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Compressed tablets based on mineral-functionalized starch and co-crystallized sucrose with natural antioxidants

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ABSTRACT

Compressed tablets based on starch–zinc carriers and co-crystallized sucrose with yerba mate antioxidants were developed. Firstly, the zinc-binding capacity of corn starch was evaluated for being used as a mineral source for the formulations. While, the yerba mate extract was entrapped within a sucrose matrix by co-crystallization. Then, tablets were obtained by compression using co-crystallized products alone and their blends with starch-carriers (85:15, 80:20 and 70:30). All these formulations led to higher tablet hardness than equivalent blends containing raw sucrose. However, high dosages of starch-carriers provoked defects in the tablets (e.g. "capping"). The weight ratio of 80:20 allowed obtaining tablets with optimal hardness values (45–55 kPa), containing zinc (5.4 mg/g tablet) and yerba mate polyphenols (1.3 mg/g tablet). These tablets showed low disintegration times (<10 min) and a fast-release in aqueous medium constituting a useful way for the oral delivery of active compounds with health benefits.

1. Introduction

The design of products that promote health benefits beyond to providing the nutritional and energetic requirements constitutes an actual challenge for the food industry. This trend has led to increase the use of functional ingredients such as antioxidants, minerals, peptides, vitamins, fatty acids, probiotic, among others. However, the incorporation of some compounds in their original state is not always possible due to their unpleasant flavor, low stability or bioavailability; therefore, a previous process to face up these disadvantages is often necessary.

Yerba mate (*Ilex paraguariensis*) is a source of bioactive ingredients (mainly polyphenols, xanthines, flavonoids, saponins, amino acids, minerals and vitamins) with potential application in food and pharmaceutical industries. These compounds may be extracted and concentrated to be used as natural additives (colorant, antioxidant, antimicrobial and/or stimulant), as functional ingredients (hepatoprotective, diuretic, hypocholesterolemic, antirheumatic and antithrombotic) and/or as nutritional supplements in tablets or capsules (Marques and Farah, 2009; Bracesco et al., 2011; Racanicci et al., 2011).

Zinc (Zn) is an essential micronutrient for human growth, development and function of the immune system (Salgueiro et al., 2000; Tapiero and Tew, 2003). Besides, Zn has antioxidant properties which could avoid the illness appearance from oxidative stress (Powell, 2000; Zago and Oteiza, 2001; Goel et al., 2005). Nevertheless, Zn deficiency is one of the ten biggest factors contributing to the burden of disease in developing countries with high mortality (WHO, 2002; Shrimpton et al., 2005). Zinc sulfate is commonly used as a Zn source for supplementation due to its low cost and bioavailability (Salgueiro et al., 2000). However, several authors have reported that this compound modifies the product sensorial characteristics rendering flavor unacceptable and it can also generate side-effects such as nausea and vomiting (Salgueiro et al., 2002; Solomons et al., 2011).

The advantage of using a combination of antioxidants and minerals was reported by several authors, since these compounds could act individually, cooperatively and synergistically (Hercberg et al., 2004; Carocho and Ferreira, 2013). Therefore, the development of systems for the simultaneous carrying from zinc and yerba mate antioxidants is a useful strategy to supply the nutritional requirements. However, both active compounds are chemically reactive and their functionality could be affected by interactions with other components of the vehicle matrix. In this sense, encapsulation is a useful way to protect sensitive materials

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against adverse conditions and to mask unpleasant flavors (Day et al., 2009). In a previous work, the compartmentalization in a alginate–starch matrix proved to be an effective tool for the simultaneous transport of zinc and yerba mate antioxidants, preventing a possible interaction between them (López-Córdoba et al., 2014b).

Co-crystallization represents a viable means of enhancing the physical properties of active compounds such as solubility, dispersibility, wettability, anticaking, antidusting, antiseparation, homogeneity, flowability and stability (Bhandari and Hartel, 2002). In this process, the crystalline structure of sucrose is modified from perfect to irregular agglomerated crystals, to provide a porous matrix in which a second active ingredient can be incorporated. Because of their agglomerated structure, all co-crystallized sugar products offer direct tableting characteristics which provide significant advantages in the candy and pharmaceutical industries (Awad and Chen, 1993; Chen et al., 1988).

Nowadays, the compressed tablets are the most popular dosage form used; they are composed of active ingredients and excipients (e.g. binders, disintegrants, lubricants and diluents). Tablets have many advantages over other dosage forms including competitive unit production costs, manufacturer simplicity, good portability and easy administration. Moreover, they offer better stability to heat and moisture compared to liquid and semi-solid formulations (Jivraj et al., 2000).

Starch is a natural, renewable, biodegradable polysaccharide composed primarily of branched and linear chains of glucose molecules, named as amylopectin and amylose, respectively (Fennema and Tannenbaum, 1996). Starch is considered a good diluent, disintegrant, tablet binder and thickening agent used in pharmaceutical dosage formulations (Jivraj et al., 2000).

The functionalization of starch with bioactive compounds constitutes a new approach for the formulation of healthy products. Several authors have reported the ability of native and modified starches to embed guest molecules such as drugs, transition metals, flavors, vitamins, among others (Zhao et al., 1996; Lii et al., 2002; Staroszczyk and Janas, 2010; Ades et al., 2012; Luo et al., 2013; Janaswamy, 2014). In the present work, starch-carriers and co-crystallized products were combined to obtain compressed tablets with zinc and yerba mate antioxidants. Also, the Zn-binding capacity of native corn starch and its possible application as a release agent were tested. The formulations of the compressed tablets were optimized and the products were characterized, as well. To our knowledge, it is the first time that a delivery system is developed using this combination of materials and techniques.

