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Cross-linked amylose as matrix for drug controlled release. X-ray and FT-IR structural analysis

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Abstract

For cross-linked amylose (CLA) tablets prepared by direct compression, a linear increase in cross-linking degree (cld) defined as percentage of epichlorohydrin cross-linker/polymer, generates non-monotonous variation of drug release time. Controlled release (up to 20–24 h) properties were obtained only for tablets from CLA (Contramid™) with relatively low cld (CLA-2 up to CLA-6). Moderate increase in cld (CLA-15) generates a sharp decrease in the release time (2–6 h). This is a particular characteristic of the CLA matrix. The controlled release properties were related to the X-ray pattern of the dry CLA network. The increase in cld induces a transition from B-type (double helix) to a predominat V-type (single helix) and to more amorphous conformation of CLA powders. Furthermore, FT-IR data indicated low free water content at low cld. For low cross-linked CLA, chains are closely located and stabilized by HO groups involved in hydrogen bonding and thus more resistant to hydration and more appropriate for the control of drug release.

Keywords: Cross-linked amylose (CLA); Cross-linking degree (cld); FT-IR data; X-ray analysis; Drug controlled release

1. Introduction

Cross-linked amylose (CLA) obtained by high amylose starch cross-linking with epichlorohydrin (Serban et al., 1975), was introduced in the early nineties as a polymeric material for drug controlled release (Lenaerts et al., 1991; Lenaerts et al., 1992; Mateescu et al., 1992; Mateescu et al., 1994) under the brand name Contramid™.[1] For CLA tablets prepared by direct compression, it was found that a linear increase in the cross-linking degree (cld[2]) generates non-monotonous variation of drug release time (Lenaerts et al., 1991; Mateescu et al., 1992). The sustained release and interesting mechanical properties were obtained only for tablets made from CLA with relatively low cross-linking (Fig. 1). The drug release appears to be controlled only by CLA with a limited range of cross-linking degree from CLA-3 up to CLA-11; maximal release time (20–24 h) was found for CLA-6. Moderate increase in cld (CLA-15) generates a sharp decrease of the release time (2–6 h). High cross-linking degrees (CLA-20 and more) afford disintegrant properties to the CLA (Cartilier et al., 1992; Dumoulin et al., 1994), which may be used as a binder and disintegrant (Liamid™). The decrease in release time with increasing cld is a particular characteristic of the CLA matrix and differs from many of the other polymeric matrices for which higher cld leads to longer release times (Kim and Lee, 1992). This particular behaviour of CLA seems to be mostly related to the network organization (probably modified by cross-linking and influenced by compression). A hypothesis that CLA can achieve different network organizations as a function of the cross-linking degree, has been advanced (Mateescu et al., 1993; Dumoulin et al., 1994).

It was supposed that both covalent cross-linking and physical association (closely related to the cross-linking degree of gelatinized high amylose starch), are critical parameters

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[1] Contramid™ is the trade mark of CLA from Labopharm Inc.; Rougier Inc. is the registered manufacturer.

[2] cld = cross-linking degree defined as the amount of epichlorohydrin (g) used to cross-link 100 g of amylose in specific reaction conditions; i.e. CLA-6 is obtained with an initial ratio 6/100 cross-linking agent/high amylose starch. However, we have to note that it is possible that the final cld can slightly differ to the initial one.

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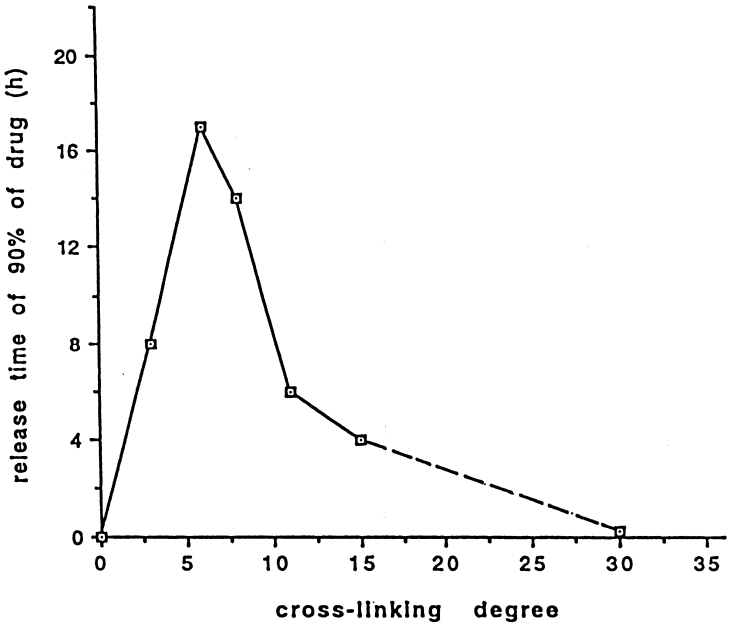


Fig. 1. The influence of cross-linking degree of CLA tablets on the theophylline release time (tablets of 500 mg containing 50 mg of drug).

for the matrix cohesion and responsible for the sustained release properties. Our hypothesis was that both network organization and water access are of determinant importance for the control of the drug release kinetics. We consider that water can have a role in the matrix organization in the CLA tablets. Correlations between water uptake and cross-linking degrees have been previously described by Dumoulin et al. (1994). Aspects of the role of water uptake in the release behaviour of swollen CLA in dissolution media, were recently reported (Moussa and Cartilier, 1996).

