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Evaluation of low-substituted hydroxypropylcelluloses (L-HPCs) as filler-binders for direct compression

C. Alvarez-Lorenzo, J.L. Gómez-Amoza, R. Martínez-Pacheco, C. Souto, A. Concheiro *

Departamento de Farmacia y Tecnología Farmacéutica, Facultad de Farmacia, Universidad de Santiago de Compostela, 15706 Santiago de Compostela, Spain

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Abstract

The aims of this study were to assess the potential value of low-substituted hydroxypropylcelluloses (L-HPCs) as excipients of direct compression, and to investigate relationships between the chemical and physical properties of the polymers and (a) the powder rheological behavior and (b) drug release profiles from direct compressed tablets elaborated with (1:1) theophylline:L-HPC mixtures. Experiments were performed with five L-HPC varieties of different nominal particle sizes and degree of substitution. The products were characterized with regard to the moisture content, density, IR and Raman spectroscopy, hydroxypropyloxy content, heat of hydration, particle size, specific surface and porosity, and important differences were found in relation with all these properties. The differences in specific surface principally determine the flow and compaction properties of the powders, and the mechanical and microstructural properties of the tablets. The control of the hydroxypropyloxy content and the particle size of the L-HPCs allow the theophylline release profile to be regulated.

Keywords: Low-substituted hydroxypropylcellulose (L-HPC); Theophylline; Tablet excipients; Direct compression; Porosimetry

1. Introduction

Hydroxypropylcellulose is a widely used excipient for topical and oral drug dosage forms. The specific utility of the various commercially available types depends on their structural characteristics, especially on the degree of substitution which greatly conditions the strength of the interaction with water (Joshi and Wilson, 1993; Alvarez-Lorenzo et al., 1999a). The varieties with a medium-high degree of substitution, which are the most studied, are appropriated for matrix tablets or as thickeners in aqueous solutions or suspensions (Vázquez et al., 1992; Doelker, 1993; Duro et al., 1998a,b). On the other hand, the varieties with a low degree of substitution swell without dissolve and have been proposed as excipients of conventional tablets (Kawashima et al., 1993a;

* Corresponding author. Tel.: +34-981-594627; fax: +34-981-547148.

E-mail address: ffancon@usc.es (A. Concheiro)

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Kanzaki et al., 1998) and pellets obtained by extrusion-spheronization (Kleinebudde, 1994).

In tablet technology, several low-substituted hydroxypropylcelluloses (L-HPCs) have been proposed as disintegrants in conventional formulations. For this purpose, the polymer is used in small proportions (2.5–5%) in combination with other excipients as microcrystalline cellulose (MCC) (Kawashima et al., 1993a). For this application the particle size of L-HPC is a critical property playing an important role on the disintegration and release properties of the tablets (Kawashima et al., 1993b).

The available information about the usefulness of L-HPCs as main excipients of tablets is very scarce. Only Nakagami et al. (1991), Kawashima et al. (1993b,c) have reported that extremely micronized L-HPC could be used as main excipients to obtain sustained-release tablets, by direct compression or by compression via wet or dry granulation. There is no general information about the properties of the L-HPCs that can determine their utility in direct compression or about the relation between the chemical and physical properties and the behavior of the tablets elaborated with L-HPCs as unique or main excipients. This information is essential in order to identify critical properties in the L-HPC selection for each particular application.

The aim of this study is to evaluate L-HPCs as directly compressible tablet excipients. We characterized in detail five varieties of L-HPC, and the implications of their physical and structural properties on the powder properties and on microstructural and drug release properties of directly compressed theophylline tablets.

2. Materials and methods

2.1. Materials

Anhydrous theophylline (batch 97F-0733, Sigma, Spain). Hydroxypropylcelluloses with low degrees of substitution (L-HPCs) LH-11 (batch 503078), LH-20 (batch 405117), LH-21 (batch 506157), LH-22 (batch 301018), and LH-31 (batch 502032), were supplied by Shin-Etsu Chemical Co. (Tokyo, Japan).

2.2. Characterization of L-HPCs

2.2.1. Chemical and structural properties

2.2.1.1. Moisture content. Moisture content was determined on the basis of weight loss after 3 h at 105°C (USP23-NF18, 1995).

