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# Effect of some physical parameters on the swelling properties of cross-linked amylose matrices

Iskandar S. Moussa [a], Vincent Lenaerts [b], Louis H. Cartilier [a,*]

[a] *Faculté de Pharmacie, Université de Montréal, C.P. 6128, Succ centre-ville, H3C 3J7 Canada*
[b] *Labopharm Inc., 1200 boul. Chomedey, Laval, Québec, H7V 3Z3, Canada*

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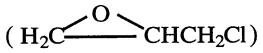
**Abstract**

The influence of compression force (CF) on initial tablet porosity and water uptake kinetics in cross-linked amylose (CLA) matrices was determined by mercury intrusion and gravimetry, respectively. Major changes in tablet porosity and pore size distribution occurred in the CF range of 1–5 T with little or no effect on the gelation properties of CLA matrices. Compression properties of CLA tablets were also characterized by electron scanning microscopy. The presence of macrovoids within micro- or non-porous regions was observed. This may reflect a certain fragmentation taking place in addition to plastic deformation during compression. The effect of pH, ionic strength and osmolarity of the medium on the uptake properties of CLA tablets was also evaluated. Although the swelling profiles of CLA matrices were found to be independent of pH (1.4–8) and of medium osmolarity (0–0.1 M sucrose solutions), a significant drop in the swelling capacity of tablets was observed with increased NaCl concentration. This decrease—not related to ionic interactions—may be due to changes in the gelation properties of the polymer. 

*Keywords:* Compression force; Porosity; Water uptake kinetics; Cross-linked amylose matrices

## 1. Introduction

Polymers are widely used as systems for controlled drug delivery in various pharmaceutical applications, especially in oral drug delivery. Among those polymers used, the biocompatibility and biodegradability of polysaccharides have favored them as systems for oral drug delivery (Kost and Shefer, 1990). Cross-linked amylose (CLA) is a semisynthetic polymer that was introduced as a novel excipient for controlled release of drugs in solid dosage forms in 1991 (Lenaerts et al., 1991). It is produced by the reaction of epichlorohydrin



* Corresponding author. Tel.: +1 514 3432470; fax: +1 514 3432102.

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with high-amylose starch in an alkaline medium, with amylose being essentially a linear polymer of glucopyranose units with $\alpha$-D-(1→4) linkages (Banks and Greenwood, 1975). Different degrees of cross-linking can be obtained by varying the ratio of epichlorohydrin to amylose in the reaction vessel.

The process of water transport into hydrophilic polymer matrices and the corresponding dimensional changes that occur have a major influence on the profile of drug release from these matrices (Colombo et al., 1995; Moussa and Cartilier, 1995, 1997). Consequently, understanding and characterizing the various aspects that may affect the hydration properties of CLA matrices would allow us a better tailoring of drug release from these polymeric systems.

CLA tablets are prepared by direct compression and are highly resistant to mechanical stress in the dry state (Dumoulin et al., 1994). Although CLA matrices are prepared by direct compression, no study has so far addressed the influence of compression force on pore size distribution and its relationship to the hydration properties of the matrices. In addition, swelling and release studies so far have been carried out in aqueous medium without taking into account the influence of medium composition on the hydration properties of CLA matrices.

The aim of the present study was to analyse the compression and swelling properties of CLA matrices over a large range of compression forces, as well as to explore the influence of swelling medium composition, such as pH, ionic strength and osmolarity on the hydration kinetics of CLA matrices. Analysing these properties would allow us a better understanding and better application of CLA as polymeric systems for controlled drug release.