The aim of this study is to contribute to the understanding of the structural characteristics in dry form of CLA powders and tablets. These structural achievements will allow a better evaluation of the functional role of the network in the control of the drug release from matrices based on the CLA of different clds. X-ray diffraction data can give information on the long-range order in a semi-crystalline biopolymer like amylose, while data on short-range structural changes can be obtained by FT-IR (infrared) spectroscopy (Koenig, 1992). It is accepted that certain polyhydroxylic compounds (alcohols, polyols, sugars, starch, etc.) can easily hydrate and that water is retained by hydroxyl groups via hydrogen bonding (Rappenecker and Zugenmaier, 1981; Brisson et al., 1991). In the case of dry CLA powders and tablets, we assumed that more crystalline structures are less susceptible to exchange free water, while in the case of amorphous structures, hydroxyl groups are free to be involved in dynamic hydrogen bonding with water. Since the network properties and crystallinity are supposed to be mostly related to the hydration state of HO groups, a study of the water retention has been carried out. From these data it will be possible to get a better understanding and to anticipate the release properties of different CLA matrices, at different cross-linking degrees.

2. Materials and methods

2.1. Materials

High amylose starch powder (corn starch Hylon VII) containing at least 70% amylose (with less than 30% amylopectin), was obtained from National Starch Co. Epichlorohydrin, mono-chloroacetic acid and sodium hydroxide (Sigma), acetic acid and acetone (BDH) as well as the other reagents, were used without further purification. Theophylline in anhydrous form (M.W. 180.2, Sigma) was used as a drug tracer for dissolution tests.

2.2. Synthesis of cross-linked amylose

High amylose starch was cross-linked with epichlorohydrin, in conditions previously described (Mateescu et al., 1995). An amount of 10 g of Hylon VII was swollen in 35 ml of 5 N NaOH at 0–2°C and homogenized on an ice bath for 30 min. For the preparation of CLA-6, an amount of 0.6 g of epichlorohydrin ($d^{20} = 1.1812$) was slowly added and the homogenization continued for another 30 min on the ice bath. The reaction medium was then heated for 1 h at 40–45°C and then for another 2 h at 60–75°C, for completion of the cross-linking reaction. After reticulation, the gel was suspended in water, neutralized to pH 6–7 with acetic acid and thoroughly washed by subsequent decantations with water. The wet gel was then sieved retaining grains of 75–300 μm and first precipitated with a solution of acetone/water 85/15 (v/v), then washed by decantation with solutions of acetone water 40/60 (v/v) and finally dried with acetone 100% (Ghetie and Schell, 1971).

Epichlorohydrin cross-linked high amylose starch (although it contains up to 30% amylopectin) will be

referred hereafter as cross-linked amylose (CLA). For the preparation of other CLA materials with different clds, the same procedure was followed, except that different amounts of epichlorohydrin were used, to obtain the desired cld (i.e. for CLA-11, the required amount of epichlorohydrin was 1.1 g, while for CLA-20, the amount was of 2 g). The CLA-0 was not cross-linked.

2.3. Synthesis of carboxymethyl amylose (CM–CLA-20)

CLA-20 was functionalized with carboxymethyl groups by treatment with monochloroacetic acid, as previously described (Schell et al., 1978). An amount of 10 g of CLA-20 was swollen in 10 N NaOH at 0–2°C and homogenized on an ice bath for 10 min. Then, an amount of 20 g monochloroacetic (α-chloroacetic) acid solubilized in a minimal volume of water was added rapidly and the homogenization continued for another 10 min on the ice bath. The reaction medium was then heated for 1 h at 60–75°C, for reaction. After carboxymethylation, the gel was suspended in water and then thoroughly washed by filtration with water, until pH 7.

The CM–CLA-20[3] was obtained in two forms: Na salt (Na^+–CM–CLA-20) and acid (protonated) form (CM–CLA-20 acid). The salt (Na^+–CM–CLA-20) was obtained by direct acetone drying of the carboxymethylated product (after washing until pH 7). For the protonated form, CM–CLA-20 was treated with 1 N acetic acid (the activation of CM-groups) and then thoroughly washed with water until neutralization. In both cases, the wet gels were sieved retaining grains of 75–300 μm. Both suspensions, CM–CLA-20 salt and CM–CLA-20 acid, were washed and dried with acetone (Ghetie and Schell, 1971), as described before. The amount of CM-groups (0.86 mEquiv/g dry product) was established by potentiometric titration (Corning 250) of determined amounts of CM–CLA-20, with a calibrated 0.1 N NaOH solution. The swelling volumes (expressed in ml/g) of CM–CLA-20 salt and acid forms were obtained by swelling 1 g of each dried powder in distilled water at 22°C and measuring the bed volume stabilized after 24 h.

2.4. Tablet preparation

For X-ray diffraction studies, tablets of each powder (400 mg) were compressed at 2.3 T/cm^2 in a die assembly having flat face punches and using a Carver hydraulic press.