2.2.1.2. True density. True density was determined with the aid of a helium pycnometer Quantachrome MPY-2 (three determinations per polymer).

2.2.1.3. Infrared and Raman spectroscopy. IR spectra and Raman spectra were recorded on a Bruker IFS 66V FTIR spectrometer equipped with an FRA 106 FT–Raman accessory incorporating an Nb:YAG laser and a germanium detector cooled with liquid nitrogen. IR spectra were obtained over the range 400–4000 cm^{-1} by the potassium bromide pellet technique. For Raman spectroscopy, powdered samples were held in glass capillary tubes. The crystallinity index was calculated as the absorbance ratio at 1370 and 2900 cm^{-1}, using the method of Nelson and O'Connor (1964).

2.2.1.4. Degree of substitution. The quantification of hydroxypropyloxy contents was determined by gas–liquid chromatography (GLC) (Alvarez-Lorenzo et al., 1999b), as follows, samples of between 50 and 55 mg of each pre-dried L-HPC were accurately weighed into 10 ml vials together with approximately the same mass of adipic acid. To each vial 3.0 ml of 57% (w/w) hydroiodic acid and 3.0 ml of toluene standard (12.5 mg toluene/1 ml *o*-xylene) were added, and the vial was then sealed, shaken to mix its contents, and incubated at 150°C for 1 h. Isopropyliodide calibration standards were prepared in similar vials adding 50–55 mg of adipic acid, 3.0 ml of 57% (w/w) hydroiodic acid, 3.0 ml of toluene standard, and 5, 15, 30, 45 or 60 μl of isopropyliodide using a Hamilton microsyringe. GLC was performed on a Hewlett-Packard Series II mod. 5890 chromatograph (PA, USA) equipped with a 25 m × 0.53 mm i.d. BP1 capillary column (Scientific Glass Engineering, Australia) and a flame ionization detector linked

via an HP ChemStation to an HP 3365A PC. The injector, detector and oven temperatures were 200, 250 and 60°C, respectively. Nitrogen was used as both carrier gas (flow rate 5.5 ml min^{-1}) and make-up gas (flow rate 44 ml min^{-1}). In each run, a 1 μl subsample of the organic phase of the standard or sample was injected manually with a split ratio of 10:1.

2.2.1.5. Heat of hydration-solution. The heat of hydration-solution of each L-HPC at 25°C was determined in duplicate in a Tronac 458 (Tronac Inc., UT, USA) isoperibol titration calorimeter (Tronac Inc., 1992). All assays used 0.050–0.100 g of sample that had been dried for 12 h at 70°C and 50 ml of distilled water.

2.2.2. Powder properties

2.2.2.1. Particle size analysis. Representative samples of each L-HPC were obtained by riffling in a Quantachrome rotary microriffler. Martin diameters were determined on the basis of measurement of 625 particles of each lot under an Olympus BH-2 light microscope. The geometric mean and geometric standard deviation were determined after logarithmic transformation of the data.

Particle size distributions were also determined using a Coulter LS100 laser scattering particle analyzer. The results are expressed in terms of the mean surface diameter.

2.2.2.2. Scanning electron microscopy. Samples were mounted on double-sided tape on aluminum stubs and sputter-coated with gold/palladium. Micrographs were obtained in a Jeol JSM-T220A scanning electron microscope.

2.2.2.3. Specific surface area and microporosity. Nitrogen adsorption experiments were carried out in a Micromeritics ASAP 2000 apparatus using samples that had been degasified by being kept for 8 h at 70°C and 10^{-3} mm Hg. Nitrogen adsorption at 77 K was measured over the relative pressure range 0.06–0.99. Each polymer variety was run in duplicate. Specific surface area (S_{BET}) was estimated from the volume of a nitrogen monolayer (*Vm*, calculated from the BET equation) using the expression (Stanley-Wood, 1983)

$$S_{BET}(m^2 \cdot g^{-1}) = 4.37\ \ Vm(cm^3 \cdot g^{-1}) \quad (1)$$

Following Barret et al. (1951), mean pore size and micropore volume were estimated from the nitrogen desorption isotherms on the assumption that equilibrium between the gas phase and the adsorbed phase during desorption is determined by (1) physical adsorption on the pore walls and (2) capillary condensation in the inner capillary volume; a numerical method was used to solve Barret et al. (1951) equation,

$$\Delta Vp = Rn \cdot (\Delta Vc - C \cdot \Delta t \cdot \sum Sp) \quad (2)$$

where ΔVp is the actual pore volume emptied in the desorption step, C the correction factor to allow for the change in curvature of the pore wall as pore size changes, ΣSp the sum of the surface areas over all the desorption steps, and Rn is calculated using the expression,

$$Rn = \frac{r_p^2}{(r_k + t)^2} \quad (3)$$

where r_p is the actual pore radius, r_k the mean capillary condensate radius, and t the decrease in multilayer thickness during the desorption step.

