



Exploring the solid-state phases and thermodynamics of calcium L-lactate

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ABSTRACT

Calcium L-lactate, an organic salt derived from L-lactic acid, is used in many fields such as food, pharmaceutical or cosmetic industry. To this date, its solid-state thermodynamics are still poorly understood: a pentahydrate crystalline and anhydrate amorphous forms were already characterized, and potential other hydrates mentioned in literature. For the development of a robust crystallization process or down-line handling of this compound, it is important to know and understand the relationship between the different solid forms to prevent uncontrolled crystallization or solid–solid transformation during storage. In this paper, we aimed at identifying and characterizing novel solid forms of calcium L-lactate. Combining analytical techniques, we confirmed the existence of the pentahydrate and an amorphous anhydrate. In addition, we played on temperature and relative humidity conditions to discover three new crystalline forms (a crystalline anhydrate, monohydrate and dihydrate). This paper is the first occasion where these forms were successfully isolated and characterized.

1. Introduction

Calcium L-lactate (CL) is an organic salt derived from L-lactic acid. It is of important economic interest due to its broad spectrum of application. Its use in food industry, under the commercial code E327, is fairly common as it is a GRAS (Generally Recognized As Safe) compound (Kiran-Yildirim et al., 2018). CL intervenes as a texturing agent for food preparations or a preservative due to its antibacterial properties. It is also used as a calcium supplement or to extend the freshness of recently cut fruits (Chemaly, Muhr, & Fick, 1999; Kiran-Yildirim et al., 2018). In addition, CL intervenes in pharmaceuticals to treat calcium deficiency, being a calcium source with an increased solubility and bioavailability compared to other common calcium sources such as calcium phosphate salts, calcium citrate or calcium oxalate (Bolhuis, Eissens, & Zoestbergen, 2001; Levenson & Bockman, 1994; Luan, Wang, Wang, Yang, & Hao, 2014; Martin, Weaver, Heaney, Packard, & Smith, 2002; Sakata, Shiraiishi, Takayama, & Otsuka, 2006; Vavrusova, Munk, & Skibsted, 2013). Its use as an excipient leads to tablet formulations with short disintegration time and rapid drug release, while showing better compaction properties compared to other excipients (Bolhuis

et al., 2001; Sakata et al., 2006).

When dealing with a solid compound in food or pharmaceutical industry, characterizing and understanding its solid-state landscape is crucial. Regulatory instances often require commercialized compounds to be present under a single form. In addition, a lack of control of the solid form during manufacture or storage can lead to unwanted phenomena such as powder caking, deliquescence, chemical degradation or form transition (Newman, Reutzel-Edens, & Zografi, 2008; Rumondor, Wikström, Van Eerdenbrugh, & Taylor, 2011; Sakata et al., 2006). Solid compounds typically present an amorphous or crystalline state. Amorphous forms do not show long-range order of the molecular packing (Hancock & Zografi, 1997) and are characterized by a glass transition temperature, T_g , below which the material is found in a glassy state and above which the material is said to be in a rubbery state (Elamin, Sebhatu, & Ahlneck, 1995). Amorphous phases are thermodynamically unstable and conversion into a crystalline form can occur over time or when molecular mobility is increased (Hancock & Zografi, 1997; Yoshioka, Hancock, & Zografi, 1994). Crystalline states, on the other hand, are characterized by the packing of their constituting elements under a long-range three-dimensional order (Carstensen, 1984). For a

Abbreviations: CL, calcium L-lactate; CLA, calcium lactate anhydrate; CLM, calcium lactate monohydrate; CLD, calcium lactate dihydrate; CLP, calcium lactate pentahydrate; DSC, differential scanning calorimetry; TGA, thermo-gravimetric analysis; DVS, dynamic vapor sorption; (VT-)PXRD, (variable temperature -) powder X-ray diffraction

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given compound different crystalline forms can exist such as polymorphic forms, salts, cocrystals, or solvates (Aitipamula et al., 2012).

The various solid-state forms of CL and the relation between them are still poorly understood. Even though the existence of different hydrates has been mentioned in literature, no actual proof of the existence of most of these has been given. Calcium lactate pentahydrate (CLP) is most frequently referred to, and, to our knowledge, the only crystalline form characterized by X-ray powder diffraction (Tansman, Kindstedt, & Hughes, 2014). Although tetra-, tri-, di- and monohydrate species have also been cited, no experimental evidence of their existence is provided (Cao, Lee, Yun, & Koo, 2001; Ezerskis, 2012; Manzurola & Apelblat, 2002; Sakata et al., 2006). Beside the pentahydrate, an amorphous anhydrate phase is the only other phase evidenced in literature (Bolhuis et al., 2001; Sakata, Shiraishi, & Otsuka, 2005). Identification of novel solid forms can be important for food industry as they potentially present improved stability over time, or behave differently under specific storage or transport conditions. For pharmaceutical industry, the importance is even higher, as novel solid forms of a drug compound can improve dissolution and solubility behavior and hence the bioavailability of a drug compound. In this paper, we propose a better understanding of CL solid-state forms, aiming at providing experimental evidence of the elusive intermediate hydrate phases and trying to understand the respective stability among these forms.

2. Materials and method

2.1. Materials

Calcium L-lactate pentahydrate (98% purity) was provided by Galactic S.A. and used without further purification.

Crystalline CL anhydrate (crystalline CLA) was obtained by applying two successive heating ramps to samples of 14 mg of pure CLP: a first heating ramp to 200 °C at a rate of 2 K min⁻¹ ensured complete dehydration. A successive heating ramp to 230 °C at a rate of 10 K min⁻¹ allowed the dry sample to undergo successively a glass transition and recrystallization. These events were monitored using differential scanning calorimetry (DSC).