2.5. Drug dissolution analysis

Drug release was followed in a USP XX (Kalish) apparatus (37°C, 50 rpm, 1 l dissolution cells), recording the release kinetics of theophylline at 254 nm, for 24 h. For each polymeric excipient, theophylline and CLA powders were dry mixed in a Turbula mixer for 5–10 min. Tablets of 500 mg (12.7 mm diameter and 2.7 mm thickness), containing 50 mg theophylline, were obtained by compression at 2.3 T/cm^2 using the die assembly with flat face punches in the Carver hydraulic press.

2.6. X-ray diffraction analysis

2.6.1. Instrument

Siemens K IV diffractometer with cobalt cathode operating in reflectance mode at Co–Kα wavelength (λ = 1.79018 Å), 30 kV and 16 mA, equipped with a graphite monochromator and scintillation detector. Peak positions and their relative intensities for CLA of different clds, in tablet and powder form, were considered for discussion.

2.7. FT-IR analysis

Absorbance spectra were recorded on a Perkin Elmer spectrophotometer equipped with a DTGS (deuterated triglycine-sulfate) detector. Samples were prepared with 6% (w/w) CLA powders (particle size below 50 μm) dispersed in KBr pellets (100 g). All powders were dried at 105°C for 24 h before tableting with KBr and several CL-amyloses, of different clds, were used. Typically, 256 scans were recorded with a 4 cm^{-1} resolution.

For the calculation, the absorbance of the bending mode of the water detected at 1646 cm^{-1} was normalized by dividing the peak area (1646 cm^{-1}) by the peak area of the CH_2 modes at 2928 cm^{-1}. The latter was corrected for the water contribution by using spectral deconvolution.

2.8. Water evaporation kinetics

Before measurements, all powders were exposed to water vapor at 50°C for 24 h in a closed vessel in order to saturate the samples with water. The samples were then dried at 50°C in the oven for 7 hrs. Thus, CLA powders lose water, finally reaching a constant mass. During this treatment, samples were withdrawn periodically and weighed. The differences between the initial and the final mass correspond to the water lost. This parameter represents the estimated amount of water retained by powders. For most of the samples, this amount ranged between 14 and 22% of the initial mass. From these data, the rates of water evaporation for CLA powders at various clds can be determinated. These experiments also allowed the determination of the water evaporation half-time (defined as the time required to evaporate 50% of the initial water content).

3. Results and discussion

Cross-linked amylose exhibits particular properties as

[3] CM-CLA-20 = carboxymethyl-CLA-20.

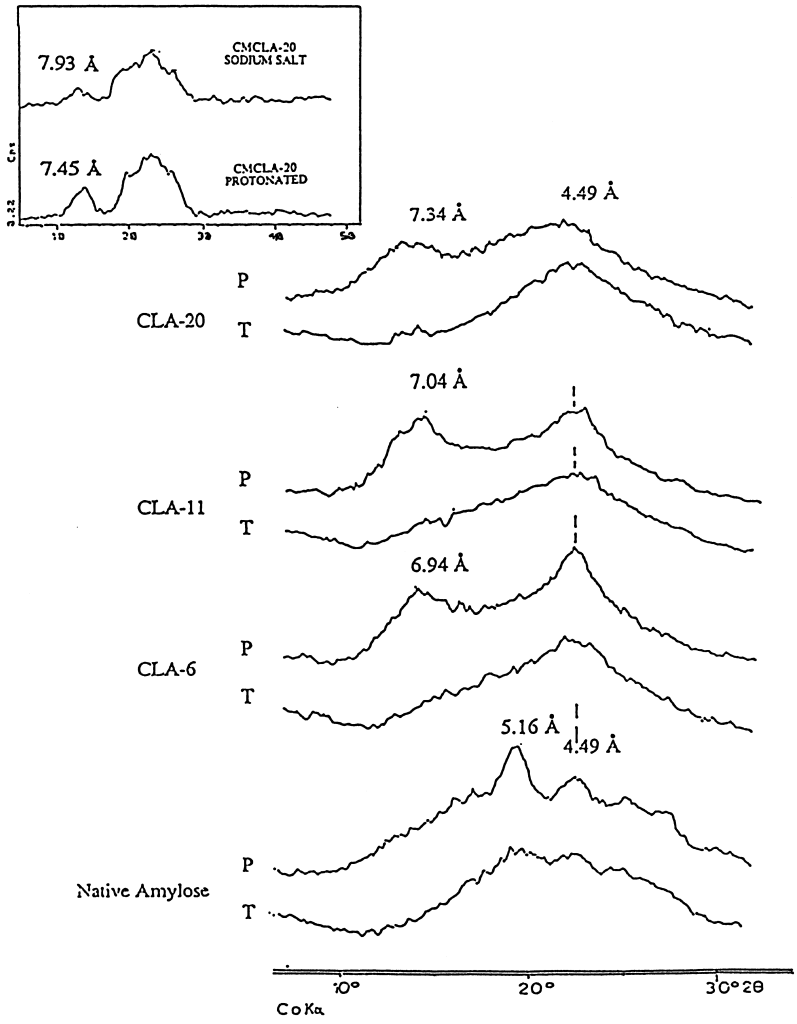


Fig. 2. X-ray diffraction pattern for native and CL-amylose of various cross-linking degrees in powder (P) and tablet (T) forms. Insert: CMCLA-20 (protonated) and CMCLA-20 sodium salt.

polymeric material (excipient) for the formulation of pharmaceutical forms where the drug release is controlled only for a limited range of cross-linking (Fig. 1). The cross-linking is essential for the tablet cohesion, but the cld should be low enough to generate a good control of the drug release. We supposed that a low cld allows the network to be stabilized by physical association, which is also essential to obtain controlled release properties. X-ray diffraction, FT-IR and water evaporation kinetics can contribute to a better characterization of the structural organization and physico-chemical behaviour of polymeric materials used in drug controlled release and to adjust preparative procedures for the best release properties.