2.2.2.4. Flow properties. Tapped bulk densities were determined in triplicate in a Hosokawa PT-E Powder Tester, tapping at 50 taps per minute for 20 min. Compressibilities (%) were then calculated from the bulk densities (Thomson, 1984).

2.2.2.5. Compression behavior. Compression behavior was investigated in the course of preparation of 125 mg tablets by direct compression in a Bonals B-MT eccentric press fitted with 9 mm punches and control instrumentation as described by Martínez-Pacheco et al. (1985). Force–displacement curves were constructed for each polymer lot (three tablets per lot), allowing an estimation of mean yield stress and elasticity by Heckel's model (Humbert-Droz et al., 1982).

2.3. Preparation and characterization of theophylline tablets

2.3.1. Preparation

Tablets containing 50 mg of anhydrous theophylline were prepared with 75 mg of each polymer by direct compression in a Bonals B-MT press equipped with 9 mm flat punches. Compression force was in all cases 2600 N.

2.3.2. Friability

The friability of ten tablets from each batch was determined using an Erweka friability tester model TAP.

2.3.3. Tensile strength

The tensile strength was calculated for each six tablets from the equation (Summers et al., 1977),

$$\text{Tensile strength} = \frac{2 \cdot CS}{\pi \cdot D \cdot E} \quad (4)$$

where CS is the crushing strength determined in an Erweka TB 2A apparatus, D denotes the diameter of the tablet, and E is its thickness (measured using a Mitutoyo digital micrometer).

2.3.4. Microporous structure

Microporous structures were determined using the nitrogen adsorption technique as described in Section 2.2.2.3 for the uncompressed products (pores < 0.1 μm), and mercury intrusion porosimetry. In the latter technique, volumes of intruded mercury were determined on triplicate samples over the pressure interval 0.6–2000 lb per inch^2 using a Micromeritics 9305 Pore Sizer (Micromeritics Instruction Manual, Pore Sizer 9305, 1984). The method is based on the capillary rise phenomenon whereby an excess pressure is required to cause a non-wetting liquid to climb up a narrow capillary. The pressure difference across the interface is given by the Washburn equation (Allen, 1997),

$$\Delta P = -\left(\frac{2\gamma}{r}\right)\cos\theta \quad (5)$$

where γ is the surface tension of the liquid, r the perpendicular radius and θ is the angle of contact between the liquid and the capillary walls. Experimental data are obtained in the form of P against volume intruded. P is converted to pore radius using the Eq. (5), assuming a surface tension for mercury of 0.480 N m^{-1} and a contact angle of 130°, with pressure P in psi and radius in μm, Eq. (5) becomes,

$$r = \frac{89.5}{P} \quad (6)$$

The pore volume distribution (pores > 0.1 μm) was then evaluated from these data.

2.3.5. Disintegration time

Measurements were carried out using a Turu Grau apparatus, which conforms to the specifications exacted in United States Pharmacopoeia 23, National Formulary 18 (1995). Mean values were calculated from the disintegration times of six compacts in distilled water.

2.3.6. Dissolution profiles

Time-course of theophylline release were determined at 37°C in a Turu Grau apparatus adapted to meet the specifications of the United States Pharmacopoeia 23, National Formulary 18 (1995), by a modification of method II (Pérez-Marcos et al., 1993). The dissolution medium was 900 ml of distilled water. Stirring rate was 50 rpm. The concentration of the active principle in periodically taken samples was determined spectrophotometrically at 271 nm. The profiles of L-HPC formulations were characterized in terms of 1 h dissolution efficiency (Khan and Rhodes, 1972).