2. Materials and methods

2.1. Active compounds

Dried and minced yerba mate leaves were used as a source of natural antioxidants. An aqueous extract was prepared according to the previously optimized methodology by Deladino et al. (2008). Briefly, a blend of 10 g of commercial yerba mate (Las Marías, Corrientes, Argentina) and 100 mL of distillated water was placed in a thermostatic bath (Viking, Argentina) at 100 °C for 40 min. After this time, samples were filtered and cooled. Zinc sulfate·$7H_2O$ (Parafarm, Argentina) was used as a source of zinc (4.4 mg of zinc sulfate provided 1 mg of elemental zinc).

Both ingredients are listed as GRAS (generally regarded as safe) by Food and Drug Administration (FDA).

2.2. Co-crystallized sucrose with yerba mate extract

The co-crystallized products with yerba mate extract were prepared as described by López-Córdoba et al. (2014a). Briefly, a blend of raw sucrose (50 g) (Ledesma, Argentina) and yerba mate aqueous extract (10 mL) was heated to 132 °C on a hot plate and stirred with a vertical agitator (IKA Labortechnik, Staufen, Germany). When a slight turbidity was detected in the syrup, indicating the beginning of the crystallization process, the mix was removed from the heat, maintaining the agitation. The co-crystallized products were dried in a convection oven (SanJor, Argentina) at 40 °C for 15 h and then they were ground and sieved through a 500 μm mesh. Blends of raw sucrose (50 g) and distillated water (10 mL) were crystallized as described above for control purposes. These samples will be referred as "re-crystallized sucrose".

The content of yerba mate polyphenols loaded in the co-crystallized products was determined by Folin–Ciocalteu method as reported in a previous work (López-Córdoba et al., 2014a). The co-crystallization yield (%) was calculated as the ratio between the amount of yerba mate polyphenols loaded per gram of co-crystallized product and the mass of yerba mate polyphenols employed in the formulation per gram of raw sucrose.

2.3. Starch–zinc carriers

The starch–zinc carriers were prepared as described in a previous work (López-Córdoba et al., 2014b). Briefly, blends of native corn starch (1 g) (Unilever, Spain), deionized water (10 mL) and zinc sulfate (1.43 g/g of starch) were prepared under continuous stirring (180 rpm, 25 °C for 15 h). Then, the samples were centrifuged (at 5000g for 15 min), the supernatant was removed and the solids were dried and milled. The Zn adsorption yield (%) on starch was calculated as the ratio between Zn mass per gram of starch-carrier and the Zn mass employed in the formulation per each gram of native corn starch. In all cases, the Zn concentration was quantified by atomic absorption spectroscopy using the flame method with a wavelength of 213.9 nm. The analyses were carried out in a Varian spectrometer model EspectrAA 300-plus (Cambridge, United Kingdom). Previously, the samples were digested with concentrated nitric acid.

2.4. Characterization experiments of the powder materials

Starch–zinc carriers were analyzed by confocal laser scanning microscopy (CLSM), intact starch granules and cross-sections obtained by cryo-fracture were tested. Fluorescein isothiocyanate (FITC) (0.3 mg/mL) was used for labeling. Starch (5 mg/mL) were suspended in Milli-Q water, then 1000 μL of starch suspensions were stained by the addition of 40 μL of FITC. The mixture was agitated in a vortex and let to rest for 1 h in closed eppendorfs in darkness at room temperature before analysis. A LEICA TCS SP5 (Mannheim, Germany) inverted microscope equipped with Ar and HeNe laser was used. The excitation wavelength was 488 nm and the emission wavelength 518 nm. Images were acquired using a HCX PL APO CS 63.0 × 1.40/UV/oil immersion objective and with 1024 × 1024 pixel resolution in a constant z-position. Software Leica Application Suite Advanced Fluorescence (LAS AF), version 2.2.1. build 4842 was employed in the image analysis. Micrographs of co-crystallized products and re-crystallized sucrose were acquired by scanning electron microscopy (SEM) using an FEI, Quanta 200 equipment (The Netherlands). Samples were attached to stubs using a two-sided adhesive tape, then coated with a layer of gold (40–50 nm) and examined using an acceleration voltage of 20 kV.

Moisture content (%) was measured gravimetrically by drying the grounded samples in a vacuum oven at 70 °C, until constant weight (AOAC, 1998).

X-ray diffraction (XRD) analysis was performed in an X'Pert PRO (The Netherlands) equipment at 40 kV with radiation of wavelength of 40 mÅ. Samples were scanned with 2θ between 5° and

60°. The crystallinity degree (%) of the starches was calculated as the ratio between the area of absorption peaks and the total diffractogram area (Hermans and Weidinger, 1948).

The identification of the main functional groups of the samples was carried out by Fourier transform infrared spectroscopy (FT-IR). The equipment used was a Nicolet IS-10 (Thermo Scientific, USA) and the spectral analysis was performed with the software Omnic version 8.1 (Thermo Scientific, Inc., USA). Disks (7 mm) were obtained by milling of sample with KBr and they were analyzed under transmission mode, taking 64 scans per experiment with a resolution of 4 cm^{-1}.