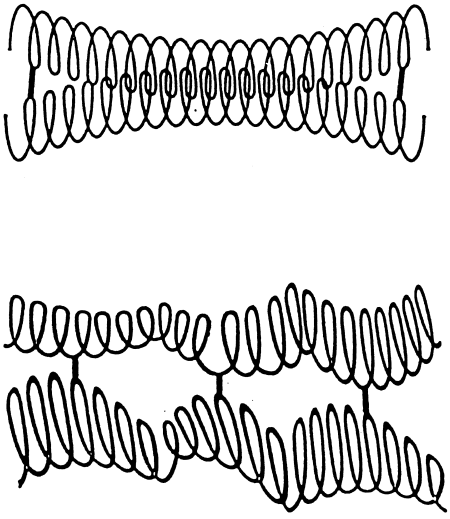
3.1. X-ray diffraction study

CLA is a semi-crystalline polymer and therefore X-ray diffraction is expected to give only a general image of network organization for CLA powders and tablets. Different X-ray patterns were observed for the powders (P) and tablets (T), as a function of cld (Fig. 2).

3.1.1. CLA-powders

For native amylose (Hylon VII) powder, two broad diffraction maxima centred on angular ranges of 19.5–20.5° and 23.5–24° (corresponding to 5.16 and 4.49 Å, respectively) were found. These values are characteristic of the B-type diffraction pattern (Zobel, 1988a; 1988b). By cross-linking (involving gelatinization and reticulation), the three-dimensional structures of CLA powders were altered and different X-ray patterns were found. Although extensive X-ray studies have been done on amylose or on starch, to our knowledge only a few X-ray data on CLA are available (Shefer et al., 1992), where cross-linking was realized in conditions different to ours. Thus, some of the obtained X-ray peaks of CLA could be ascribed by analogy with non-modified amylose and starch diffractograms.

With increasing cross-linking (CLA-6 – CLA-11) the 5.16 Å peak practically disappeared, while the 4.49 Å



Scheme 1. Hypothetical representation of the covalent and H-bonding stabilization of CLA for low–moderate (a) and high (b) cross-linking degree. This simplified model of a limited network section shows that at hydration only low cld will favor enough chains to mobilize allowing their stability by H-bonding.

peak became more important, but broader. At the same time, a new peak appeared at 6.94–7.04 Å (2θ angle of 15°). For higher cld (CLA-20), the diffractogram showed a general loss in crystallinity of the powder, surprisingly, associated with the shifting of the 6.94 Å peak to 7.34 Å. The modifications in the X-ray diffraction patterns for powders could be correlated with physical and chemical transformations undergone by cross-linking and drying processes. In a first step, cross-linking involves gelatinization in alkaline media, leading to partial or complete disruption of the initial order of the native high amylose starch granule. By covalent cross-linking and drying, a new type of order and a new morphology can appear. Increasing cross-linking density (the glycerine bridges introduced by epichlorohydrin reaction) may limit the mobility of chains and, consequently, hinder the formation of advanced ordered structures (i.e. double helix). Instead, less organized structures and a peak at 6.95–7.34 Å (considered a kind of pseudo V-type) can become predominant. In our experimental conditions, the most predominant peak at 5.16 Å for the native amylose (Hylon VII) practically disappears by cross-linking; it is then possible to assume that this distance (5.16 Å) is related to the presence of the B-type double helix structure, organized in crystalline regions. The peak at 4.49–4.50 Å (Fig. 2) can tentatively be ascribed to the pitch of helix coils stabilized by H-bonding (calculated length 5–5.7 Å).

The presence of the 6.94–7.34 Å peak can be ascribed to the V-type single helix and the continuous shift at higher clds associated with a larger structure (pseudo V-form) of CL-amylose. The V-type helix is a form of order existing in both crystalline and amorphous regions (Veregin et al., 1987). The overall diffraction patterns for increasing cld become broader (possible overlap of peaks corresponding to larger structures).