2.4. Statistical analysis

The influence of the characteristics of the L-HPCs on the flowability of the powders and the properties of the tablets was evaluated by stepwise multiple linear regression using Statgraphics® v. 7.0 (1993) with a significance α level of 0.05. Goodness of fit was assessed by analysis of variance of the regression (Walpole and Myers, 1985).

3. Results and discussion

The results of characterization of the five L-HPC varieties are summarized in Table 1. LH-22 is the

Table 1
Physical and structural properties (means with standard deviations in brackets) of the five L-HPC varieties studied

Property	LH-11	LH-20	LH-21	LH-22	LH-31
Moisture content (%)	2.05 (0.25)	2.83 (0.32)	2.22 (0.29)	3.82 (0.17)	3.56 (0.22)
True density (g cm^{-3})	1.439 (0.009)	1.424 (0.009)	1.438 (0.006)	1.456 (0.006)	1.435 (0.003)
Crystallinity index	0.51	0.43	0.60	0.69	0.46
% Hydroxypropoxyl	10.84 (0.12)	13.15 (0.03)	10.61 (0.05)	7.50 (0.08)	11.05 (0.06)
Enthalpy of hydration (J g^{-1})	−70.92 (1.88)	−69.97 (2.90)	−69.95 (2.71)	−62.86 (0.30)	−71.35 (0.17)
Martin diameter (μm)	32.55 (2.25)	25.48 (2.41)	22.02 (2.11)	23.94 (2.41)	13.97 (1.92)
Mean surface diameter (μm)	12.54 (0.14)	12.31 (0.21)	11.81 (0.16)	11.51 (0.11)	8.35 (0.24)
Specific surface area (m^2 g^{-1})	1.103 (0.050)	0.768 (0.006)	1.225 (0.011)	0.993 (0.058)	2.199 (0.025)
Mean pore size (nm)	15.21 (0.67)	15.89 (0.39)	14.56 (0.74)	16.00 (1.09)	15.09 (0.49)
Micropore volume (cm^3 g^{-1})10^3	4.272 (0.551)	2.964 (0.187)	4.587 (0.268)	3.879 (0.167)	8.972 (0.694)
Compressibility (%)	46.38 (0.42)	45.29 (1.24)	46.90 (0.92)	42.26 (0.25)	56.82 (0.22)
Mean yield stress (MPa)	59.1 (3.6)	50.2 (7 0)	49.5 (2.5)	47.3 (2.6)	59.8 (1 7)
Elastic recovery (%)	26.2 (1.7)	29.0 (0.6)	27.3 (3.5)	29.1 (3 5)	31.1 (2.0)

variety with a smaller hydroxypropyloxy content and a higher true density. These properties are related with the crystallinity indexes of L-HPCs determined by spectroscopy (Fig. 1A) as the relationship between the absorbances at 1327 and 2900 cm^{-1}. The band around 1327 cm^{-1}, from CH bends (1500–1200 cm^{-1}), is very dependent on the crystallinity of the substance but it is hardly affected by the amount of absorbed water into cellulose. On the contrary, the band around 2900 cm^{-1} is practically independent of the crystallinity of cellulose and can be used as a reference (Nelson and O'Connor, 1964). As can be seen in Table 1, all L-HPCs present crystallinity indexes lower than the characteristic values for MCC, in the range 0.62–0.86 (Landín et al., 1993), which indicates that the structure of these polymers is principally amorphous. The amorphous structure and the low degree of substitution are also noticeable in the Raman spectra of all the L-HPCs, which present bands very similar to cellulose II and clearly different to those of cellulose I (Atalla, 1976) (Fig. 1B). The Raman spectra show the characteristic bands of unsubstituted cellulose from ether at 1097 and 1122 cm^{-1}, from CC at 1153 cm^{-1}, and from CH bends at 1367, 1338 and 1294 cm^{-1} (Langkilde and Svantesson, 1995). The bands around 1260 and 1458 cm^{-1}, of less intensity, are characteristic of the hydroxypropyl substituent.