## 2. Materials and methods

### 2.1. CLA synthesis

Corn amylose (300 g, Amylose Hylon VII, National Chemical Starch) and sodium hydroxide (1.8 l, 1.0 N, 54°C) were mixed in a planetary mixer (Hobart Model N-50, USA). After homogenization (15 min), epichlorohydrin ($d_4^{25} = 1.1750$; 15.3 ml) was slowly added with continuous homogenization (15 min). The CLA gel was then neutralized with acetic acid and washed three times through a Büchner funnel with a solution of water:acetone (60:40 v/v). In the final step, the resulting solid gel was washed and dried with pure acetone over a Büchner filter. The polymer was then exposed to air (72 h) and stored in hermetic glass bottles. Granulometric fractions between 75 and 250 $\mu$m were used to prepare the tablets. By convention, this polymer is referred to as CLA-6, with 6 being the amount in grams of epichlorohydrin added per 100 g of amylose. CLA-8 was synthesized under exactly the same conditions except for the amount of epichlorohydrin added.

Granulometric fractions between 75 and 250 $\mu$m were used to prepare the tablets. An extensive study of the influence of CLA particle size upon the in vitro dissolution profiles from CLA simple matrices has already been done (Zolia, 1994). No significant variation in drug release profiles was observed between granulometric fractions in the range of 45–250 $\mu$m.

### 2.2. Tablet preparation

Tablets consisting of CLA powder were directly compressed in a manual pneumatic press (Research and Industrial Instruments Company, UK). Flat disk-shaped tablets 1.295 cm in diameter were produced.

### 2.3. Matrix hydration measurements

CLA tablets were suspended in an aqueous medium (1 l) at a constant temperature of 37°C on a metal mesh in such a way that swelling could occur three-dimensionally with water penetrating all sides of the tablets (Moussa and Cartilier, 1996). These conditions were similar for all hydration experiments reported in the present study.

At appropriate time intervals, each tablet was removed from the hydration medium with forceps, briefly patted with lint-free cleaning tissues to remove the solution wetting its surface, and then weighed. All measurements were done at

least in triplicate. Complete hydration conditions were considered when the change in subsequent water uptake measurements was less than 0.5%. Enough time was left between each measurement to account for any possible discontinuous absorption phenomena.

The influence of compression force (CF) on water uptake profiles was studied on CLA-8 matrices (400 mg) swollen in deionized water as swelling medium.

The influence of ionic strength on water uptake profiles was studied on CLA-8 matrices (350 mg, 2 T CF) swollen in aqueous NaCl solutions of different concentrations (0, 0.01 and 0.1 M). No buffer was used, so the value of ionic strength would correspond to that of NaCl molarity.

The influence of osmolarity on water uptake profiles was studied on CLA-8 matrices (350 mg, 2 T CF) swollen in aqueous sucrose solutions (with no buffer) of different concentrations (0, 0.01 and 0.1 M).

The influence of pH on water uptake profiles was studied on CLA-8 matrices (350 mg, 2 T CF) swollen in buffer solutions of different pHs (1.2, 3.6, 5.8 and 8.0). The standard buffer solutions were prepared as described in USP XXI. Zeta ($\zeta$) potential measurements were taken as an indirect measurement of the surface charge of the polymer as a function of pH. A total of 30 mg of CLA-8 powder were dispersed in 20 ml of USP buffer solutions of different pHs, containing sucrose as a suspending agent. A sonication of 30 min preceded the measurement of $\zeta$ potential using a Delsa 440SX (Coulter Electronics, FL).

### 2.4. Measurements and characterization of tablet porosity

Porosity of CLA-6 tablets (400 mg) was determined by mercury intrusion with a Micrometrics Poresizer 9320 between 0.5 and 30000 psi. Pores with a diameter below 3 nm cannot be accounted for by mercury porosimetry (Smith et al., 1994). The nomenclature used to define size dimensions is based on the specific nomenclature recommended by IUPAC (International Union of Pure and Applied Chemists) (Gregg and Sing, 1982; Schaefer, 1994).

Samples for scanning electron microscopy (SEM) analysis were prepared by gold-plating the fractured surface of CLA tablets prepared at different compression forces. Imaging of the samples was carried out on a JEOL JSM 840 electron scanning microscope.