2.2. Differential scanning calorimetry

DSC analysis was performed on a TA instrument D2500. Samples of approximately 6 mg were placed in a 40 µL aluminum pan. The pan was sealed with an aluminum lid that was perforated with five holes to ensure the volatilization of water upon heating. Two heating ramps were applied under a constant flow of nitrogen. After an isothermal hold of 5 min at 30 °C the temperature was increased at a rate of 2 K min⁻¹ up to 200 °C. The sample was then cooled down to 30 °C at a rate of 20 K min⁻¹ and held at this temperature for 30 min, after which it was heated once again to 240 °C at a rate of 10 K min⁻¹. The DSC experiment was repeated 9 times.

2.3. Thermo-gravimetric analysis

Thermo-gravimetric analysis (TGA) was performed on a 821e Mettler Toledo. A sample of approximately 6 mg was put in a 70 µL aluminum oxide crucible under a nitrogen flow and gradually heated at a rate of 5 K min⁻¹ from 30 °C to 300 °C.

2.4. Dynamic vapor sorption

Dynamic vapor sorption (DVS) experiments were performed on a TA Q5000 SA instrument. Samples of approximately 6 mg of crystalline CLA, prepared as explained in the "Materials" section, were placed in an open metalized quartz pan. Prior to the analysis, a drying step was performed at 60 °C and 0% relative humidity (RH) for 3 h. The sample was then brought to the temperature of analysis and the RH increased

by steps of 10% up to 90% RH. The RH was brought down again to 0% at 10% steps. If the sample mass variation was lower than 0.01% for 2 h, the next step was initiated, with a maximum of 20 h for each step (unless indicated otherwise). Such analysis was performed at 30 °C and 60 °C.

2.5. X-ray diffraction

Laboratory powder X-ray diffraction (PXRD) measurements were performed on a Siemens D5000 diffractometer equipped with a Cu X-ray source operating at 40 kV and 40 mA and a secondary monochromator allowing to select the K α radiation of Cu ($\lambda = 1.5418 \text{ \AA}$). A scanning range of 2θ values was applied from 2° to 50° at a scan rate of 0.6 min⁻¹ and a step of 0.02°. For variable temperature PXRD (VT-PXRD), a sample of approximately 20 mg was placed in an open pan, without control of RH. The temperature was increased from 30 °C to 200 °C by steps of 5 °C every 10 min, after which the PXRD was acquired.

Synchrotron VT-PXRD data were measured at the Swiss-Norwegian beamline BM1A (SNBL) at the European Synchrotron Radiation Facility (ESRF) (Grenoble, France). A 0.5 mm glass capillary was filled with CLP, sealed with vacuum grease, and exposed to a synchrotron radiation at a wavelength of 0.78487 Å. The capillary was heated between 30 °C and 230 °C at 10 °C/min with a nitrogen blower (Oxford Cryosystems) while accumulating PXRD data on a PILATUS 2 M hybrid pixel detector. PXRD data allowed resolving the structure of the crystalline phase appearing at 99.5 °C. Indexation was performed using the EXPO program, while the structure was resolved by global optimization in direct space (Monte Carlo/parallel tempering algorithm) using the FOX program (Favre-Nicolin & Černý, 2002) and further refined by the Rietveld method in the Fullprof suite. Simulated diffraction patterns were calculated from their crystal structures with the Mercury program (Macrae et al., 2006).

3. Results and discussion

3.1. Thermal analysis

Heating at 5 K min⁻¹ under a continuous nitrogen flow, CLP shows a one-step dehydration (Fig. 1). Dehydration under such a 0% RH atmosphere occurs from the onset of the analysis up until 120 °C and corresponds to a weight loss of 4.5 equivalents of water. The remaining 0.5 equivalent of water is supposed to have been lost already prior to data recording. At 240 °C degradation occurs. Such a single step dehydration process under a continuous nitrogen flow was already observed by Sakata et al. (2005).

A similar result is obtained when analyzing the sample using DSC analysis (1 K min⁻¹). An endotherm with onset at $69 \pm 5 \text{ °C}$ corresponds to the single dehydration of CLP to CLA (Fig. 2a). The heat of dehydration is estimated at $\Delta H = 250 \pm 20 \text{ kJ mol}^{-1}$. As no melting endotherm nor a recrystallization exotherm can be observed, the resulting phase is likely the amorphous dehydrated phase. Cooling this phase to 30 °C and heating it at a faster rate (20 K min⁻¹) allows observing a glass transition temperature at $175 \pm 1 \text{ °C}$, with a small enthalpy recovery signal. Further heating shows a recrystallization exotherm starting at $221 \pm 3 \text{ °C}$ ($\Delta H = 7 \pm 1 \text{ kJ mol}^{-1}$) (Fig. 2b). The measured enthalpy is quite low for a recrystallization. As this event is directly followed by the degradation of the material, it is suspected that the recrystallization is only partial. VT-PXRD analysis confirms this partial recrystallization event to an anhydrous crystalline state as will be discussed later on.

DSC and TGA analyses were all performed under continuous nitrogen flow, and both showed a single dehydration step, only evidencing pentahydrate (crystalline) and anhydrate (amorphous and crystalline) phases. For hydrate phases, however, both the water activity and temperature are crucial factors impacting form stability (Hilfiker,

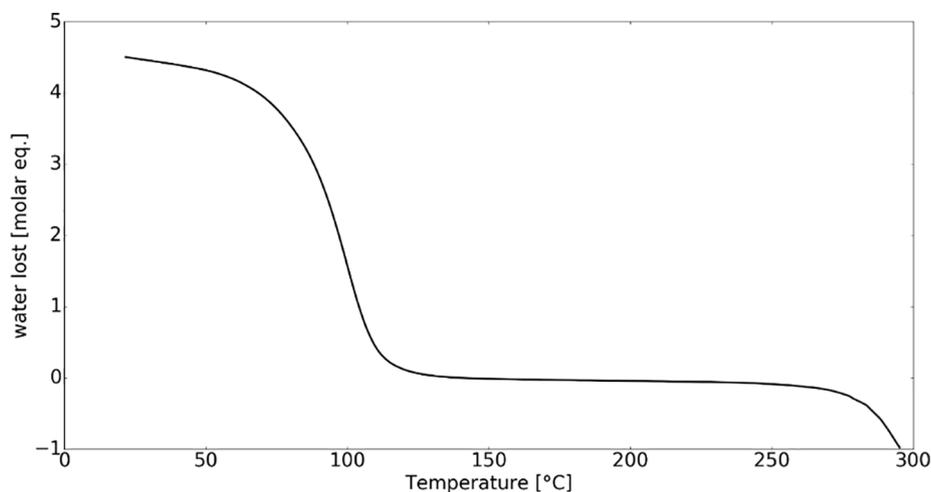


Fig. 1. One-step dehydration of CLP to CLA as recorded by TGA.