In order to elucidate the significance of the 6.94–7.34 Å shift, additional X-ray diffractograms were recorded with the carboxymethyl amylose (CM–CLA-20) derivative, in both sodium salt (carboxylate, $-COO^-Na^+$) and protonated (–COOH) forms. These two forms were different from each other and different from the non-derivatized CLA-20, in terms of X-ray pattern and water retention. Both forms of CM–CLA-20 showed large and diffuse X-ray peaks suggesting lower crystallinity than CLA-20. Interestingly, CM–CLA-20 (protonated) showed a shift of the peak at 7.34 Å (for CLA-20) to 7.45 Å, while for the sodium salt, the shift was even higher, up to 7.93 Å (Fig. 2, insert). Thus, CM–CLA-20 acidic and salt forms, showed a low crystallinity and high water retention and swelling. The sodium salt of CM–CLA-20, had the highest water retention and swelling volume (90 ml/g), while for the protonated form the swelling was of 28 ml/g. Previous studies on amylose crystallinity pointed out that with the transition from anhydrous (V_a) to hydrated (V_h) single helix, a displacement to smallest angular range was observed and correlated with a larger structure (Zobel et al., 1967). Thus, it is possible to assume that amylose derivatization may be correlated with the X-ray peak shift, corresponding to the larger size in the structure. This peak (6.94–7.34 Å) can, in certain limits, be ascribed to single helix (type V), which becomes larger when new functional groups are grafted on the chains. These data support our hypothesis that increase in cld and substitution can generate a transition from helix to random coil of the polysaccharidic chains.

The X-ray data for powders and tablets can be correlated with the drug release kinetics. The longest theophylline release times were obtained with CLA-6 compared to the other CLAs (Fig. 1). The CLA-6 presented a moderate crystallinity, where both B- and V-type diffraction patterns were found (Fig. 2) and showed the smallest size (6.94 Å) for the V-type structure. Hydrogen bonding is known to be greatly

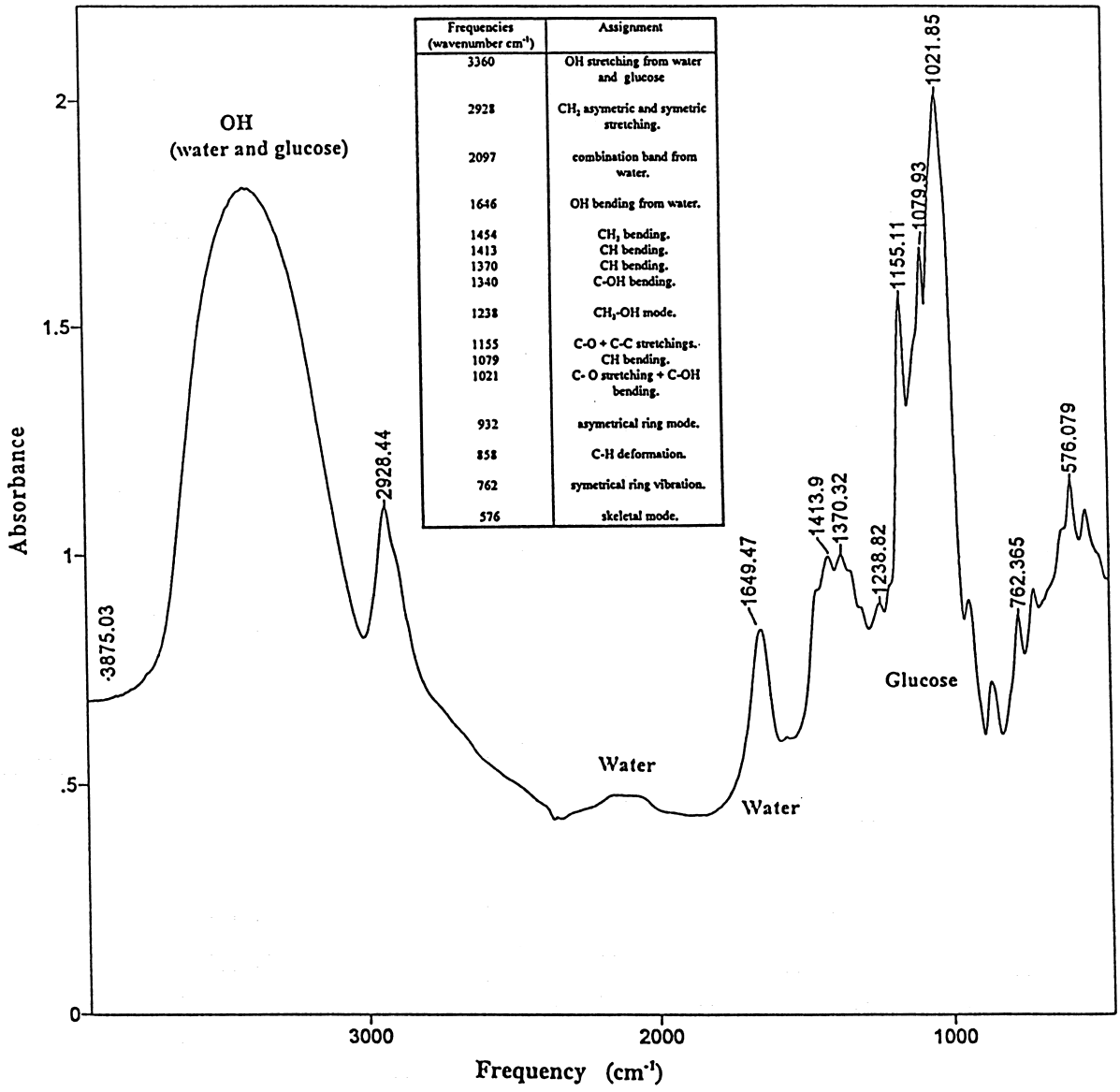


Fig. 3. Typical FT-IR spectrum of CLA-6 with the assignment of the main bands.