## 3. Results and discussion

### 3.1. Effect of compression force on tablet porosity and water uptake kinetics

The pore size distribution of the tablets was measured using mercury intrusion technique over a range of compression forces. Fig. 1 shows the pore size distribution in non-hydrated CLA-6 tablets at four different compression forces. In order to be able to cover a very broad pore size distribution (PSD), the log-differential distribution (rather than incremental intrusion) was plotted as a function of pore diameter. The log-differential distribution corresponds to $dV/d\log_{10}(d)$, where $V$ is the intrusion volume and $d$ is the corresponding pore diameter (Smith et al., 1994).

At a compression force (CF) of 1 T, the pore size distribution was very large with pores ranging from over 100 $\mu$m down to below 7 $\mu$m. A large portion of tablet porosity corresponds to the presence of macropores in the range of 0.06–2 $\mu$m as well as another distribution of small pores of a diameter of about 10 nm. The presence of a large amount of macropores would explain the relatively high porosity of the matrix at a CF of 1 T. The total porosity ($\varepsilon_{total}$) of the tablets was evaluated based on $\varepsilon_{total} = TIV^{*}\rho_b^{*}100$ where $TIV$ is the total mercury intrusion volume and $\rho_b$ is the estimated bulk density of the tablet.

An increase in CF from 1 to 3 T led to a sharp drop in average pore diameter (APD) from around 90 nm to less than 30 nm as well as a decrease in tablet porosity to less than 7% (Table 1). This significant drop of more than 60% in APD and more than 50% in tablet porosity may be attributed to quasi-elimination of pores greater than 0.8 $\mu$m in diameter. At a CF of 3, two pore size distributions are, however, still apparent: one

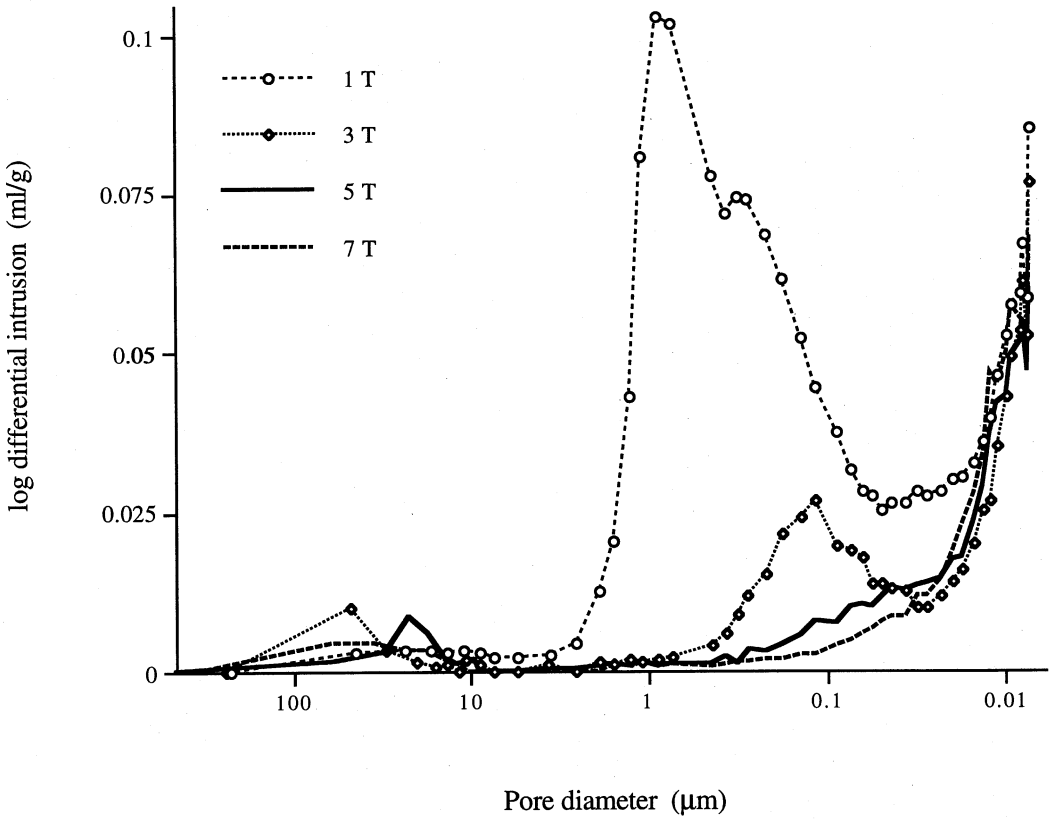


Fig. 1. Influence of compression force on pore size distribution in CLA-6 tablets prior to hydration, as measured by mercury intrusion porosimetry.

around 150 $\mu$m and another more pronounced at below 30 nm diameter.