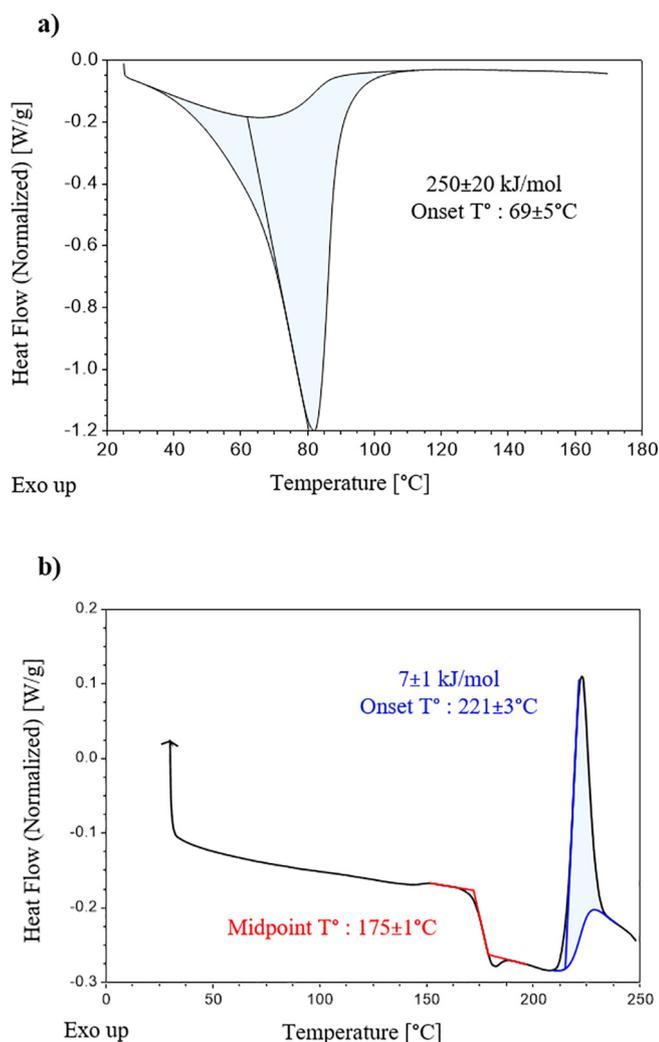


Fig. 2. (a) Endotherm of dehydration of CLP to CLA and (b) glass transition of CLA at 175 °C followed by crystallization at 215 °C.

2006). Therefore, DVS analyses were performed to study the effect of ambient relative humidity on the stability of CL solid forms.

Solid compounds interact with water from air, following three main mechanisms: (i) adsorption on the surface of the solid, (ii) absorption of water with penetration in the bulk of the solid and (iii) liquefaction that

is caused by the dissolution of the solid in the adsorbed water, a phenomenon called deliquescence (Newman et al., 2008). Water absorption is by far more critical than adsorption, as it triggers dramatic changes in the physico-chemical properties of the material. This phenomenon will occur differently for crystalline or amorphous materials. For stoichiometric hydrates, water absorption leads to novel crystalline forms with a strict molecular water ratio (Giron et al., 2002). Hydrate stability will depend on both temperature and relative humidity and the transition between two hydrates or a hydrate and a non-hydrate occurs sharply at a distinct RH, as expected for a first-order transition (Giron et al., 2002; Newman et al., 2008). For non-stoichiometric hydrates, the level of hydration uptake varies in a given range according to experimental conditions. This phenomenon is often due to the existence of pores or channels within a crystal structure where water molecules can be trapped (Edwards et al., 1997; Trask, Samuel Motherwell, & Jones, 2005). Depending on RH and temperature, a given fraction of these pores will be occupied by water molecules. The level of hydration is seen to increase in a gradual manner upon RH increase (Authelin, 2005; Suzuki, Araki, Kitaoka, & Terada, 2012). A similar gradual uptake is also observed for amorphous compounds (Kunz & Gieseler, 2018), with amorphous substances often absorbing significantly more water compared to the crystalline counterparts of the molecule (Rumondor et al., 2011).

A first DVS experiment performed at 30 °C with crystalline CLA as starting material showed a one-step hydration. The uptake of five equivalents of water leads to the crystalline CLP form (Fig. 3a) at 70% RH. Upon humidity decrease, these five equivalents of water are lost at 0% RH, showing the reversibility of the hydration-dehydration process. The resulting anhydrous material was amorphous, as confirmed by PXRD. The remaining traces of water at 0% RH are probably due to water trapped in the amorphous phase. Indeed, as kinetics of water absorption and desorption are particularly slow in this case, the equilibrium was still not reached even after 5 days at 0% RH. However, this water would eventually evaporate over time as long as the water activity of the solid is greater than the relative humidity. Similarly, the value obtained at 70% RH does not correspond to an equilibrium value, as the sample mass was not stable at the end of the 20 h holding time. The equilibrium value would have corresponded to full transformation to CLP, as suggested by water absorption kinetics (see Supporting information). Finally, one should note the strong hysteresis in both curves evidencing the stability of CLP towards dehydration.

In a second DVS experiment, the temperature was set at 60 °C (Fig. 3b). Upon increasing the RH, crystalline CLA gradually absorbs water up to 50% RH due to surface adsorption. At 60% RH, water absorption increases dramatically, with the weight stabilizing at a new weight corresponding to the uptake of two water equivalents.

