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Co-crystallization of zinc sulfate with sucrose: A promissory strategy to render zinc solid dosage forms more palatable

Alex López-Córdoba [a, *], Loreana Gallo [b], Verónica Bucalá [b], Miriam Martino [a], Alba Navarro [a, c]

[a] CIDCA, Centro de Investigación y Desarrollo en Criotecnología de los Alimentos, CONICET, Fac. Cs. Exactas (UNLP), 47 y 116, La Plata, Argentina
[b] Departamento de Ingeniería Química, PLAPIQUI, Universidad Nacional del Sur, CONICET, Camino La Carrindanga Km. 7, 8000, Bahía Blanca, Argentina
[c] Fac. Ingeniería (UNLP), 1 y 47, La Plata, 1900, Argentina

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ABSTRACT

The objective of this work was to develop solid dosage forms to improve zinc nutrition in high-risk populations. Powders containing zinc (17 mg/g) were obtained through co-crystallization in sucrose matrix with high encapsulation efficiency (98%). Co-crystallized powders showed water activity (0.6) and moisture content (2.0%) values characteristic of good stability. Moreover, these products showed an infrared spectrum similar to that of sucrose, indicating that no chemical interactions took place between the matrix components. Co-crystallized powders showed excellent compactibility leading to suitably hard compacts at a low compression force (4.9 kN). Besides, tablets were obtained with optimal values of hardness (4.8 kg_f) and low disintegration times (<5 min) using blends of co-crystallized powder (80% w/w), native corn starch (20% w/w) and magnesium stearate (1 g/100 g). The sensory evaluation of the tablets was performed obtaining a mean overall acceptability rating of 5, which corresponds to the neutral point of the hedonic scale used.

1. Introduction

Zinc (Zn) has an important role for human health, growth and development (Salgueiro et al., 2000; Tapiero and Tew, 2003). This mineral is an essential component of a large number (>300) of enzymes participating in the synthesis and degradation of carbohydrates, lipids, proteins, and nucleic acids as well as in the metabolism of other micronutrients (Chasapis et al., 2012; Salgueiro et al., 2000). Zn has pro-antioxidant properties which could help prevent the illnesses associated with oxidative stress (Goel et al., 2005; Powell, 2000; Zago and Oteiza, 2001). Several authors have reported that Zn inhibits NADPH oxidases, induces the production of metallothionein and competes with metal ions for binding to the cell membrane (e.g. Fe and Cu), thus decreasing the production of OH radicals (Prasad et al., 2004). Foods from animal origin, such as red meat, are considered the major dietary sources of Zn (25–50 mg/kg raw weight). Nevertheless, some populations in developing countries do not have access to micronutrient-rich foods, usually because they are too expensive to buy or are locally unavailable.

Zn deficiency could generate serious physiological disorders including growth retardation, a delay in sexual and skeletal maturation, respiratory infections, diarrhea, loss of appetite and appearance of behavioral change (Shrimpton et al., 2005; WHO, 2002). It is estimated that Zn deficiency is responsible for 4.4% of childhood deaths in Africa, Asia, and Latin America (Fischer Walker et al., 2008; Liberato et al., 2015). The most vulnerable groups to micronutrient deficiencies are pregnant, lactating women and young children, mainly because they have a relatively greater need for vitamins and minerals and they are more susceptible to the harmful consequences of deficiencies.

Nutrition intervention strategies that can be used to reduce the global prevalence of Zn deficiency are fortification, supplementation, and dietary diversification/modification. Several studies showed that the incidence of acute lower respiratory tract infections and malaria may also be reduced by zinc supplementation. Moreover, oral Zn treatment reduced the duration and severity of diarrhea in children from six months to five years old (Liberato et al., 2015). Therefore, the World Health Organization (WHO) and the United Nations Children's Emergency Fund (UNICEF)

* Corresponding author.
E-mail address: alexlcordoba@gmail.com (A. López-Córdoba).

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suggested new diarrhea management policies advocating oral Zn to decrease diarrhea deaths in the world's most vulnerable children (WHO and FAO, 2004).

Zn supplementation is most commonly provided as tablets or syrup. The following Zn sources are listed generally regarded as safe (GRAS): Zn gluconate, Zn oxide, Zn stearate, Zn chloride and Zn sulfate. The last is the most commonly used because it has the advantages of low cost and bioavailability (Allen, 1998; Rosado et al., 2012). It has been observed that the Zn from water-soluble salts (e.g. zinc sulfate) is more bioavailable than the Zn from water-insoluble compounds (e.g. zinc oxide) (Allen, 1998). Several authors have reported that some Zn compounds can generate side-effects such as nausea and vomiting (Salgueiro et al., 2002; Solomons et al., 2011). Unpleasant taste has been suggested as a reason for vomiting, but this is more likely due to zinc being a gastric irritant (Liberato et al., 2015). Therefore, the incorporation of these salts in their original state is not always possible and a previous process to face these disadvantages is often necessary.