involved in amylose and starch crystallinity (Brisson et al., 1991; French, 1984; Imberty et al., 1988). Since the longest release times were obtained with low cld (CLA-6), which shows a higher degree of crystallinity when compared to CLAs with higher clds (more amorphous), these results suggest that a structure with a low chemical modification (having the higher ordered organization) is desired for good drug controlled release properties. Low cross-linked amyloses, with higher chain mobility (i.e. CLA-6), have a higher availability to assume conformations in which hydrogen bonding are greatly involved (Scheme 1). A high cld limits the chain flexibility. Furthermore, a high density of interchain glycerine bridges (calculated length of 8.64 Å, Mateescu et al., 1984), will not allow the chain stabilization by hydrogen bonding (as hypothetically presented in Scheme 1). Thus, these high cross-linked amyloses have many hydroxyl groups free to hydrate and swell. This water can be easily lost and is different from the water retained in the helix channels (i.e. 36 molecules per elementary cell for B-type form). In fact, B, A and V high crystalline forms are more hydrated than less crystalline conformations which, however, can easier be hydrated or dehydrated.

Since the starting material was high amylose starch, cross-links are also possible between amylose and amylopectin polysaccharidic chains (Marchessault et al., 1998; Lenaerts et al., 1998). It is known that amylopectin is responsible for native granular starch crystallinity (French, 1984). In the CLA synthesis the initial order of the high amylose starch is disrupted and it is possible that after gelatinization, cross-linking and drying, amylopectin could assume another role. Being large and branched, amylopectin may indeed prevent the amylose chains from coming close to each other and

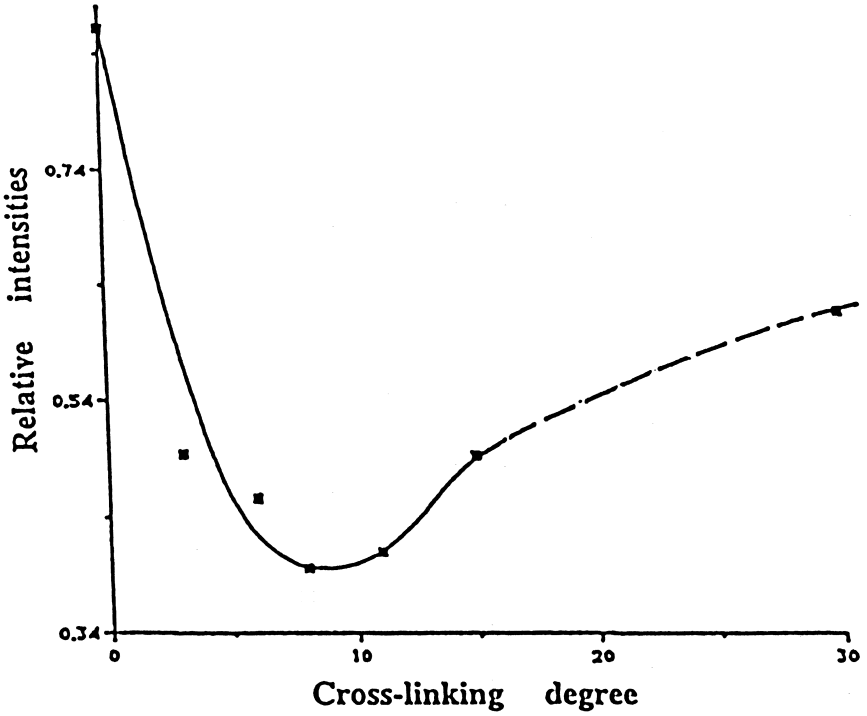


Fig. 4. Relative intensities of FT-IR water deformation vibration mode ($A_{1646cm^{-1}}/A_{2928cm^{-1}}$) as a function of cross-linking degree. Before tableting in KBr the powders were dried at 105°C for 24 h.

from reaching an advanced ordered structure (type B double helix). Hence, the ratio amylose/amylopectin could be an important parameter for the tri-dimensional structure and for drug control release properties. Previous data has shown that cross-linked starch or cross-linked amylopectin alone are not adequate for release control. Aspects of optimal ratio amylose/amylopectin will be dealt with in a further note.

For increasing values of cld from CLA-6 to CLA-20 powders, the diffractograms show a loss in crystallinity, which can explain the low potential to form double helix structures (gelification) and thus the faster hydration of the matrix. This is consistent with the reported short release times and poor mechanical stability for CLA of higher clds (Lenaerts et al., 1991).

3.1.2. CLA tablets

For tablet forms, only a diffuse peak at 4.5 Å can be observed for all the CLA types (Fig. 2), irrespective of the cld, clearly indicating a loss in crystallinity (compared to the corresponding powders). A unique diffuse peak signifies that after compression, the size around 4.49–4.50 Å becomes predominant in the tablet network, while the other size elements observed in powders (i.e. 6.94–7.43 Å) become negligible. Only for tablets made from CLA-20 (high cld) was an additional low peak observed (at 15°, corresponding to 7.04–7.10 Å).