Both scanning electron microscopy (microphotographs not showed) and optical microscopy particle size analysis (Table 1) indicate very

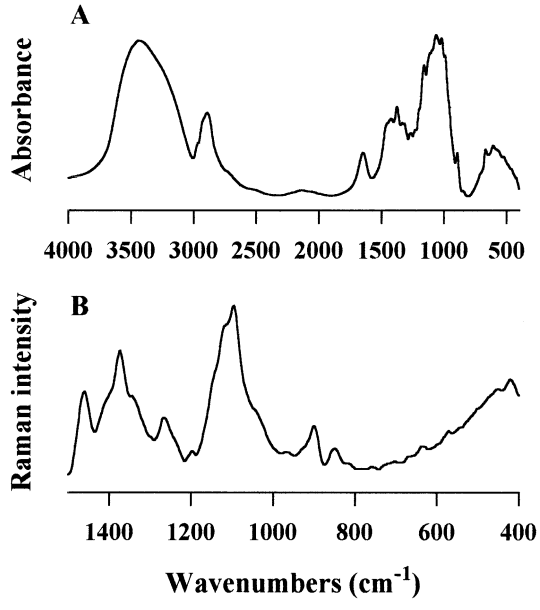

Fig. 1. IR (A) and Raman (B) spectra of L-HPC LH-22.

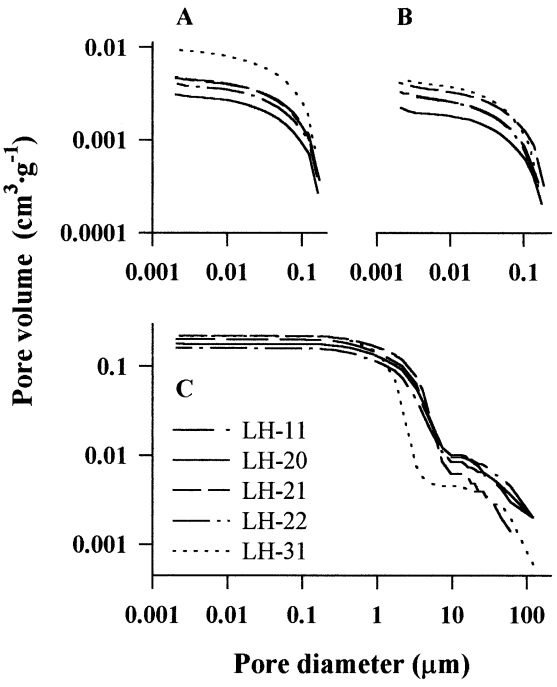

Fig. 2. Pore size distributions of L-HPC powder samples (A) and theophylline tablets (B) obtained by nitrogen adsorption, and pore size distributions of L-HPC, theophylline tablets (C) obtained by nitrogen adsorption and intrusion porosimetry.

marked differences between the varieties of L-HPC; specifically, LH-11, LH-20, LH-21, and LH-22 are composed of fibrous particles larger than more spherical particles of LH-31. Nitrogen adsorption experiments (Fig. 2A) clearly show that the latter variety has the greater intraparticular porosity. This fact together with the small particle size leads to a very large specific surface area (Table 1). LH-31 has also a slightly greater compressibility than the other LHPC varieties (Table 1), although for all of them the high compressibility values obtained, denotes that they have a poor flowability. These differences on compressibility can be attributed to the different specific surface of the L-HPC varieties as the strong linear correlation found between these variables ($r = 0.9415$, $F = 23.43$, 1 and 3 d.f., $\alpha < 0.05$) shows. These values of compressibility are much bigger than obtained previously by Landín et al. (1993) for MCCs (35–38%), an excipient widely used for direct compression.

The small mean yield pressures obtained for the five products (Table 1) suggest that the predominant consolidation mechanism was plastic deformation (Humbert-Droz et al., 1982), as has been found for other cellulose ethers (Malamataris et al., 1994; Nokhodchi et al., 1996) and MCCs (Landín et al., 1993).

The isoperibol microcalorimetry was used to quantify the heat involved in various processes during the addition of L-HPC to water; such as hydration and swelling. For all the L-HPCs, the interaction with water is an exothermic process (Table 1). The less heat liberated by LH-22 may be attributed to its relative high crystallinity and low degree of substitution, high crystallinity generally implies that a large amount of energy is required to break the bonds responsible for the crystalline solid state (Salvetti et al., 1996), while the replacement of hydroxyl groups by ether groups reduces the number of intramolecular hydrogen bonds (Kondo, 1997).