Increasing the compression force from 3 to 5 T seemed to be adequate to reduce tablet macroporosity by decreasing pore size mainly to below 50 nm. Further increasing CF to 7 T seemed to offer little advantages for further tablet porosity reduction. However, from Fig. 1 the presence of large voids within the tablets may be observed. These macrovoids, characterized by a pore size larger than 10 $\mu$m seemed to vary little over a CF range of 1–7 T.

Table 1
Influence of compression force on initial tablet porosity in CLA-6 tablets

| Compression force (T) | Average pore diameter (nm) | Total tablet porosity (%) |
|---|---|---|
| 1 | 89 | $16 \pm 1$ |
| 3 | 27 | 7 |
| 5 | 19 | 5 |
| 7 | 17 | 5 |

Electron scanning microscopy analysis of transversal sections of CLA matrices prepared at different CFs shows that progressive plastic deformation occurs with increased compression force. At low CF (1 T; Fig. 2a) individual particles and large interparticle voids can be easily identified. At higher CFs (5 T; Fig. 2b) individual particles cannot be detected even at much larger magnifications. However, the presence of macrovoids percolating within micro- or non-porous regions of the tablets can be observed at high compression forces (Fig. 2b). These large voids (also characterized by mercury intrusion data) may correspond

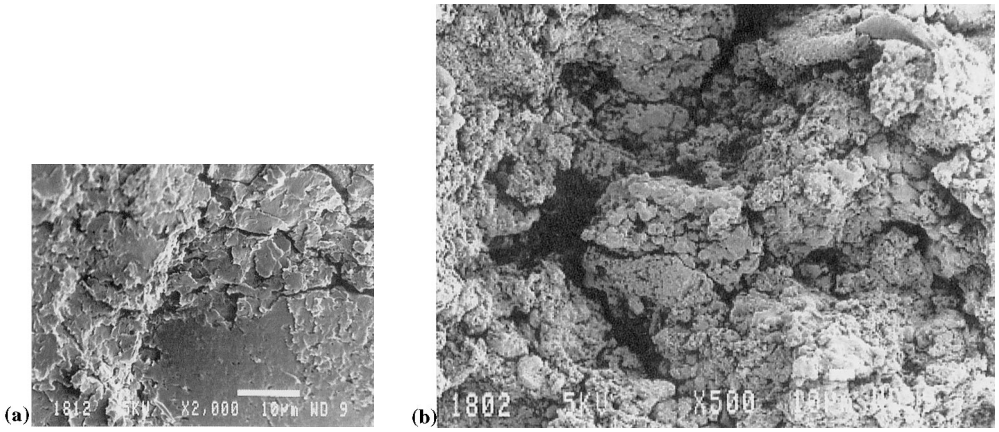


Fig. 2. Electron scanning micrographs of transversal sections of CLA-8 tablets prepared at compression forces of 3 T (a) and 5 T (b).

to fractures occurring due to a certain fragmentation of the material under compaction load.

The preliminary data generated in the present study are sufficient to demonstrate that increasing the CF (from 1 to 7 T) causes major changes in the pore size distribution and in the porosity of CLA matrices. Hence, by evaluating the water sorption kinetics in CLA matrices as a function of CF we were able to evaluate the relative effect of initial tablet porosity on the swelling properties of CLA matrices.