2.5. Compressed tablets

2.5.1. Preparation of the compressed tablets

Tablet formulations containing co-crystallized products alone and their blends with starch-carriers (85:15, 80:20 and 70:30) were prepared. In a similar way, equivalent blends of starch zinc-carriers with re-crystallized sucrose, corn starch with raw sucrose and corn starch with re-crystallized sucrose, were prepared as controls. In all cases magnesium stearate (1 g/100 g of blend) was added as a lubricant. All ingredients were sieved through a 500 μm mesh before their use. The powder blends were prepared by shaking in plastic bags. Previous to the compression, the repose angle was determined with a rotating cylindrical chamber, which was tilted gradually until slipping occurred and then the angle was measured (Solids handling study bench, CEN, Armfield, United Kingdom). The Hausner (HI) and Carr (CI) indexes of the formulations were calculated as follows (USP 30-NF 25, 2007):

$$\mathrm{HI} = \frac{\rho_T}{\rho_B} \tag{1}$$

$$\mathrm{CI} = \frac{\rho_T - \rho_B}{\rho_T} \times 100 \tag{2}$$

The loose bulk density (ρ_B) of the powder blends was determined by pouring a known mass delivered freely by gravity into a measuring cylinder. The value of ρ_B parameter was calculated by dividing the mass by the bulk volume. The tapped bulk density (ρ_T) was calculated from the weight of powder and the volume occupied in the cylinder after being hand tapped until a constant value was reached.

Then, the powder blends were directly compressed on a single punch-tablet machine (Model SC1, Sanchez, Argentina), regulated to obtain tablets of around 400–450 mg and constant thickness, using flat-punches with a diameter of 9 mm.

2.5.2. Characterization of the tablets

The characterization of the tablets was carried out according to United States Pharmacopeia (USP 30-NF 25, 2007). For the weight uniformity test, ten tablets were weighed individually and the results were expressed as a mean value of the determinations. The thickness of 10 tablets was measured using a Vernier caliper. The density was calculated as the ratio between the mass and the volume of the tablets. The tablet hardness was measured with the Erweka hardness tester (Erweka, Germany). The disintegration time was evaluated on 6 tablets per each formulation employing a disintegrator tester (Erweka, Germany).

2.5.3. Load of active compounds of the tablets

The zinc content was quantified by atomic absorption spectrometry as described earlier for starch-carriers (Section 2.3). The total polyphenols content was determined by the Folin–Ciocalteu method (Singleton et al., 1999). Moreover, the quantification of major phenolic compounds and caffeine was carried out by high performance liquid chromatography (HPLC). The analysis were done using a HP 1100 liquid chromatograph (Hewlett Packard, USA) equipped with a binary pump, a thermostated column compartment, auto injector, degasser and diode-array detector (DAD) connected to an Agilent workstation. A Zebra 300 SB-C18 column (4.6 × 250 mm; 5 μm) connected to a guard column was used. A modified method from Chandra and Gonzalez de Mejia (2004) was carried out as follows: the mobile phases "A" and "B" consisted of a mixture of water, methanol and formic acid (79.7/20/0.3) and a mixture of methanol and formic acid (99.7/0.3), respectively. A staggered gradient elution program at 0.9 mL/min prepared as follows: 0% B/15 min, 40% B/15 min; 75% B/10 min; 100% B/5 min, was employed. Commercial standards (Sigma–Aldrich, USA) of chlorogenic acid, caffeic acid, rutin and caffeine were used. Stock solutions of each standard (0.25 mg/mL) were prepared in 50% methanol-Milli-Q water. Calibration curves at four different concentration levels were performed. Each level was tested by duplicate. The retention times and DAD absorbance spectral matching were used for identification purposes. Based on the absorption maxima, the wavelengths selected for each compound were 275 nm for caffeine, 330 nm for chlorogenic and caffeic acids and 360 nm for rutin.

2.5.4. Release studies

The release studies of tablets with yerba mate extract and zinc were carried out. Besides, zinc release assays from starch-carriers were performed for comparison purposes. Samples of 0.450 g of tablets or 1 g of starch-carriers were placed in an Erlenmeyer containing 20 mL of Milli-Q water and agitated at 37 °C and 120 rpm (Orbit Environ Shaker, Lab Instruments, USA). Aliquots of the supernatant were removed at different times during 2 h. The released percentage of each active compound was calculated with the following equation:

$$\text{Released compound amount}\,(\%) = \left(\frac{M_t}{M_\infty}\right) \times 100 \tag{3}$$

where M_t is the mass of active compound quantified at each time t and M_∞ is the mass of active compound loaded in the samples. M_t and M_∞ for each active compound were determined as described above.

The zinc release profiles from starch-carriers and the compressed tablets were compared using the similarity factor, f_2, calculated by the following equation:

$$f_2 = 50 \log \left\{ \left[1 - \left(\frac{1}{q}\right) \sum_{t=1}^{q} (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\} \tag{4}$$

where q is the number of dissolution time points, R_t and T_t are the percentages of compound released at each time of the two samples compared. A f_2 value between 50 and 100 indicates similarity between the release profiles of the samples (Costa and Sousa Lobo, 2001).

2.5.5. Release data analysis

The fitting of the release profiles of the active compounds to the empirical models of power law (Eq. (5)), diffusion–relaxation (Eq. (6)) and first order (Eq. (7)) (Ritger and Peppas, 1987; Peppas and Sahlin, 1989) was evaluated, using the corrected correlation coefficient (R^2_{cor}) and the residual analysis.

$$\frac{M_t}{M_\infty} = kt^n \tag{5}$$

$$\frac{M_t}{M_\infty} = k_d t^m + k_r t^{2m} \tag{6}$$

$$\frac{M_t}{M_\infty} = e^{-k_1 t} \quad (7)$$

In Eq. (5), k is a constant related to structural and geometric characteristics of the matrix and n is the transport exponent indicating the type of release mechanism involved. In Eq. (6) k_d, k_r and m are constants. The first term represents the diffusional contribution and the second term represents the case-II relaxation contribution. In Eq. (7), k_1 is the first-order release constant. Eqs. (5) and (6) are only valid for the first 60% of the release curve, which means that M_t/M_∞ is <0.6 (Ritger and Peppas, 1987; Peppas and Sahlin, 1989).

