Solid dosage forms (powders and tablets) as an alternative to prevent zinc nutritional deficiency

Alex Fernando López Córdoba¹, Alba Sofía Navarro¹,², Miriam Nora Martino¹

1. Abstract

The objective of this work was to develop solid dosage forms (powders and tablets) containing zinc to supply the requirements of at-risk populations. Firstly, zinc loaded powders (17 mg/g powder) were obtained through co-crystallization in sucrose matrix with high encapsulation efficiency (98%). The co-crystallized products showed values of water activity (0.6) and moisture content (2%) characteristics of good stability. These products were also analyzed by differential scanning calorimetry (DSC) and no degradation peaks were found below 100 °C, showing a high thermal stability. Moreover, the zinc loaded powders showed similar FTIR spectra than raw sucrose indicating that interactions between the active compound and the matrix would not take place. Then, tablet formulations were obtained based on the co-crystallized powders with zinc (80% w/w), native corn starch (20% w/w) and magnesium stearate (1g/100g of blend). These blends showed low moisture content and acceptable flowability and compressibility. Finally, the formulations were directly compressed and tablets with high zinc content (4.5 mg per tablet) and optimal values of hardness (around 18 kPa) were obtained. In vivo disintegration time was evaluated by an untrained panel of ten judges obtaining values of around 3 min. Sensory evaluation of the tablets showed an acceptance level of 55%, thus, these systems could be a good alternative to help in preventing zinc deficiency.

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2. Introduction

Zinc (Zn) is an essential micronutrient for human growth, development and function of the immune system. Besides, Zn has antioxidant properties which could avoid the illness appearance from oxidative stress. Nevertheless, Zn deficiency is one of the ten biggest factors contributing to the burden of disease in developing countries with high mortality. Therefore, nowadays World Health Organization suggests the incorporation of this mineral in government nutritional programs (WHO, 2002).

Zinc sulfate is commonly used as a Zn source for supplementation due to its low cost and bioavailability. 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). Therefore, the incorporation of this salt in their original state is not always possible and a previous process to face these disadvantages is often necessary.

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. Co-crystallized products can be used as sugar-based excipients to mask the bitter taste of active ingredients. Moreover, they offer direct tableting characteristics which provide significant advantages in the candy and pharmaceutical industries (Awad and Chen, 1993). In the current work, solid dosage forms (powders and tablets) containing zinc were developed. The characterization of the products was carried out and the sensory acceptability was tested, as well.

3. Materials and methods

Co-crystallized powders with zinc

Zinc sulfate 7H2O (Parafarm, Argentina) was used as a source of zinc (4.4 mg of zinc sulfate provided 1 mg of elemental zinc). The co-crystallized products were prepared as described by López-Córdoba et al. (2014). Briefly, a blend of raw su-
sucrose (50 g) (Ledesma, Argentina), zinc sulfate (3.5 g) and distilled water (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 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 were ground and sieved through a 500 µm mesh. Blends of raw sucrose (50 g) and distilled water (10 mL) were crystallized as described above for control purposes. These samples will be referred as “control products”.

The zinc content of the products was quantified using a atomic absorption spectrometer model EspectrAA 300-plus (Cambridge, United Kingdom). The co-crystallization yield (%) was calculated as the ratio between the Zn mass loaded per gram of co-crystallized product and the Zn mass employed in the formulation per gram of raw sucrose.

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

The moisture content and the water activity (AquaLab Serie 3 TE equipment, USA) of the products were determined according to . The thermal behavior of the samples was tested by differential scanning calorimetry (DSC) (Q100 equipment, TA Instruments, USA). The main functional groups of the samples were identified by Fourier transform infrared spectroscopy (FTIR) (Nicolet IS-10 equipment, Thermo Scientific, USA). The flowability of the products was evaluated in terms of the dynamic repose angle and the Hausner (HI) and Carr (CI) indexes . HI is widely used as measurement of interparticle friction; HI values less than 1.2 are indicative of the good flowability of the material, whereas values of 1.5 or higher suggest a poor flow display by the material. CI is considered a good indicator of the potential bridge strength and stability; the lower CI values are indicative of better compressibility properties.

**Compressed tablets**

Tablet formulations were prepared based on co-crystallized powders (80 % w/w), native corn starch (20 % w/w) and magnesium stearate (1g/ 100 g of blend). Pre-
previous to the compression, the moisture content and the flowability of the blends were determined. Then, these were directly compressed on a single punch-tablet machine (Model SC1, Sanchez, Argentina), regulated to obtain tablets of around 325-370 mg, using flat-punches with a diameter of 9 mm.

The Zinc content of the compressed tablets was determined by atomic absorption spectrometry following the method mentioned above.

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 using a Erweka hardness tester (Erweka, Germany).