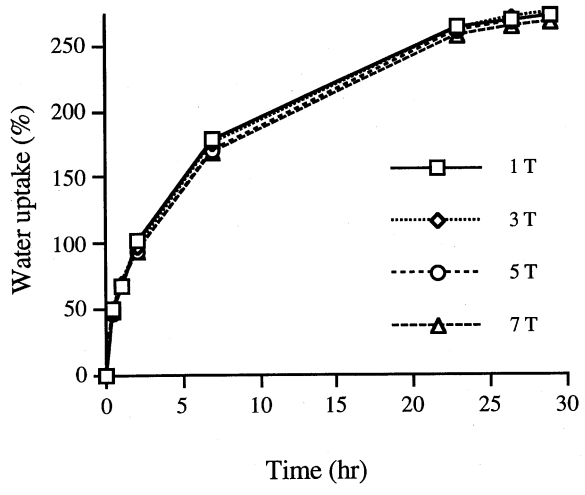


Fig. 3. Influence of compression force on the water uptake profiles of CLA-8 tablets.

Fig. 3 corresponds to water uptake profiles of CLA-8 matrices at different values of CF. The percentage water uptake was calculated as $(p - p_0)/p_0^*100$ where $p$ and $p_0$ are the tablet weight at time zero and at selected hydration intervals, respectively. While the gelation properties of higher plants hydrocolloidal matrices are drastically affected by a change in compression (Kuhrts, 1992), CLA matrices displayed identical swelling kinetics regardless of the compaction forces (between 1 and 7 T). Although the diameter of pores at 1 T was relatively large compared to that at higher CFs (Fig. 1), tablets appeared not to gel faster, since no lag-time in matrix hydration was observed (Fig. 3).

### *3.2. Influence of ionic strength, pH and osmolarity of the medium on the uptake properties of CLA tablets*

The influence of ionic strength of hydration medium on the gelation properties of CLA matrices was studied in order to evaluate its impact on the performance of CLA as matrices for controlled release. CLA-8 tablets were therefore suspended in NaCl solutions of different ionic strengths (0, 0.01 and 0.1) and the water uptake values were recorded at appropriate time intervals. Fig. 4 describes the obtained water uptake profiles. The addition of NaCl to the hydration medium seemed to affect the gelation properties

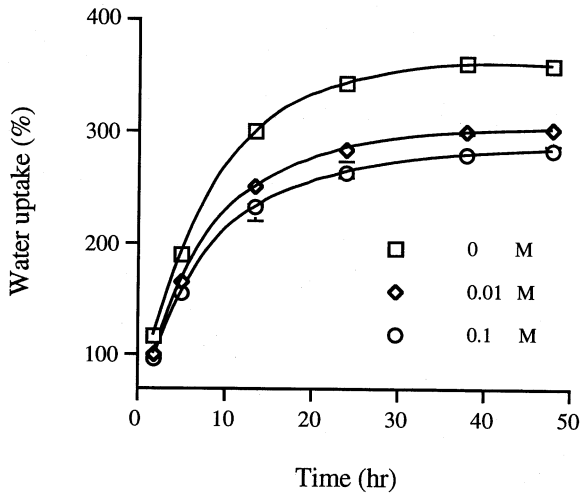


Fig. 4. Influence of the NaCl concentration (M) in swelling medium on the water uptake profiles of CLA-8 matrices.

of CLA-8 matrices. The rate of water uptake progressively decreased with a rise in NaCl concentration. The equilibrium swelling capacity (%) of the matrices decreased by more than 15% (from $359 \pm 2$ to $302 \pm 2\%$) in 0.01 M NaCl compared to deionized water. An additional decrease of 7% was observed when the NaCl concentration was increased to 0.1 M.

To verify whether this difference was related to osmotic pressure changes, CLA tablets prepared under identical conditions were swollen in aqueous solutions containing different concentrations (0 to 0.1 osmol) of a non-ionizable substance. Results of the water uptake profiles of CLA-8 tablets swollen in sucrose solutions (Fig. 5) of different osmolalities showed an independence of the gelation properties of CLA-8 matrices from medium osmolality up to 0.1 osmol.