2.6. Statistical analysis

Analysis of variance (ANOVA) and mean comparisons were carried out using the software SYSTAT INC. (Evanston, USA). Unless indicated, a level of 95% of confidence ($\alpha = 0.05$) was used.

3. Results and discussion

3.1. Co-crystallized sucrose with yerba mate antioxidants

Co-crystallized products showed a content of yerba mate polyphenols around 1.8 mg/g of sample. This concentration corresponds to 85% of the polyphenols mass employed for their preparation. The polyphenols amount not recovered (about 15%) could be attributed to the degradation of some heat-sensitive compounds of the yerba mate extract during the co-crystallization process. In a previous work, the effect of the co-crystallization process on the antioxidant activity of the yerba mate extract was evaluated by the DPPH radical method and high performance liquid chromatography (HPLC). It was found that this property was maintained along the whole process (López-Córdoba et al., 2014a). In addition, the co-crystallized sucrose with yerba mate extract was fully stable along 120 days of storage at 75% RH and 20 °C.

Fig. 1 shows X-ray diffraction patterns and SEM micrographs of re-crystallized sucrose and co-crystallized products with yerba mate extract. The samples showed a typical structure corresponding to cluster-like agglomerates with irregular cavities between them (Bhandari et al., 1998; Chen et al., 1988). Moreover, amorphous regions were not observed in both diffractograms suggesting that after the co-crystallization process the crystalline structure of sucrose was maintained. Similar observations were reported by other authors (Bhandari and Hartel, 2002; Sardar and Singhal, 2013). The position of the peaks at 2θ (°) = 11.7, 12.7, 18.8, 19.6, 24.8, 25.2 and 38.3 showed coincidence with the "fingerprint" of crystalline sucrose (JCPDS, 1999). However, these peaks exhibited higher intensity values for the co-crystallized sucrose with yerba mate extract than for re-crystallized sucrose, suggesting a higher crystallinity which could be attributed to the presence of the yerba mate extract (Fig. 1). Deladino et al. (2010) working with freeze-dried yerba mate extract (an amorphous material), instead of liquid extract, did not find significant changes in its X-ray pattern compared to raw sucrose.

In addition, the diffractograms of re-crystallized sucrose exhibited two peaks at 2θ (°) = 47 and 52, which could not be identified by comparison with the available standards. The first peak was also detected in the diffractogram of the co-crystallized products but with lower intensity; whereas the last one was even disappeared. Sardar and Singhal (2013) also found peaks in this diffractogram region for raw sucrose and co-crystallized products with cardamom oleoresin.

Table 1 shows the main functional groups detected in the FTIR spectra of re-crystallized sucrose and co-crystallized products with

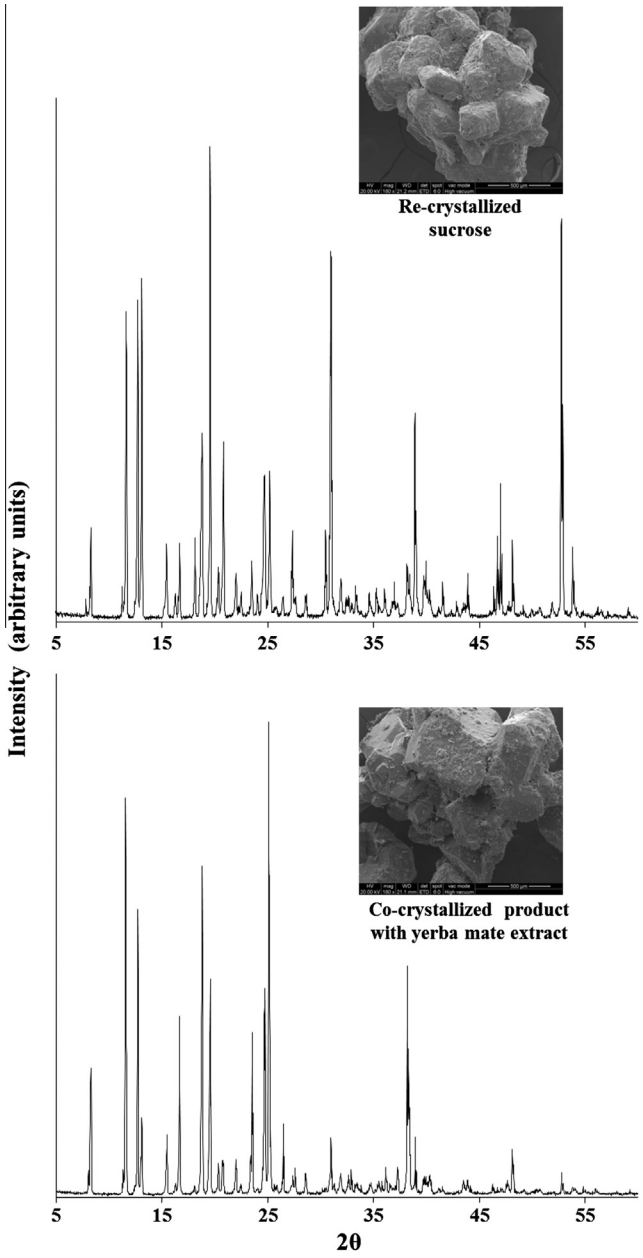

Fig. 1. X-ray diffraction patterns of re-crystallized sucrose and co-crystallized products with yerba mate extract. Inserts correspond to SEM micrographs of both samples.

yerba mate extract. In both samples only signals characteristic of sucrose molecule were found, which indicates that strong interactions between the yerba mate extract and the sugar did not take place during the co-crystallization (Brizuela et al., 2012; Gopi et al., 2013). The bands characteristic of polyphenols in the co-crystallized products were not detected probably due to the low amount of these compounds in the products. As it is well known, the positions of absorption bands in the IR spectrum give information about the presence or absence of specific functional groups in a molecule; a whole spectrum constitutes a "fingerprint" that can be used to determine the identity of the sample (Kačuráková and Wilson, 2001).

