades of L-HPC is the minimal L-HPC amount sufficient to counteract the capping tendency of metronidazole and to obtain a tablet that survives decompression and ejection. Apparently, the best tableting conditions combine low compression speed and the presence of lubricant, because in a such situation tablets are obtained for all the L-HPCs with a minimal relative proportion of 10% of L-HPC. If lubricant is removed, LH-11, the grade with greatest particle size, is the only one to fail. At increased speeds, LH-11, LH-21, and LH-31, the grades with high hydroxypropyl content, all fail, while if lubricant is removed and speed increased at the same time, all grades fail. According to this criterion of minimal active amount, it seems that both low particle size and low hydroxypropyl content are preferable characteristics for L-HPC.

It can seem strange that the most efficient grades (LH-22 and LH-32) for capping prevention are not those that exhibit the best compression behavior when compressed alone. This can be partially explained by considering mixture compressibility. It can be observed in compressibility charts that porosity of L-HPC-MTZ tablets is more or less invariable, irrespective of mixture composition, L-HPC grade, presence of lubricant, and compression speed. This becomes more and more obvious when the MTZ amount is increased. Rough estimation of average mean porosity of binary tablets is more or less 20%, an intermediate porosity value, lower than those of pure LH-21 and LH-22 tablets, equal to that of LH-32 and higher than those of pure LH-11and LH-31 tablets (Table 3). During the study of compression behavior of pure L-HPC, it was found that important grade to grade differences in tabletability derive from compressibility differences, and that differences in compactibility play a minor role. In the case of binary MTZ-L-HPC tablets, differences in compressibility of pure L-HPC are completely leveled off. Consequently, differences in compactibility, even moderate, loom out of the fog and give some advantage to LH-22 and LH-32. It is probable that the higher bonding capacity of these "low-low-HPCs" extends to MTZ-L-HPC interparticle bonds.

CONCLUSION

The various L-HPCs exhibit differing compression behaviors, a fact that has repercussions on the compression properties of physical mixes, as do factors as lubricant addition and compression speed. Even though LH-31 shows the best compression and densification behavior when compressed alone, the addition of the MTZ strongly affects tabletability, because of the increase in tablet porosity. LH-32 exhibits lower tabletability than LH-31 when compressed alone, but shows the same tabletability in the mix and a better capacity to support a high MTZ amount without capping. Also, LH-22 behaves

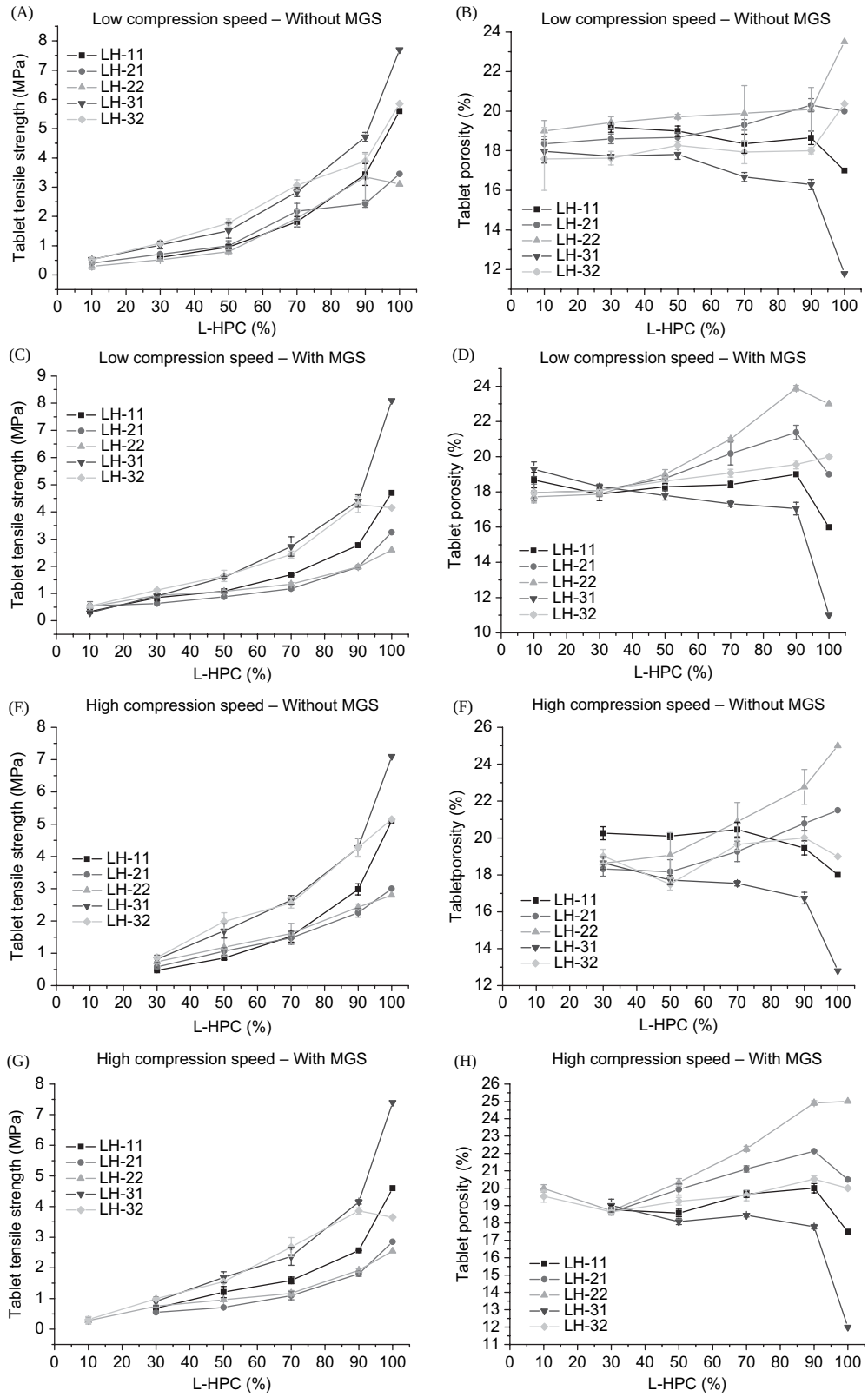


FIGURE 4. Compression behavior of MTZ and L-HPC binary mixtures (compression pressure 120 MPa). (A–B) Tabletability and compressibility at low compression speed, without lubricant. (C–D) Tabletability and compressibility at low compression speed, with lubricant. (E–F) Tabletability and compressibility at high compression speed, without lubricant. (G–H) Tabletability and compressibility at high compression speed, with lubricant.

better than expected on the basis of its own tabletability. Even so, compressibility improves in presence of the MTZ particles, leading to the conclusion that better particle-particle arrangement occurs during densification. Clearly, the ability of the mixes to densify (compressibility) is influenced by the hydroxypropyl content of the L-HPCs. Both LH-22 and LH-32, which possess lower hydroxypropyl content, densify better when mixed with MTZ. Probably a low degree of substitution enhances the interaction between MTZ and L-HPC particles by increasing adhesion forces.

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