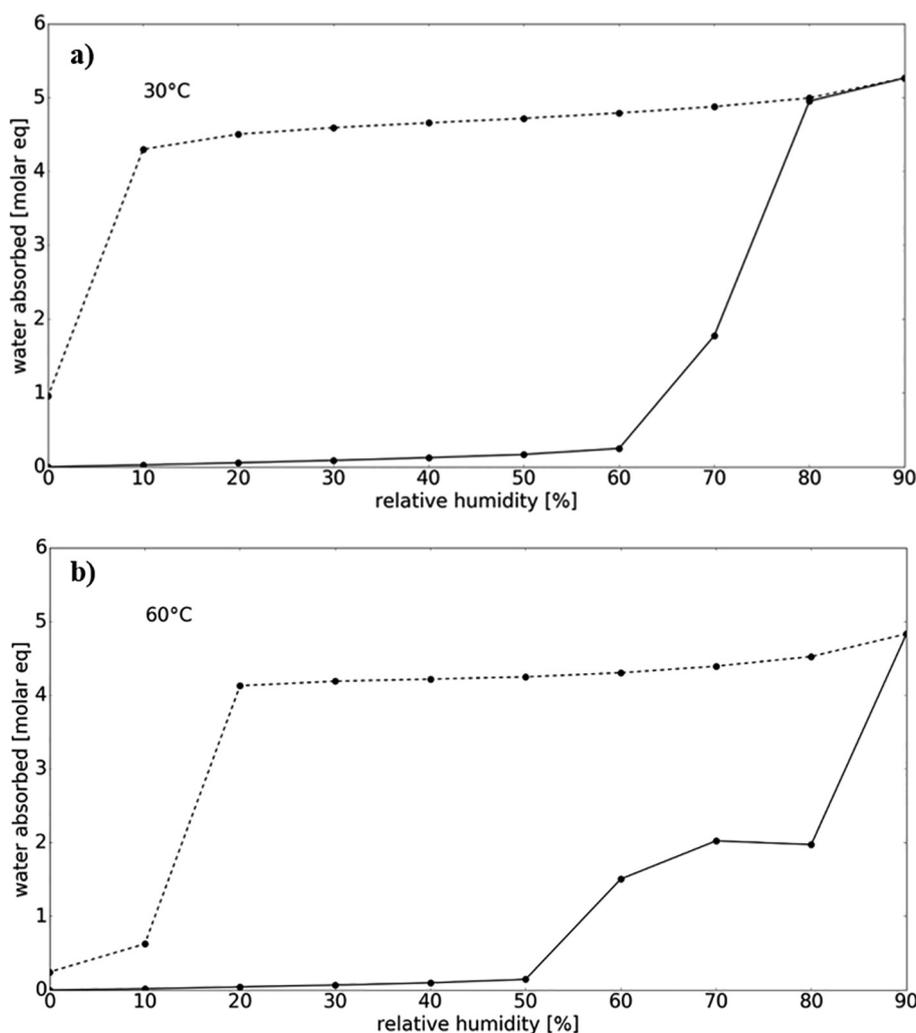


Fig. 3. Sorption (solid line) and desorption (dashed line) isotherms of crystalline CLA at (a) 30 °C and (b) 60 °C.

Hydration kinetics (see [Supporting information](#)) show a water absorption followed by a minor desorption upon RH increase, which is typical for the formation of a hydrated crystal structure. This dihydrated form is stable up to 90% RH at which point a sudden mass increase is observed, corresponding to CLP formation. The dihydrate and pentahydrate forms are likely not isomorphous as such an abrupt transition and absorption of 3 water equivalents is rather typical for the transition between two stoichiometric hydrates. A more gradual transition between both would have been observed if they were isomorphous channel hydrates. Upon RH lowering, the mass decrease is gradual until 20% RH, with less than one equivalent of water being lost. Between 20 and 0% RH, once more 5 equivalents of water are lost to form amorphous CLA.

The DVS analysis at 60 °C reveals the existence of a transitory calcium lactate dihydrate (CLD) between 60 and 80% RH at 60 °C. Formation of this dihydrate therefore requires specific conditions of temperature and relative humidity as it is not observed at 30 °C or under different conditions of RH.

3.2. Structural analysis

X-ray diffraction experiments were conducted at room temperature as well as variable temperature to evaluate structural changes. The CLP diffractogram is similar to the one presented by Sakata et al. ([Sakata et al., 2005](#)). In a first VT-PXRD experiment, performed in a heated open pan on a Siemens D5000 diffractometer, a phase transition was

observed at 80 °C and a new crystalline phase of unknown stoichiometry formed. Further heating led to an amorphisation, evidenced by the lack of well-defined peaks between 100 and 200 °C. At 220 °C, another crystalline form was identified, as new peaks appeared on the diffractogram ([Fig. 4a](#)). This crystallization event at 220 °C is similar to the one observed during DSC analysis and can therefore be attributed to formation of crystalline CLA. The low intensity of the diffraction peaks confirm the relatively low amount of recrystallization occurring, with likely a large part of amorphous material remaining.

A second VT-PXRD experiment was conducted using synchrotron radiation as X-ray source at SNBL/ESRF, Grenoble. A temperature increase from 40 to 230 °C was applied on a sample of CLP placed in a capillary sealed with vacuum grease ([Fig. 4b](#)). Upon heating this sample, a novel intermediate phase was identified between 90 and 150 °C different from the known CLP or CLA forms and from the intermediate observed at 80 °C in the first VT-PXRD experiment. Further heating led to degradation of CL and no recrystallization of anhydrate CLA was observed. The high-quality diffractogram obtained at 99.5 °C during this second experiment allowed determining the crystal structure of the novel intermediate phase, using PXRD-structure resolution. The form corresponds to a stoichiometric monohydrate form as evidenced by the resolved crystal structure (CLM, [Fig. 5](#)), which we are the first to report.