Based on a $pK_a$ value of $\alpha$-D-glucose of 12.1 (Martin, 1993), negligible ionization of CLA chains would be expected at a pH around 7. Hence, the observed effect of NaCl concentration on the gelation properties of CLA matrices would not be primarily related to the charge of the polymer chains of cross-linked amylose.

The swelling properties of CLA matrices were then tested at different pH values and the $\zeta$ potential values measured. Results obtained showed identical hydration properties of CLA-8 matrices, and no measurable ionization over the pH range of 1.2–8 (Table 2). The absence of detectable charge on the polymer chains of cross-linked amylose, although not surprising considering the $pK_a$ value of $\alpha$-D-glucose ($pK_a = 12.1$) (Martin, 1993), implies that ionic interaction would not explain the effect of NaCl concentration on the gelation properties of CLA-8 matrices (Fig. 4). The observed results may be, however, extrapolated to some reports by other authors on possible interactions between starch and electrolytes (Evans and Haisman, 1982). These authors found that low concentrations of sodium chloride ( $< 1$ M) slightly increased the gelatinization temperature of starch. The role of electrolytes seems complex and several observations have been proposed to explain starch behaviour in presence of electrolytes (Biliaderis, 1991). In the case of CLA, more work and information are required in order to better understand the mechanism of these interactions.

## 4. Conclusions

Preliminary mercury intrusion porosimetry and electron scanning microscopy indicate a loss in CLA tablet macroporosity when CF is raised to

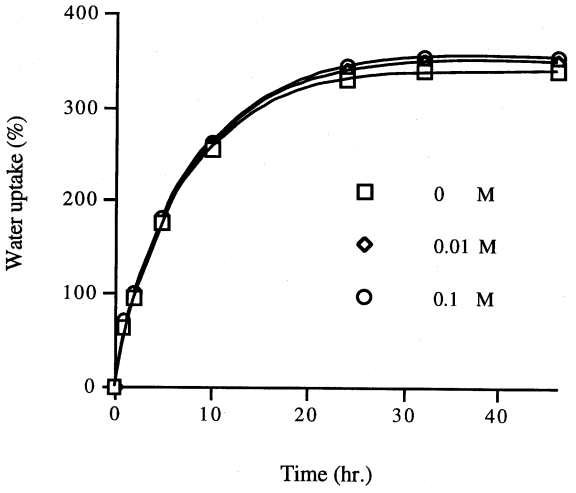


Fig. 5. Influence of sucrose concentration in swelling medium on the water uptake profiles of CLA-8 matrices.

Table 2
Respective water uptake and $\zeta$ potential values of CLA-8 matrices as a function of pH

| pH | Water uptake ± S.D. (%) ($n = 4$) | | | $\zeta$ Potential (mV) ± S.D. |
|---|---|---|---|---|
| | After 5 h | After 8 h | After 78 h | |
| 1.2 | 178 ± 1 | 224 ± 1 | 313 ± 3 | −2 ± 7 |
| 3.6 | 190 ± 1 | 242 ± 2 | 314 ± 1 | −1 ± 2 |
| 5.8 | 182 ± 2 | 230 ± 1 | 295 ± 2 | N/A |
| 8.0 | 192 ± 1 | 244 ± 2 | 321 ± 3 | −1 ± 2 |

more than 3 T. The decrease in porosity seems to occur by plastic deformation of the material under compaction load. The presence of large cracks greater than 10 $\mu$m in diameter was observed at different CFs (1–7 T) indicating that the material may be also exhibiting some fragmenting properties during compression.

Within the range of compression forces covered, the gelation properties of CLA-8 matrices were to a large extent independent of initial tablet porosity and of compaction load.

The gelation properties of CLA matrices were little affected by the osmolarity and pH of the medium. The presence of NaCl in the aqueous medium affected the gelation properties of CLA matrices by causing a drop in the swelling capacity of CLA matrices with increased NaCl concentration. Additional experiments are needed in order to elucidate the mode of action of electrolytes on the gelation properties of CLA matrices.

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