The native high amylose starch tablet form showed the same loss of crystallinity in comparison to powder. For the tablets, the X-ray profile is diffuse, with a maximal peak (18–20°) corresponding to a size of 5.16 Å, and a minor one, corresponding to 4.49 Å (similar, but not identical to the powder profile). Native amylose tablets differ also to the CLA tablets. Diffractograms suggest that native amylose tablets still retain elements of double helix (B-type), but to a lesser extent than the powder. Despite the relative high degree of crystallinity, native amylose is not a good matrix for drug controlled release (in fact, it is known as a tablet disintegrant [Trubiano, 1983]. Covalent stabilization of gelatinized high amylose starch in addition to physical stabilization, seems to be essential for good release profiles. These can be obtained only with low cross-linked CLA-6 tablets.

3.2. FT-IR analysis

The availability of hydroxyl groups to be involved in a dynamic exchange with water is known to affect the three-dimensional structure and the network properties. It was of interest to evaluate by FT-IR analysis whether physical associations are involved in the CLA network stabilization. FT-IR absorbance spectra have been used to record the hydration state of these polymers. Fig. 3 shows a typical FT-IR spectrum of CLA in KBr pellets. The main IR bands and their tentative assignments are summarized in the insert (Fig. 3). Vibrational modes of amylose are known to be very

similar to the ones of glucose (Vasko et al., 1972; Cael et al., 1973) and occur at approximately the same frequencies. This assumption could be extended to CLA. The main IR features remain identical to those reported in Fig. 3, whatever the clds. The spectra are dominated by a broad band assigned to the stretching vibration modes of HO-groups from water and from polymer, at ca. 3360 cm^{-1}. This band tends to broaden and becomes more and more asymmetric when the cld increases. However, these variations can not be directly assigned to variations in H-bonding or water concentration as there is an overlap of these vibrations. Other IR domains give more valuable information on the hydration state of the polymers. With the increase in clds, a staggered band due to the libration mode (libration is a lattice mode of vibration) of water molecules appears below 1000 cm^{-1}, indicating that the water content increases. This is confirmed by the rising of the broad profile observed at ca. 2200 cm^{-1} which originates from the mixing of this libration mode and the bending mode of water. This particular vibration is known to be proportional to water concentration and has been used as an internal standard for water subtraction (Dousseau et al., 1989). Unfortunately, this signal is rather weak and cannot be used, in our case, to reliably evaluate the water content. Therefore, the absorbance of the bending mode of water detected at 1646 cm^{-1} was chosen, even if it is known to be slightly sensitive to H-bonding. The plot of the normalized absorbencies of this vibration (Fig. 4) as a function of clds shows that the water content strongly depends on the cld. It was found that for low-moderate clds (from 6 to 11) the polymers exhibit the lowest water content and, after a minimal value, the H_2O content increases again for clds greater than 15. Calculations of normalized absorbencies were realized by dividing the intensity of the peak at 1646 cm^{-1} by the intensity of the peak of CH_2 modes at 2930 cm^{-1}, used as an internal standard (described in the experimental section).

The FT-IR data are in line with the X-ray results showing that for low clds, interchain H-bonds are favoured, possibly tending to further double helix formation and thus reducing the number of hydroxyl groups which can interact with free water. For larger clds, the interchain glyceric bridges create a rigid network with periodic chain sections which may promote water penetration, enhanced by the availability of the free hydroxyl group to hydrate and to swell. Except for the water modes, the other IR bands are of little help as they are poorly resolved.

3.3. Water evaporation kinetics

Evaporation kinetics can give information on the water state, important for a better understanding of the network organization. At room temperature (18–22°C) and humidity, all CLA samples (stored in closed glass bottles) contained between 7 and 11% water. The upper value is consistent with reported results for native amylose, known to retain 10–17% water, depending on structural features and storage conditions (French, 1984).

The plot of percentage of free water lost at half-time evaporation as a function of cld (Fig. 5) has a similar shape as the one derived from the IR data (Fig. 4). The minimum observed for CLA-6–CLA-11, supports the fact that water retention is relatively low when the polysaccharidic chains are involved in a double helix formation. Hydroxyl groups being involved in these physical interactions allow only a limited water uptake. Then, for increased clds, the water loss was higher (Fig. 5(a)).

The evaporation rate also provides valuable information. Evaporation data follow a first order kinetics model and the evaporation half-time ($t_{1/2}$ H_20) has been calculated (Dumoulin et al., 1991). The evaporation half-time represents the time required to evaporate 50% of the total content of water. The plot of this parameter as a function of cld (Fig. 5(b)) also exhibits a minimum which coincides with the IR (Fig. 4) and water loss (Fig. 5(a)) data. This is an argument that the water concentration is minimal for intermediate–low clds, as already quoted. From the evaporation rate, it appears easier to remove water from intermediate–low clds than from highly cross-linked amylose. Consequently, the highest percentage of absorbed water is with crystalline amylose (gelatinized, not cross-linked or at very low cld). When cld increased to low and moderate values, there was less crystallinity and less hydration, while at high cld more water can be changed. This is due to the fact that water can only form H-bonds with exposed, available HO groups (frequent in highly cross-linked CLA); for low cross-linked CLA tablets, a larger number of HO-groups are involved in intramolecular H-bonding and therefore are less available for hydration.