CLM crystallizes in a $P2_1$ space group, with crystallographic data listed in the [Supporting information](#). The crystal structure is essentially formed by coordination bonds that form planes normal to the a -axis.

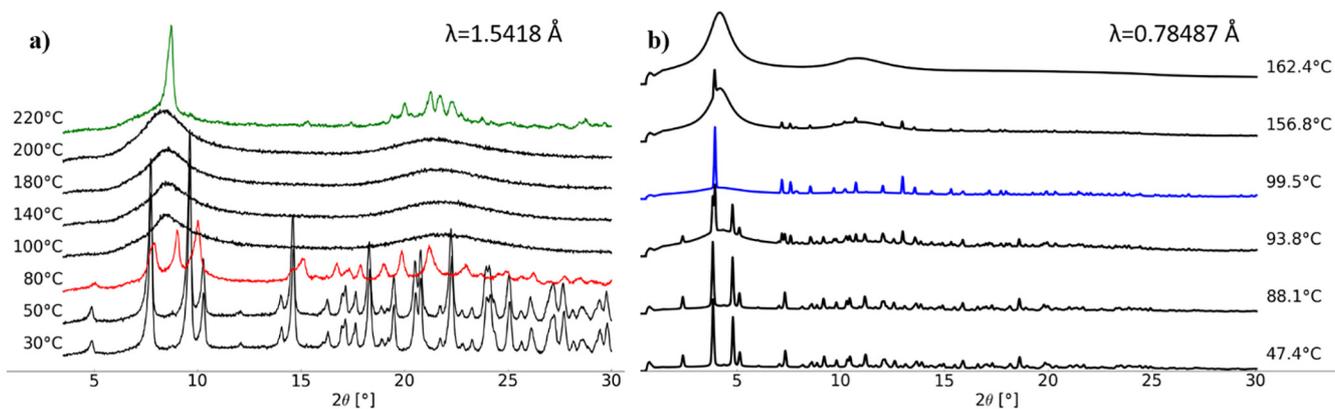


Fig. 4. Variable Temperature PXRD of CLP performed (a) in an open pan using Siemens D5000 evidenced an intermediate form at 80 °C, and (b) experiment in a sealed capillary using synchrotron radiation showed that a monohydrate was formed at 99.5 °C. These experiments allowed identifying an intermediate hydrate (red), an anhydrate (green) and a monohydrate (blue).

These planes are held together by hydrophobic interactions between the methyl groups of CL. Calcium has a coordination number of eight with the carboxylic (6) and alcohol oxygen atoms (1) of the lactate group, as well as the water oxygen (1) coordinating to the metal. In the crystal structure, lactate ions show two different positions. One type of lactate is coordinated with two different calcium atoms, while a second type of lactate is coordinated with three different calcium atoms and forms a hydrogen bond with the water molecule.

As mentioned above, the XRPD pattern of this monohydrate does not overlap with the pattern emerging at 80 °C during the first VT-XRPD

experiment. We suspect this pattern could correspond to the dihydrate phase observed during the DVS analysis. However, due to poor resolution of the pattern, the crystal structure could not be determined and it is possible that this form corresponds to a hydrate of different stoichiometry or a polymorphic form of one of the know hydrates.

3.3. Five solid forms of CL

The different experiments performed evidenced the existence of at least five different forms of CL (Fig. 6). We confirmed the pentahydrate