Experiments performed with theophylline tablets showed a clear difference among the porous characteristics of the compacts made with each L-HPC (Fig. 2B and Fig. 2C). The LH-31 compacts presented a smaller macropore volume (pores > 0.1 μm) than the other L-HPC compacts. This could be related with the small particle size of this variety, which permits the particles to adopt a closer structure during the compactation. By comparison of Fig. 2A and Fig. 2B, it can also be noted that there is an important reduction of the intraparticular porosity during the compactation only in the case of LH-3 1. This leads to very similar cumulative micropore distribution curves for all the tablets (pores < 0.1 μm). The mechanical properties of the tablets are shown in Table 2. The observed differences in the friability and the tensile strength can be attributed to their divergent microstructural properties due to the above cited differences in particle size and microstructural properties of the polymers. The matrix tablets elaborated with the finer excipient should have a more continuous and firmer structure due to the increase in the contact point and area between the polymer particles around the drug particles, which is reflected in the lower porosity of the tablet. Fig. 3 shows the strong linear correlation found between tensile strength and specific

Table 2
Disintegration time and dissolution efficiency of theophylline tablets[a]

Polymer	Friability (% loss)	Tensile strength (MPa)	Disintegration time (min)	Dissolution efficiency
LH-11	1.00	0.45 (0.07)	15.3 (1.76)	95.0 (0.85)
LH-20	1.17	0.40 (0.05)	19.4 (0.86)	71.5 (5.52)
LH-21	1.16	0.55 (0.04)	10.4 (1.19)	83.8 (3.34)
LH-22	1.32	0.46 (0.09)	9.73 (0.81)	89.1 (3.51)
LH-31	0.31	0.75 (0.09)	26.1 (1.29)	85.4 (5.19)

[a] Means with standard deviations in brackets.

surface ($r = 0.9837$, $F = 89.92$, 1 and 3 d.f., $\alpha < 0.01$), and friability and specific surface ($r = -0.9360$, $F = 21.23$, 1 and 3 d.f., $\alpha < 0.05$).

Table 2 also includes the disintegration times and the drug dissolution efficiency of the tablets elaborated with mixtures of L-HPC and theophylline 1:1. The marked differences in this latter parameter can be seen in the release theophylline profiles (Fig. 4). It has been previously shown that the swelling rate and work of L-HPC powder beds are very dependent on the degree of hydroxypropyloxy substitution and the particle size of the polymer (Kawashima et al., 1993a, 1994). This suggests that both variables must also exert a strong influence on the disintegration time of the tablets. To quantify the effect of the hydroxypropyloxy content and the specific surface of the polymer, multiple linear regression was applied (Fig. 5A). The slower disintegration of LH-31 compacts is doubtless due to their smaller total porosity, particularly the sizeable contribution to this from macropores (pores > 0.1 μm). The influence of the hydroxypropyloxy content on the disintegration time can be explained by the diminution of the crystallinity that takes place when the degree of substitution increases (Table 1). Thus, for the tablets elaborated with the more substituted varieties, a stronger interparticular hydrogen bonding network can be formed, which might retard the penetration of water (Kawashima et al., 1993a; Kondo, 1997). The differences in the interaction with water among the L-HPC varieties with similar particle size (LH-20, LH21, and LH-22), showed by the values obtained in the determination of the heat of hydration may also play an important role. In this sense, the energy released during the hydration of the variety LH-22 with lower degree of substitution was the smallest one, which means a lower affinity for water. When water penetrates

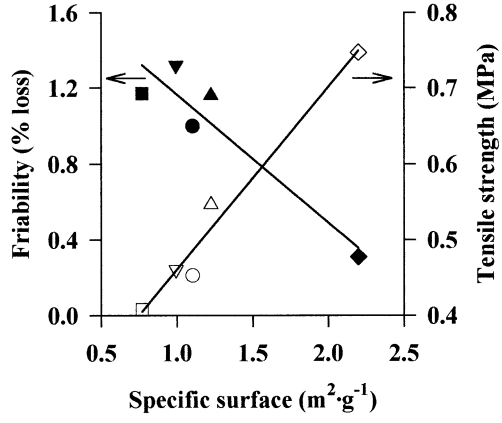

Fig. 3. Effect of specific surface of L-HPCs on the physical properties of LHPC, theophylline tablets. LH-11 (○, ●), LH-20 (□, ■), LH-21 (△, ▲), LH-22 (▽, ▼), LH-31 (◇, ◆).