3.2. Starch–zinc carriers

The total zinc content in the carriers was determined by atomic absorption spectroscopy, obtaining values around 38 mg/g of

Table 1
Signals assignment for infrared spectra of starches, re-crystallized sucrose and co-crystallized products.

Signals (cm^{-1})		IR band assignment	Signals (cm^{-1})		IR band assignment
Native starch	Starch–zinc carrier		Re-crystallized sucrose	Co-crystallized sucrose with yerba mate	
nd	624	SO_4^{2-} groups from ZnSO4	734	733	C–O stretching
711	711	Skeletal modes of pyranose ring	908	908	CH_2 twisting
766	766	C–C stretching	921	922	C–C stretching
864	864	C–H, CH_2 deformation	941	941	C–C stretching
929	929	Skeletal mode vibrations of α−1,4 glycosidic linkage (C–O–C)	991	990	C–O stretching
1018	1021	C–O stretching	1014	1014	C–O stretching
1080	1080	C–O–H bending	1053	1059	C–O stretching
1104	1105	C–O stretching	1069	1069	C–C stretching
1155	1158	C–O stretching, C–O–H bending	1127	1127	C–O stretching
1204	1207	O–H deformation	1209	1209	O–H deformation
1243	1244	CH_2OH (side chain) related mode	1238	1241	O–H deformation
1305	1303	C–H rocking	1279	1280	C–H deformation
1335	1337	C–O–H bending, CH_2 twisting	1323	1324	C–H rocking
1370	1369	C–H rocking	1345	1346	CH_2 rocking
1420	1419	CH_2 bending, C–O–O stretching	1387	1389	Deformation of OH groups
1458	1458	CH_2 bending	1460	1461	C–H deformation
1645	1649	Water absorbed in the amorphous regions of starch	2938	2940	Symmetric and anti symmetric stretching –CH_2 groups
2934	2934	CH_2 deformation	3328	3335	OH stretching
3390	3358	O–H stretching	3564	3564	OH stretching

starch-carrier. This concentration corresponds to an adsorption yield of 12% with respect to the initial amount of the zinc used in the formulation.

Confocal scanning laser microscopy allows the visualization of the native corn starch and the starch–zinc carrier in their original environment (Fig. 2). Starch–zinc carriers showed granules well-preserved as compared with native corn starch suggesting that these were not affected by the preparation process. Besides, both samples showed internal channels as was previously reported by Chen et al. (2011). In a previous work (López-Córdoba et al., 2014b), a mapping of the zinc distribution on the surface of starch–zinc carriers was performed by SEM–EDX analysis, observing a homogeneous distribution of zinc and sulfate ions on the surface of the granules. Ciesielski et al. (2003) and Tomasik et al. (2001) found that starch-metal complexes are formed because the anion penetrates into the starch granules, and the cation is held by electrostatic attractions.

X-ray diffraction patterns of the native starch and starch–zinc carrier are shown in Fig. 3. Both samples showed a semi-crystalline structure with sharp diffraction peaks at 2θ (°) 15.3, 17.5 and 23.1, characteristic of A-type pattern (Zobel, 1988). The crystallinity degrees of native starch and starch–zinc carriers were around 20% and 27%, respectively. The increase in the crystallinity was attributed to the presence of zinc sulfate salt.

The main signals identified in the FT-IR spectra of the native starch and the starch–zinc carriers are listed in Table 1. Similar IR spectra for both systems were obtained indicating that zinc ions did not provoke significant conformational changes on the starch polymer. On the other hand, the spectra of the starch–zinc carriers showed a signal at 624 cm^{-1}, also observed in the zinc sulfate spectrum corresponding to the vibration modes of the SO_4^{2-} groups (Wang et al., 2004). The broad band corresponding to the stretching of the –OH groups was turned narrower and shifted from 3390 cm^{-1} for native starch to 3350 cm^{-1} for starch–zinc carriers. Similar observations were reported by Luo et al. (2013) and Staroszczyk and Janas (2010) working with zincatated-modified starches. These authors stressed that the changes of –OH band were due to coordination of zinc ions to the oxygen atoms of the glucose unit (6-CH_2OH).

3.3. Tablet formulations

The tablet formulations containing co-crystallized products alone and their blends with starch-carriers (85:15, 80:20 and 70:30) showed moisture contents lower than 2%, characteristic values of stable dried products (Fennema and Tannenbaum, 1996; Fu and Labuza, 1993). With respect to the flowability, the co-crystallized products exhibited similar repose angle values than raw and re-crystallized sucrose (around 41°); whereas, their blends with starch-carriers (85:15, 80:20 and 70:30) showed repose angles higher than 50°. Several authors have reported that the values of repose angle between 40° and 45° are characteristic of free-flowing materials, while values higher than 50° correspond to very cohesive materials (Antequera et al., 1994; Peleg, 1977).

Fig. 4 shows the Hausner and Carr indexes of co-crystallized products, raw and re-crystallized sucrose. Hausner index (HI) is also a useful quality criterion to evaluate powder flowability due to its good correlation with the potential bridge strength and stability (Juliano and Barbosa-Cánovas, 2010). Both co-crystallized products and re-crystallized sucrose showed HI values below than 1.2, as raw sucrose, characteristics of good flowability and handling properties (Fig. 4). With respect to the weight ratios 85:15, 80:20 and 70:30, the starch presence led to form powder blends with acceptable flowability properties (HI: 1.2–1.5) (USP 30-NF 25, 2007). As it is well known, native starches are generally cohesive and have higher HI values (Jivraj et al., 2000).