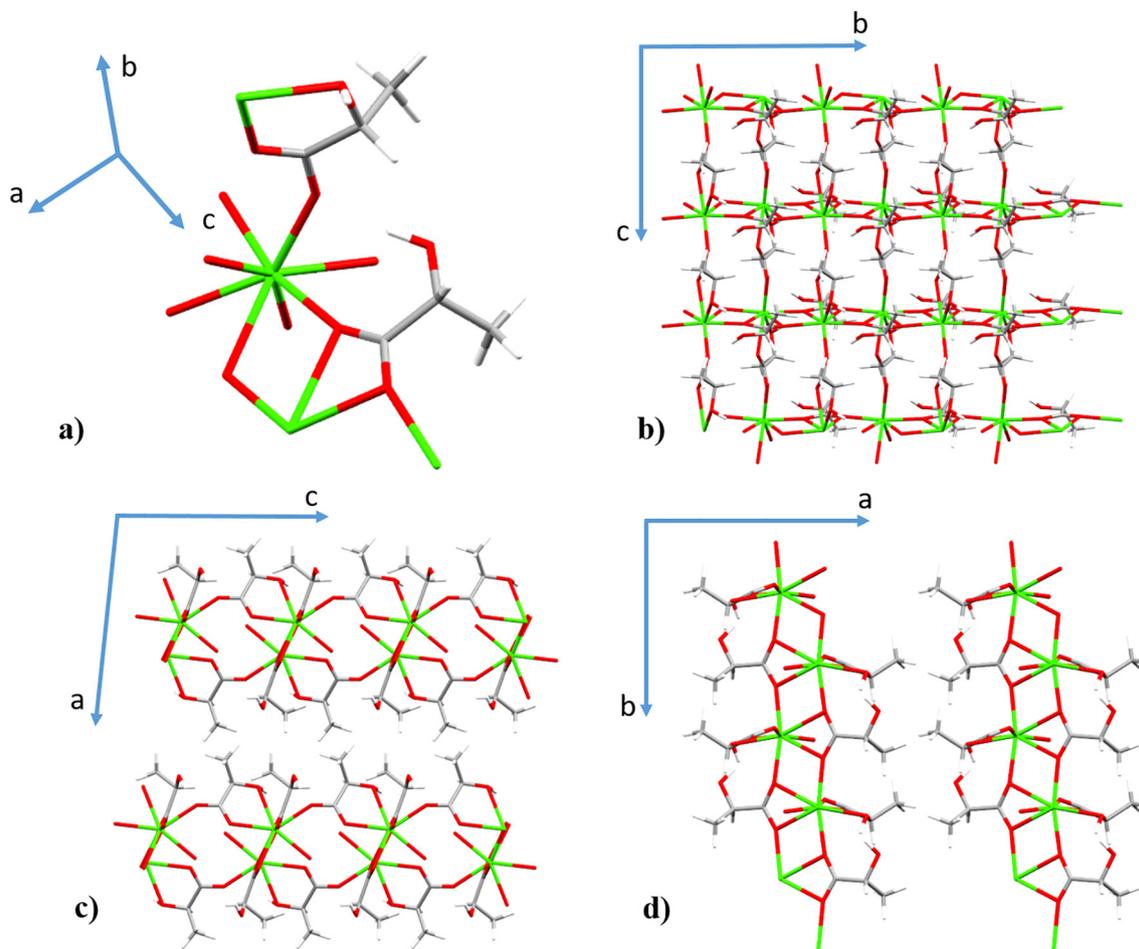


Fig. 5. Structure of CLM isolated at 99.5 °C in sealed capillary: (a) extended asymmetric unit – (b), (c) and (d) projections along the a, b and c axis, respectively.

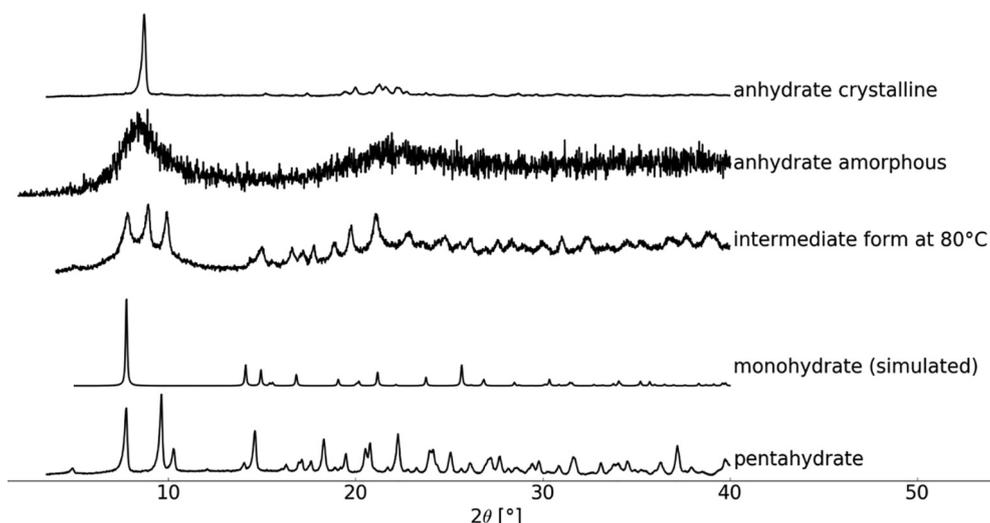


Fig. 6. Normalized PXRD diffractograms of the different solid forms of CL identified: CLP, intermediate hydrate (unknown stoichiometry), CLM (simulated in Mercury), CLA amorphous and CLA crystalline (from bottom to top).

CLP to be stable under ambient conditions, with thermal analysis showing this form to transit to an anhydrous amorphous form upon heating, as already evidenced by Sakata et al. (Sakata et al., 2005). The amorphous form shows a glass transition at 175 °C, with potential recrystallization into a crystalline anhydrate form (CLA), as evidenced in DSC and VT-XRPD analysis. This recrystallization was not always observed and only occurs partially. DVS analysis shows this amorphous phase to transform into the pentahydrate phase upon increase of the RH at 30 °C, whilst an intermediate dihydrate phase is evidenced between 70 and 90% RH at 60 °C. No matter what temperature used, decreasing the RH will lead always to immediate formation of the amorphous phase. Transformations are kinetically hindered as highlighted by the large hysteresis occurring during analysis.

Working under non-controlled RH conditions during VT-PXRD experiments, heating of a sealed capillary containing the pentahydrate phase, led to a novel monohydrate form identified at 100 °C for which the structure was fully resolved. Performing this experiment in an open environment a fifth crystalline form was identified at 80 °C. As the pattern does not match with the monohydrate, pentahydrate nor anhydrate crystalline forms, this pattern is believed to correspond to the dihydrate form mentioned above, to a hydrate of different stoichiometry or a hydrate polymorphic form.

The analyses performed allow delimiting conditions under which the different forms can be obtained. However, one should keep in mind that due to the slow transformation kinetics, these conditions are indicative, and do not allow delimiting the exact thermodynamic conditions under which the different forms are stable (Fig. 7). CLP appears to be the most stable form under ambient conditions as it only starts dehydrating at 10% RH at 30 °C and 20% RH at 60 °C. This dehydration will always lead to an amorphous phase. This makes CLP the most stable form for long-term storage under ambient conditions. It is not recommended to store CLP under dry atmosphere at higher temperatures as it will likely transform into the amorphous form. This latter has a glass transition at 175 °C, above which a recrystallization into an anhydrous crystalline form can occur. The amorphous phase is also unstable below 175 °C under conditions of humidity with transformations occurring to either the pentahydrate CLP phase at lower temperature, or intermediate hydrates at higher temperatures (e.g. the dihydrate phase at 60 °C and 50% RH) or a monohydrate phase as shown by the uncontrolled conditions of the VT-XRPD experiment.

4. Conclusion

In this work, we give experimental evidence of at least five different solid-state forms of CL, three of which were hitherto not evidenced. The pentahydrate phase is the most stable under ambient conditions, and transforms into an anhydrate amorphous phase in a dry atmosphere (either upon heating in a dry atmosphere or by decreasing the RH). The amorphous phase shows a glass transition at 175 °C above which it can recrystallize to an anhydrate crystalline phase. Varying conditions of temperature and RH, we were able to identify hydrates of intermediate stoichiometry. A monohydrate form was obtained at 100 °C heating CLP in a closed environment. Using a more controlled environment a dihydrate form was evidenced at 60 °C forming between 50% and 80% RH.