Co-crystallization is a relatively new method that offers an economic and flexible alternative due to its operational simplicity. This encapsulation technique represents a viable means of enhancing the physical properties of active compounds such as solubility, dispersibility, wettability, anticaking, antidusting, anti-separation, homogeneity, flowability and stability (Bhandari and Hartel, 2002). In the sucrose co-crystallization process, the crystalline structure of this sugar is modified from perfect to irregular agglomerated crystals, to provide a porous matrix in which a second active ingredient can be incorporated. The co-crystallization process involves the concentration of sucrose syrups by evaporation at high temperature until the spontaneous crystallization of sucrose is achieved (Bhandari et al., 1998; Chen et al., 1988). At this point, the rate of crystal formation is so high that nuclei are formed spontaneously (Beristain et al., 1994). This is evidenced by the turbidity observed in the syrup due to the formation of irregular agglomerates. Commonly, the second ingredient is added at the time of spontaneous crystallization followed by cooling. Besides, the addition of the active ingredient into the concentrated syrup can improve the homogeneity of the final product, as it was reported in previous studies (López-Córdoba et al., 2014). The latent heat of crystallization is usually enough to evaporate the moisture, thus the product is substantially dry (i.e., moisture content below 1 wt.%), followed by screening, milling and packaging (Chen et al., 1988).

Co-crystallized products can be used as sugar-based ingredients to mask the bitter taste of active agents. Moreover, they offer direct tableting characteristics which provide significant advantages in the candy and pharmaceutical industries (Awad and Chen, 1993). As direct compression has become the preferred method of tablet manufacturing, demand for compressible sugar-based excipients has increased (Bowe, 1998). Few studies have been published reporting on the use of co-crystallization to drive the encapsulation process (Astolfi-Filho et al., 2005; Awad and Chen, 1993; Beristain et al., 1994, 1996; Bhandari et al., 1998; Bhandari and Hartel, 2002; Chen et al., 1988; Deladino et al., 2007, 2010; López-Córdoba et al., 2014; Maulny et al., 2005; Sardar and Singhal, 2013; Sardar et al., 2013). In addition, the tableting properties of co-crystallized materials containing Zn have not been reported. Recently, we investigated the development of tablets based on co-crystallized sucrose with natural antioxidants of yerba mate (*Ilex paraguariensis*) (López-Córdoba et al., 2015). In the present work, solid dosage forms (powders and tablets) containing Zn were developed based on WHO manufacturing guidelines. Zn-sucrose based excipients were obtained by co-crystallization, characterization of the products was carried out and sensory acceptability was tested. To the best of our knowledge, it is the first time that Zn delivery systems are developed using the co-crystallization technology.

2. Materials and methods

2.1. Preparation of the co-crystallized products

Zn sulfate.7H_20 (Parafarm, Argentina) was used as a source of Zn (4.4 mg of Zn sulfate provided 1.1 mg of elemental Zn). The initial moisture content of Zn salt, determined gravimetrically in an oven (SanJor, Argentina) by drying at 105 °C until constant weight, was 37% w/w.

The co-crystallized products were prepared as described by López-Córdoba et al. (2014). Briefly, blends of commercial sucrose (50 g) (Ledesma, Argentina), Zn sulfate (3.5 g) and distilled water (10 mL) were heated on a hot plate at different temperatures (80 and 132 °C). This stage was performed under continuous stirring at 500 rpm, using a vertical agitator (IKA Labortechnik, Staufen, Germany). The temperature and the solid soluble content of the blends were monitored continuously and the supersaturation ratio (S) was calculated as follows:

$$S = \frac{C}{C_o} \quad (1)$$

where C is the concentration of sucrose in the solution and C_o is the saturation concentration of the sugar at the same temperature. Values of $S > 1$ are characteristic of supersaturated solutions while $S = 1$ indicates saturation conditions. The parameter C_o was calculated as described by Hartel et al. (2011).

When the syrup reached the final temperature (80 or 132 °C), the thermal level was kept constant until a slight turbidity was detected, indicating the beginning of the crystallization process. Then, the blends were removed from the heat source and allowed to cool down to room temperature under constant agitation at 700 rpm. The co-crystallized products were dried in a convection oven (SanJor, Argentina) at 40 °C for 15 h and then 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 “control products”.

2.2. Determination of the Zn content

The Zn content 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.

The entrapment yield (%) was calculated as the ratio between the Zn mass loaded per gram of co-crystallized product and the Zn mass used in the formulation per gram of raw sucrose.

2.3. Characterization of the co-crystallized products

Moisture content (%) was measured gravimetrically by drying the grounded samples in a vacuum oven at 70 °C, until constant weight (AOAC, 1998). Values of water activity (a_w) were determined using AquaLab Serie 3 TE (USA) equipment.

Micrographs of the co-crystallized products were acquired by scanning electron microscopy (SEM) using FEI Quanta 200 equipment (The Netherlands). Zn sulfate distribution on the co-crystallized samples was tested by energy-dispersive X-ray microanalysis (EDX).

The thermal behavior of the powders was evaluated by