Carr index (CI) was used as a compressibility indicator since it is an indirect measure of the ability of powders to form tablets (Peleg, 1977). Low CI values indicate a best compressibility. The re-crystallized sucrose and the co-crystallized products showed a better ability to decrease in volume under pressure than raw sucrose. The compressibility showed a significant increase in the following order: raw sucrose < re-crystallized sucrose < co-crystallized products (Fig. 4). CI values of 18%, 26% and 31% have been reported for monohydrate lactose, corn starch and magnesium stearate, respectively, which are commonly used excipients in the pharmaceutical industry (Raymond et al., 2006). In the case of the blends of co-crystallized products with starch–zinc carriers, all of them showed

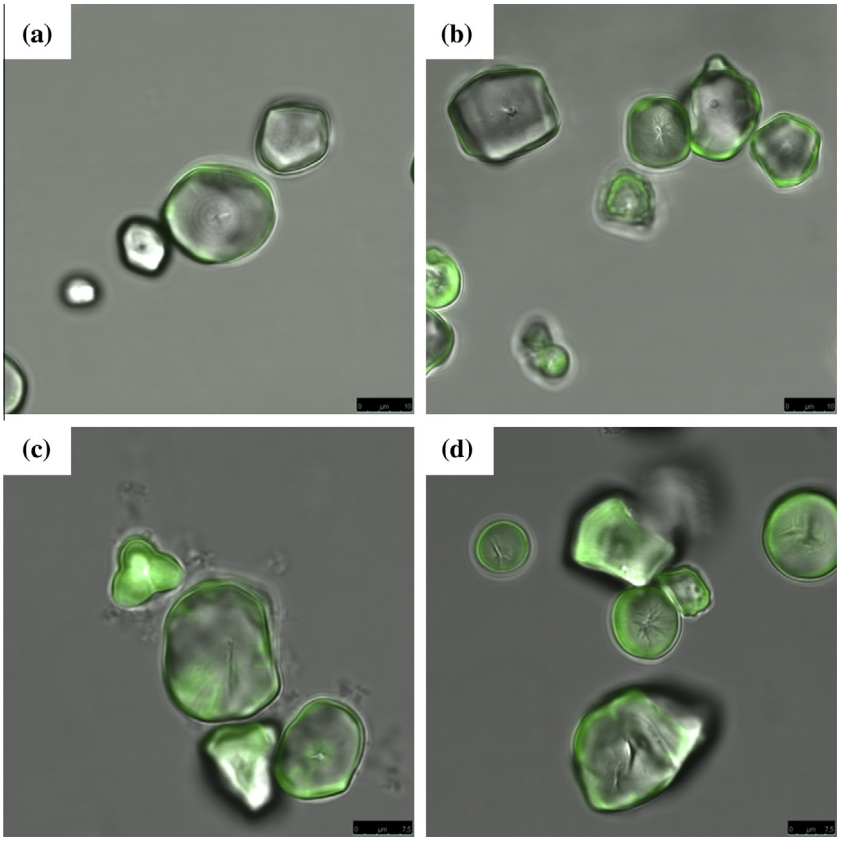

Fig. 2. Corn starch and starch–zinc carriers micrographs of intact granules (a and c) and cross-section (b and d); respectively. Scale bar = 7 μm.

CI values between 21% and 26%, characteristic of materials with acceptable flow properties (USP 30-NF 25, 2007).

3.4. Compressed tablets

3.4.1. Physical properties of the tablets

The tablets made of co-crystallized products alone and their blends with starch-carriers at 85:15 showed hardness values around 52 kPa. These results suggest that the co-crystallized products have good compactability properties, allow obtaining similar tablet hardness without starch use. The weight ratio 70:30 led to hardness values around 67 kPa; but these tended to get stuck in the compression machine which led to tablets with visual defects (e.g. "capping"). Several authors have reported that tablet hardness greater than 17 kPa will readily withstand the stresses imposed by conventional commercial packaging and distribution; whereas, tablets having a hardness greater than 60 kPa are considered very hard (Lee, 2007). In this sense, the weight ratio 80:20 was found to be the more appropriate not only to obtain tablets with optimal hardness (48–56 kPa) but also to incorporate a higher zinc amount in the tablets. This ratio was selected for future assays. From now on, the compressed tablets of the formulations used will be referred as follow: S–S: native starch and raw sucrose; S–C: native starch and re-crystallized sucrose; SZn–C: starch–zinc carrier and re-crystallized sucrose; and SZn–CYm: starch–zinc carrier and co-crystallized sucrose with yerba mate extract.

All tablets showed similar values of weight (420 ± 20 mg), thickness (5.0 ± 0.2 mm) and density (1.3 ± 0.2 g cm^{-3}) which enable the comparison of their physical properties. The tablets S–C, SZn–C and SZn–CYm showed higher hardness than the S–Sc tablets ($p < 0.05$), i.e. re-crystallized sucrose and the co-crystallized products lead to form a higher amount of interparticle bridges (interlocking) than raw sucrose (Fig. 5). Rizzuto et al. (1984), working with co-crystallized sucrose with dextrin, found that co-crystallized materials are deformed readily by plastic fracture leading to much harder compacts compared with sucrose (which is a brittle material). Besides, non-significant differences were found between the hardness values of the tablets S–C, SZn–C and SZn–CYm, which means that the presence of the active compounds did not provoke important changes on this property.

Disintegration time is a useful tool to quantify the kinetic process of water uptake into the tablet until complete disintegration is reached. This effect depends on the porosity of the tablet and on the wettability of the pores (Luginbühl and Leuenberger, 1994). In our case, all tablets showed disintegration times below than 10 min, which are indicative of good characteristics for oral applications.