These results emphasize the importance of controlling both temperature and relative monohydrate and dihydrate forms can potentially appear if these parameters are not well controlled. Considering the current results and the slow transformation kinetics further solid forms of calcium lactate, such as a trihydrate, a tetrahydrate, or hydrate polymorphs, can be expected to appear in the coming years.

CRediT authorship contribution statement

Jean-Baptiste De Maere D'aertrycke: Conceptualization, Methodology, Investigation, Writing - original draft, Visualization. **Julien Morlot:** Resources. **Koen Robeyns:** Software, Validation. **Yaroslav Filinchuk:** Software, Validation. **Tom Leyssens:** Supervision, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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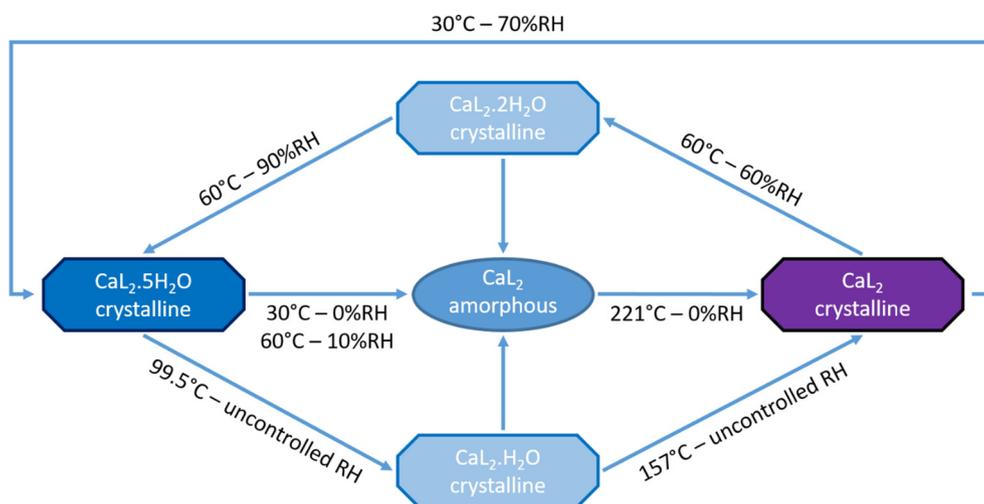


Fig. 7. Experimental conditions allowing Phases transformation observed and conditions upon which they occur.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.foodchem.2020.126884>.