4. Conclusions

X-ray diffraction analysis of the chemically modified high amylose starch, conducted in our specific conditions, clearly indicates that the gelatinization and the chemical modification of amylose result in the transition from B form of native amylose (double helix) to a predominant pseudo V form and more amorphous structure of CLA. The structure disorganization is enhanced for CLA powders at increasing cld. The morphological evolution followed by X-ray diffraction analysis was successfully correlated with the release control properties of the CLA materials.

FT-IR data, showing low free water retention for low cross-linking, are consistent with the hypothesis that for CLA of relatively low cld, the amylose chains are more available to be involved in a double helix conformation which is more resistant to hydration. Thus,

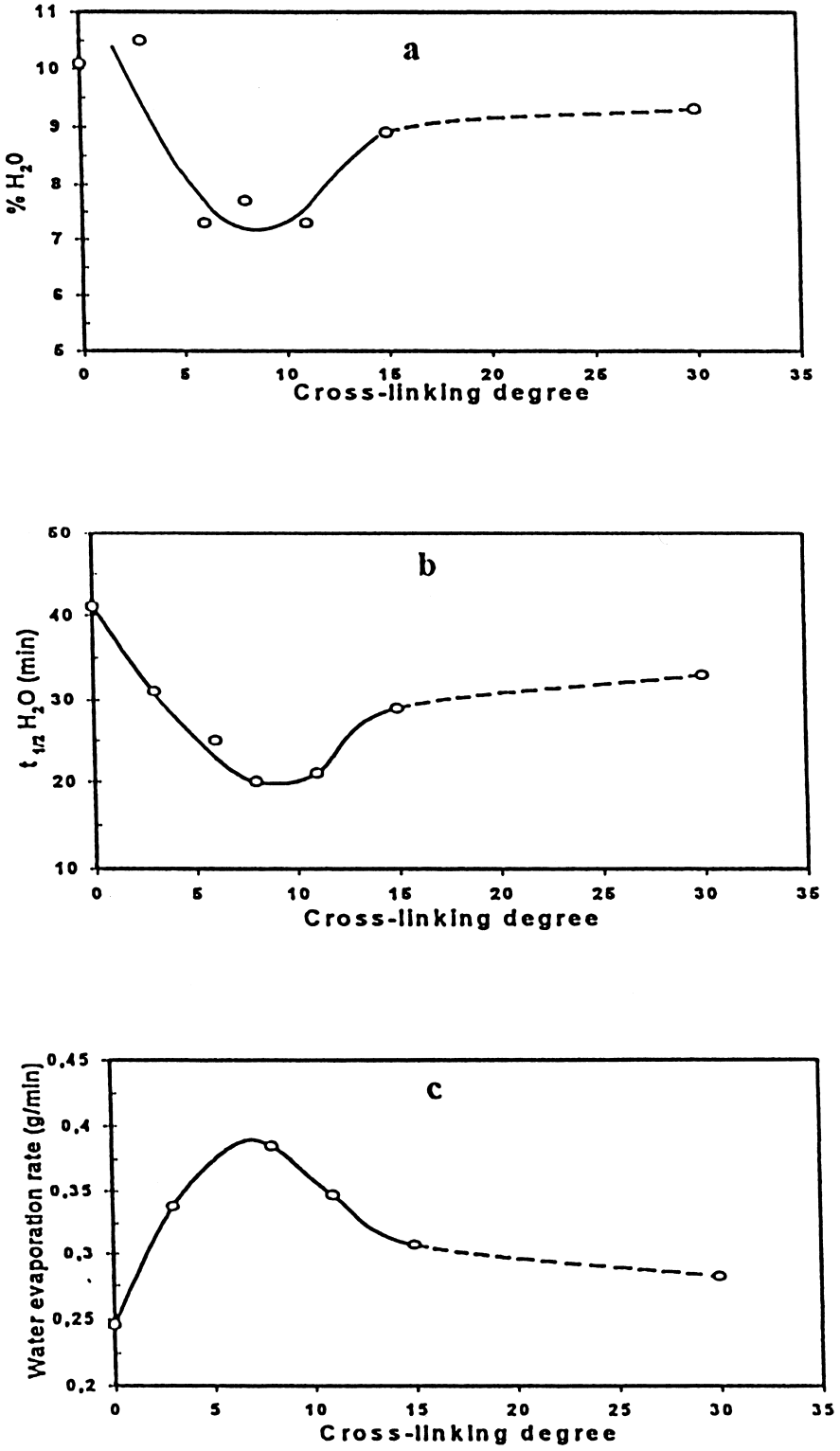


Fig. 5. Water evaporation kinetics: water percentage lost (a) and evaporation (b) at half-time drying of CLA powders (at 50°C in owen) and the evaporation rate (c), as a function of the cross-linking degree. Prior to drying, samples were exposed for 24 h at 50°C in a closed vessel saturated in water vapors.

the water retention is the lowest for CLA of low–moderate cld.

Water evaporation kinetics have shown that networks of CLA of high cld are able to retain more water and the rate of free water loss is the lowest for these powders. The morphological differences between CLA of various clds, were correlated successfully with the drug control release properties of CLA tablets obtained by direct compression.

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