3.4.2. Active compounds content of the tablets

Combinations of co-crystallized products and starch-carriers allow obtaining tablets for the simultaneous carrying of minerals and antioxidants (SZn–CYm). The zinc content was around 2.3 mg per tablet (around 5.4 mg/g tablet) including the endogenous zinc concentration of the raw extract of yerba mate (between 2 and 5 mg Zn^{2+}/L of extract). This Zn dosage corresponds to 21% of the recommended daily intake (RDA) for adults, useful to avoid deficiency and prevent toxicity (FAO/WHO). Meanwhile, the polyphenols content was 1.3 mg/g tablet; this value represents an important contribution in relation to the daily intake of polyphenols compounds from fruits and vegetables (around 5 mg/g dry matter) (Saura-Calixto and Goñi, 2006). The concentrations of chlorogenic acid, rutin and caffeine determined by HPLC were 160, 90 and 180 μg/g tablet, respectively. The caffeic acid was not detected probably due to the low amount of this compound

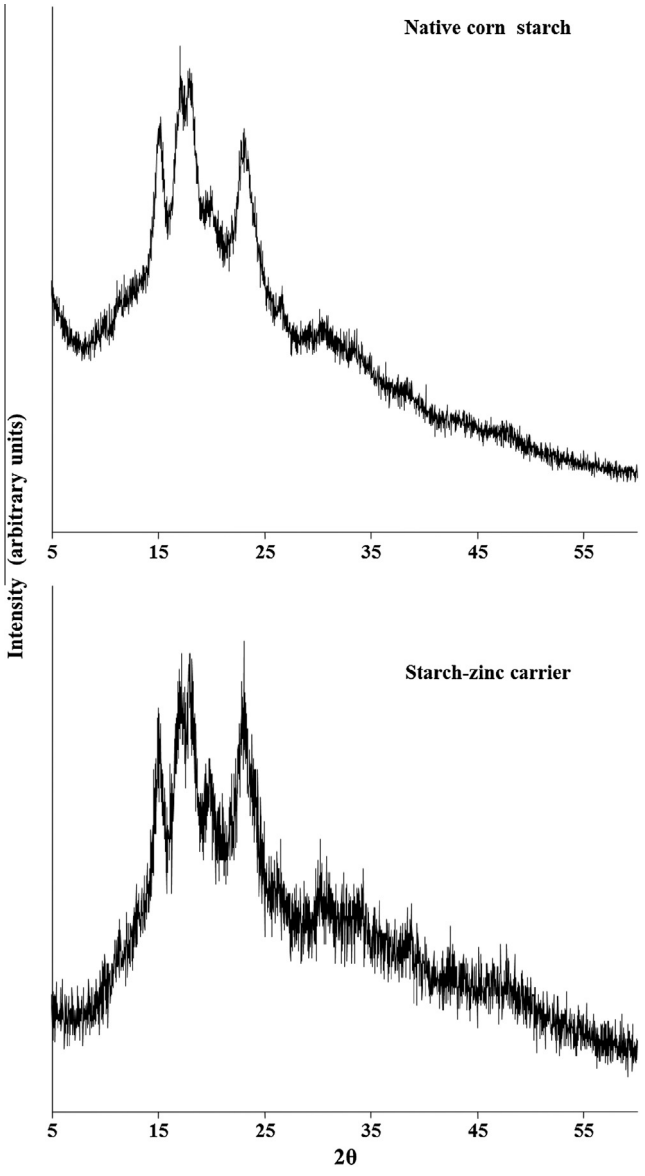

Fig. 3. X-ray diffraction patterns of native corn starch and starch–zinc carrier.

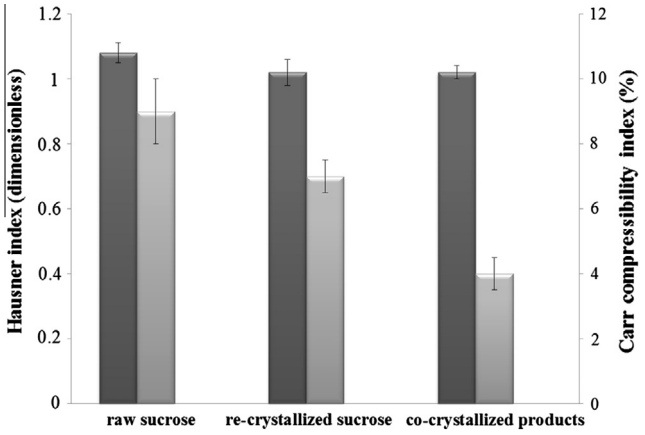

Fig. 4. Hausner index (black bars) and Carr compressibility index (%) (grey bars) of raw and re-crystallized sucrose and co-crystallized products with yerba mate extract.

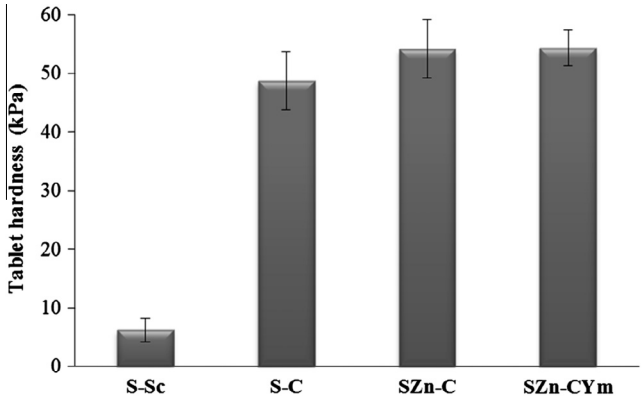

Fig. 5. Hardness of the compressed tablets obtained using blends 80:20 of native starch and raw sucrose (S–Sc); native starch and re-crystallized sucrose (S–C); starch–zinc carrier and re-crystallized sucrose (SZn–C); and starch–zinc carrier and co-crystallized sucrose with yerba mate extract (SZn–CYm).

in the tablet. Several studies dealing with yerba mate polyphenols and its relation with human health showed that its beverage reduced risk of several chronic diseases due to its antioxidant, anti-inflammatory, antimutagenic and lipid-lowering properties (Gugliucci, 1996; Bracesco et al., 2011).