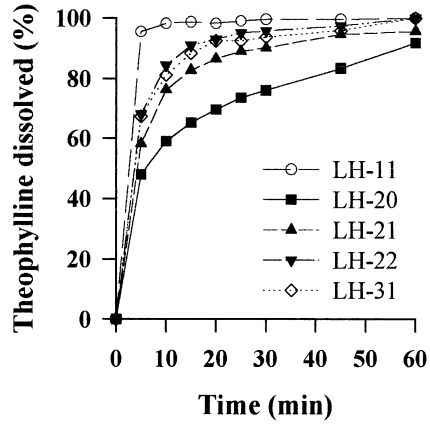

Fig. 4. Dissolution profiles of theophylline, L-HPC tablets.

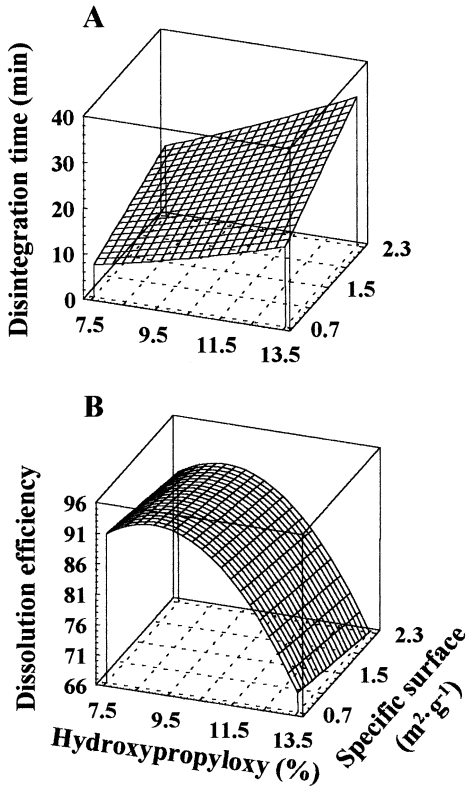

Fig. 5. Response surfaces, (A) disintegration time = 0.0602*(% hydroxypropyloxy)^2 + 0.6988*(% hydroxypropyloxy*specific surface), $r^2 = 0.9748$, $F = 58.17$, 2 and 3 d.f., $\alpha < 0.01$; (B) dissolution efficiency (%) = 21.042*(% hydroxypropyloxy) − 2.0141*(specific surface) − 1.1708*(% hydroxypropyloxy)^2, $r^2 = 0.9961$, $F = 2294$, 3 and 37 d.f., $\alpha < 0.01$.

L-HPC tablets, it inserts itself into the hydrogen-bonded links between the drug molecules and the polymer chains. The polymer swells and exerts a pressure, which results in the disintegration of the tablet. It is likely that the rate of water uptake increases by decreasing the capacity of polymer to bind water (Alvarez-Lorenzo et al., 1999a), then the water can diffuse easily towards the core of the tablet (Kawashima et al., 1993a). It is interesting to note that the theophylline tablets elaborated with LH-22 that has the lowest enthalpy of hydration, presenting the fastest disintegration time and a larger drug dissolution efficiency than tablets made with LH-20 or LH-21.

The dependence of theophylline dissolution efficiency (Table 2) on the degree of substitution and the specific surface of the polymer is shown in Fig. 5B. As was seen before, the effects of these two factors on the disintegration time can explain again the differences observed on the theophylline release rate.

4. Conclusions

The flow properties of the L-HPCs are very dependent on the specific surface and on the microstructure of their particles and the values of compressibility revealed that these polymers are, from the point of view of their rheological properties, inadequate for use as direct compression excipients and require for this type of application a physical modification. The specific surface of the particles also exerts an important effect on the mechanical properties of the tablets. The control of determined properties of the L-HPCs, such as degree of substitution and particle size, can allow the release characteristics of the tablets to be regulated. The tablets elaborated with the varieties with the lower degree of substitution and higher particle size HPC released the theophylline quickly. Nevertheless, tablet disintegration and drug release slow down when reduced particle size and higher hydroxypropyloxy content HPC are used.

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