References

- Aitipamula, S., Banerjee, R., Bansal, A. K., Biradha, K., Cheney, M. L., Choudhury, A. R., ... Zaworotko, M. J. (2012). Polymorphs, salts, and cocrystals: What's in a name? *Crystal Growth & Design*, 12(5), 2147–2152. <https://doi.org/10.1021/cg3002948>.
- Authelin, J.-R. (2005). Thermodynamics of non-stoichiometric pharmaceutical hydrates. *International Journal of Pharmaceutics*, 303(1), 37–53. <https://doi.org/10.1016/j.ijpharm.2005.07.007>.
- Bolhuis, G. K., Eissens, A. C., & Zoestbergen, E. (2001). DC Calcium lactate, a new filler-binder for direct compaction of tablets. *International Journal of Pharmaceutics*, 221(1–2), 77–86. [https://doi.org/10.1016/S0378-5173\(01\)00657-3](https://doi.org/10.1016/S0378-5173(01)00657-3).
- Cao, X., Lee, H.-J., Yun, H. S., & Koo, Y.-M. (2001). Solubilities of calcium and zinc lactate in water and water-ethanol mixture. *Korean Journal of Chemical Engineering*, 18(1), 133–137. Scopus.
- Carstensen, J. T. (1984). Solid-state chemistry of drugs. By Stephen R. Byrn. Academic Press, 111 Fifth Avenue, New York, NY 10003. 1982. 346 pp. 15 × 23 cm. Price \$55.00. *Journal of Pharmaceutical Sciences*, 73(4), 573–573. <https://doi.org/10.1002/jps.2600730441>.
- Chemaly, Z., Muhr, H., & Fick, M. (1999). Crystallization Kinetics of Calcium Lactate in a Mixed-Suspension-Mixed-Product Removal Crystallizer. *Industrial & Engineering Chemistry Research*, 38(7), 2803–2808. <https://doi.org/10.1021/ie9806904>.
- Edwards, H. G. M., Lawson, E., De, M., Shields, L., & York, P. (1997). Metamorphosis of caffeine hydrate and anhydrous caffeine. *Journal of the Chemical Society. Perkin Transactions*, 2(10), 1985–1990. Scopus.
- Elamin, A. A., Sebbatu, T., & Ahlneck, C. (1995). The use of amorphous model substances to study mechanically activated materials in the solid state. *International Journal of Pharmaceutics*, 119(1), 25–36. [https://doi.org/10.1016/0378-5173\(94\)00364-B](https://doi.org/10.1016/0378-5173(94)00364-B).
- Ezerskis, Z. (2012). EURL Evaluation Report on the Analytical Methods submitted in connection with the Application for the Authorization of Feed Additives according to Regulation (EC) No 1831/2003 (FAD-2010-0133-CRL/100046, p. 8). European Reference Laboratory for Feed Additives. <https://ec.europa.eu/jrc/sites/jrcsh/files/FinRep-FAD-2010-0133.pdf>.
- Favre-Nicolin, V., & Černý, R. (2002). FOX, 'free objects for crystallography': A modular approach to ab initio structure determination from powder diffraction. *Journal of Applied Crystallography*, 35(6), 734–743. <https://doi.org/10.1107/S0021889802015236>.
- Giron, D., Goldbronn, C., Mutz, M., Pfeffer, S., Piechon, P., & Schwab, P. (2002). Solid state characterizations of pharmaceutical hydrates. *Scopus Journal of Thermal Analysis and Calorimetry*, 68(2), 453–465. <https://doi.org/10.1023/A:1016031517430>.
- Hancock, B. C., & Zografi, G. (1997). Characteristics and significance of the amorphous state in pharmaceutical systems. *Journal of Pharmaceutical Sciences*, 86(1), 1–12. <https://doi.org/10.1021/js9601896>.
- Hilfiker, R. (Ed.). (2006). *Polymorphism in the pharmaceutical industry*. Wiley-VCH.
- Kiran-Yildirim, B., Titz-Sargut, S., & Sayan, P. (2018). Effect of the amino acids L-methionine and D-threonine on calcium lactate pentahydrate crystallization. *Scopus Journal of Engineering and Technology*, 41(6), 1252–1258. <https://doi.org/10.1002/ceat.201700670>.
- Kiran-Yildirim, B., Titz-Sargut, S., & Sayan, P. (2018). Calcium lactate pentahydrate crystallization in the presence of pentanoic acid. *Chemical Engineering & Technology*, 41(6), 1244–1251. <https://doi.org/10.1002/ceat.201700672>.
- Kunz, C., & Gieseler, H. (2018). Merits and limitations of dynamic vapor sorption studies on the morphology and physicochemical state of freeze-dried products. *Journal of Pharmaceutical Sciences*, 107(8), 2179–2191. <https://doi.org/10.1016/j.xphs.2018.04.016>.
- Levenson, D. I., & Bockman, R. S. (1994). A review of calcium preparations. *Nutrition Reviews*, 52(7), 221–232. <https://doi.org/10.1111/j.1753-4887.1994.tb01427.x>.
- Luan, Q., Wang, Y., Wang, G., Yang, J., & Hao, H. (2014). Measurement and correlation of solubility of calcium-L-lactate pentahydrate in ethanol + water and acetone + water systems. *Scopus Journal of Chemical and Engineering Data*, 59(8), 2642–2648. <https://doi.org/10.1021/je500416k>.
- Macrae, C. F., Edgington, P. R., McCabe, P., Pidcock, E., Shields, G. P., Taylor, R., ... van de Streek, J. (2006). Mercury: Visualization and analysis of crystal structures. *Journal of Applied Crystallography*, 39(3), 453–457. <https://doi.org/10.1107/S002188980600731X>.
- Manzurola, E., & Apellblat, A. (2002). Solubilities of L-glutamic acid, 3-nitrobenzoic acid, p-toluic acid, calcium-L-lactate, calcium gluconate, magnesium-DL-aspartate, and magnesium-L-lactate in water. *Scopus Journal of Chemical Thermodynamics*, 34(7), 1127–1136. <https://doi.org/10.1006/jcht.2002.0975>.
- Martin, B. R., Weaver, C. M., Heaney, R. P., Packard, P. T., & Smith, D. L. (2002). Calcium absorption from three salts and CaSO₄-fortified bread in premenopausal women. *Scopus Journal of Agricultural and Food Chemistry*, 50(13), 3874–3876. <https://doi.org/10.1021/jf020065g>.
- Newman, A. W., Reutzel-Edens, S. M., & Zografi, G. (2008). Characterization of the "hygroscopic" properties of active pharmaceutical ingredients. *Scopus Journal of Pharmaceutical Sciences*, 97(3), 1047–1059. <https://doi.org/10.1002/jps.21033>.
- Rumondor, A. C. F., Wikström, H., Van Eerdenbrugh, B., & Taylor, L. S. (2011). Understanding the tendency of amorphous solid dispersions to undergo amorphous-amorphous phase separation in the presence of absorbed moisture. *AAPS PharmSciTech*, 12(4), 1209–1219. <https://doi.org/10.1208/s12249-011-9686-y>.
- Sakata, Y., Shiraishi, S., & Otsuka, M. (2005). Characterization of dehydration and hydration behavior of calcium lactate pentahydrate and its anhydrate. *Colloids and Surfaces B: Biointerfaces*, 46(3), 135–141. <https://doi.org/10.1016/j.colsurfb.2005.10.004>.
- Sakata, Y., Shiraishi, S., Takayama, K., & Otsuka, M. (2006). Effect of pulverization and dehydration on the pharmaceutical properties of calcium lactate pentahydrate tablets. *Colloids and Surfaces B, Biointerfaces*, 51(2), 149–156. <https://doi.org/10.1016/j.colsurfb.2006.07.004>.
- Suzuki, T., Araki, T., Kitaoka, H., & Terada, K. (2012). Characterization of non-stoichiometric hydration and the dehydration behavior of sitafloxacin hydrate. *Chemical and Pharmaceutical Bulletin*, 60(1), 45–55. <https://doi.org/10.1248/cpb.60.45>.
- Tansman, G. F., Kindstedt, P. S., & Hughes, J. M. (2014). Powder X-ray diffraction can differentiate between enantiomeric variants of calcium lactate pentahydrate crystal in cheese. *Journal of Dairy Science*, 97(12), 7354–7362. <https://doi.org/10.3168/jds.2014-8277>.
- Trask, A. V., Samuel Motherwell, W. D., & Jones, W. (2005). Pharmaceutical cocrystallization: Engineering a remedy for caffeine hydration. *Scopus Crystal Growth and Design*, 5(3), 1013–1021. <https://doi.org/10.1021/cg0496540>.
- Vavrusova, M., Munk, M. B., & Skibsted, L. H. (2013). Aqueous solubility of calcium L-lactate, calcium D-gluconate, and calcium D-lactobionate: Importance of complex formation for solubility increase by hydroxycarboxylate mixtures. *Scopus Journal of Agricultural and Food Chemistry*, 61(34), 8207–8214. <https://doi.org/10.1021/jf402124n>.
- Yoshioka, M., Hancock, B. C., & Zografi, G. (1994). Crystallization of indomethacin from the amorphous state below and above its glass transition temperature. *Scopus Journal of Pharmaceutical Sciences*, 83(12), 1700–1705. <https://doi.org/10.1002/jps.2600831211>.