To our knowledge, a recommended daily intake of yerba mate extract has not been established. However, to not exceed the RDA of the Zn, the serving sizes of the tablets with both active compounds should be up to 4 tablets per day.

3.4.3. Release kinetics of active compounds

The compressed tablets showed a fast release rate of yerba mate polyphenols, releasing around 80% within the first 5 min. The remaining amount of phenolic compounds was released after 20 min (Fig. 6). With respect to the zinc release, the tablets showed a quick release rate to the aqueous medium, as the starch–zinc carriers; a zinc recovery percentage of 50% was obtained after 5 min (Fig. 7). This behavior could be attributed to both the rapid disintegration of the tablets in water and the migration of some weakly bound $ZnSO_4$ molecules on the granules, as it was above mentioned.

The remaining amount of mineral in both systems was not released along the assay. These results are in agreement with the observed by FTIR analysis suggesting a slight interaction between a mineral fraction and the starch building units, that could avoid its total release in aqueous media. For both samples, the remaining amount of the mineral could be released by pancreatic enzymes

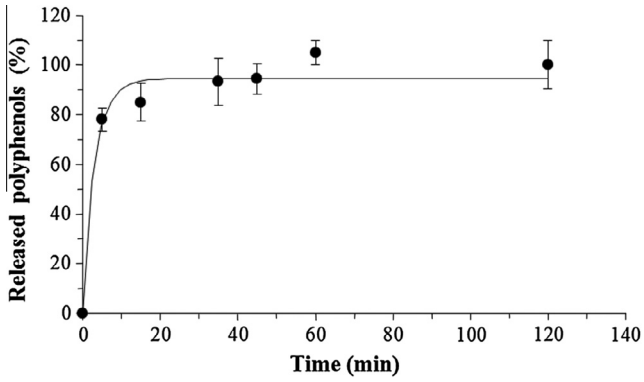

Fig. 6. Release kinetics of yerba mate polyphenols from SZn–CYm tablets in aqueous medium. Symbols represent experimental data, while lines corresponding to the predicted values by the first-order kinetic model.

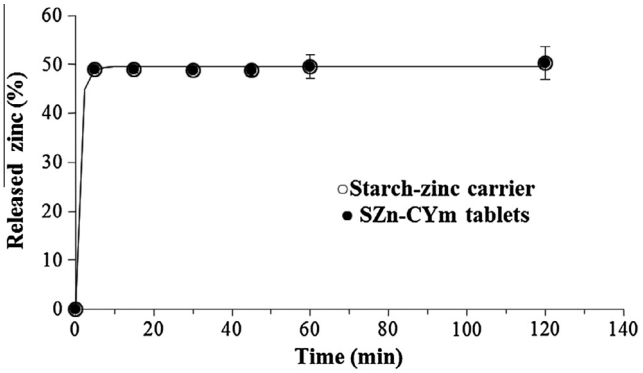

Fig. 7. Zinc release kinetics from the starch–zinc carrier (○) and the SZn–CYm tablets (●) in aqueous medium. Symbols represent experimental data, while lines corresponding to the predicted values by the first-order kinetic model.

action. According to Mundargi et al. (2008) and Vilivalam et al. (2000), the native starch is almost completely broken down, after its oral ingestion, by the pancreatic enzymes that lead to subsequent absorption from the small intestine into the systemic circulation.

The value obtained for the similarity factor (Eq. (4)) was 75, which indicates a high similarity between the release profiles of zinc from the compressed tablets and the starch-carriers. These results suggest that the tablet hardness did not interfere with the release profile of the mineral. As it is well known, the hardness is a critical factor for the disintegration time and the dissolution behavior of the tablets. Frequently, harder tablets take longer to disintegrate than softer tablets (Lee, 2007). In this case, the blends of starch-carriers and co-crystallized products allow obtaining tablets with appropriate hardness which release fast the active compounds; i.e. fast release tablets.

The fitting of the release data for zinc and yerba mate polyphenols to the models of power law (Eq. (5)) and diffusion–relaxation (Eq. (6)) could not be applied because these models are valid up to 60% release. Fast release rates were also reported for tablets based on hydrophilic matrices such as lactose and sodium carboxymethylcellulose containing herbal extracts of *Cynara scolymus* and *Hamamelis virginiana* (Gallo et al., 2013; Gavini et al., 2005).

The first-order model showed the best fitting ($R^2_{cor} = 0.99$) to the release data of yerba mate polyphenols and zinc (Figs. 6 and 7). According to Costa and Sousa Lobo (2001), the systems following first-order release profile, release the active compound in a way that is proportional to the amount remaining in its interior, thus, the amount released by unit of time diminish.

4. Conclusions

Compressed tablets for the simultaneous carrying of zinc and yerba mate extract were developed. Corn starch allowed obtaining an effective zinc-carrier for tablet preparations. Co-crystallized sucrose with yerba mate antioxidants showed good flowability and compressibility properties and led to tablets with higher hardness than sucrose.

The fast-release profile showed by the tablets makes them suitable for oral applications. The multicomponent systems constitute an effective path to improve the intake of antioxidant compounds and essential minerals.

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