Besides, the time required for complete oral disintegration and the sensory acceptability were tested by 10 untrained judges (6 Males and 4 Females) aged between 28 and 35 years. The volunteers did not move their tongues during the test. The end point of oral disintegration was considered when a tablet placed on the tongue had disintegrated until no lumps remained. The disintegrated material was held in the mouth for another 30 s, and then spat out. The mouth was rinsed with water between samples and, finally, the acceptability level was recorded on a hedonic numerical scale ranging from 1 to 9 (1: dislike very much; 5: neither like nor dislike; 9: like very much)

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

4. Results and discussion

Co-crystallized products
The co-crystallization process allowed obtaining products with high zinc content (17 mg/g powder) with a yield process around 98%. Taking into account the Zn
recommended daily intake (RDA) for an adult established by FAO/WHO (11 mg), these products constitute a useful alternative to supply the mineral requirements.

Figure 1 shows morphological aspect and the superficial mapping of the zinc sulfate performed on the co-crystallized products, by SEM–EDX. The samples showed a typical structure corresponding to cluster-like agglomerates with irregular cavities between them. Moreover, energy dispersive X-ray microanalysis (EDX) confirmed a homogeneous distribution of both, zinc and sulfate, on agglomerates surface.

The co-crystallized products with zinc showed lower values of moisture content (2 %) than the raw zinc sulfate (37 %), suggesting that during the co-crystallization process the Zn salt was significantly dehydrated. The water activity of the products was around 0.6, which is favorable to prevent microbial spoilage (Fu and Labuza, 1993).

Figure 2 shows the DSC thermograms of raw zinc sulfate, control samples (without zinc) and co-crystallized products with zinc. The Zn salt showed several endotherms around 48, 82, 167 and 197 °C. The control samples exhibited an endothermic peak around 192 °C, typical of sucrose melting (Bhandari and Hartel, 2002). For the co-crystallized products with zinc no degradation peaks were found below 100 °C, showing a high thermal stability. These powders showed an endotherm around 201 °C, which was broad probably due to the overlapping of the bands located at 192 °C for the control sample and at 197 °C for the raw Zn sulfate. Besides, in the co-crystallized products, the others endotherms present in the thermograms of Zn sulfate were not found (Figure 2). This fact was attributed to both, the dehydration of the salt during co-crystallization process and the incorporation of the mineral into the sucrose matrix.

FTIR spectra of control samples (without zinc) and co-crystallized products with zinc are shown in Figure 3. Both samples showed signals at 3319, 3012, 2970, 2941, 2983, 1128, 1069, 991 and 942 cm⁻¹ corresponding to the “fingerprint” of sucrose (Brizuela et al., 2012). This fact suggests that conformational changes on the sugar did not take place during the co-crystallization process. Besides, bands corresponding to the zinc salt were not detected in the co-crystallized products, probably due to the low amount of mineral in relation to the sucrose mass.

The flowability parameters of the raw materials, the control samples and the co-crystallized products with zinc are shown in Table 1. The dynamic repose angle ranged between 40 and 50° in all cases. Several authors have reported that materials
with repose angle between 40 and 50° can be handled satisfactorily, while products with repose angle higher than 50° correspond to very cohesive materials (Geldart et al., 2006; Santomaso et al., 2003).

Hausner (HI) and Carr (CI) indexes are useful quality parameters to evaluate the flowability and also the ability of powders to form tablets. Both parameters, HI and CI, suggested that the raw materials and the co-crystallized products showed good flowability and compressibility. These indexes were agreed with the results of the repose angle measurement (Table 1).

**Compressed tablets**

Co-crystallized products with zinc led to compressed tablets with optimal characteristics (Table 2). In addition, the tablet formulations showed low moisture content (around 2%) and acceptable flow properties (repose angle greater than 50; HI: 1.2-1.5; CI: 21-26%).

The tablets showed a Zn content around 4.5 mg per tablet. This mineral dosage corresponds to 41% of the recommended daily intake (RDA) for adults, useful to avoid deficiency and prevent toxicity (FAO/WHO). The tablet hardness values were around 18 kPa, which are suitable to facilitate their handling. Working with co-crystallized sucrose with dextrin, found that these co-crystallized materials were deformed readily by plastic fracture leading to much harder compacts compared with sucrose which is a brittle material.

With respect to the *In vivo* disintegration times, values of around 3 min were obtained. 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, compressed tablets with appropriate hardness but also fast disintegration were achieved. This behavior could be attributed to the high solubility of sucrose and zinc sulfate in water and also to the action of starch as disintegrating agent.

The sensory evaluation of the tablets showed a mean overall acceptability rating of 5, corresponding to the neutral point of the 9-points hedonic scale (“neither like nor dislike”). This score correspond to a consumer acceptance level around 55%. On the other hand, the frequency distribution analysis showed that 22% of judges evaluated the tablets with rating between 7 and 9, 56% with rating between 4-6 and 22% with rating between 1 and 3. These results suggest that the use of co-crys-
tallized sucrose with zinc in tablet preparations constitute a potential strategy to render more palatable the bitter taste of zinc-dosage forms.

5. Conclusions

Zinc solid dosage forms in powder and compressed tablets were developed. Co-crystallization process proved a useful technique for the preparation of powders with high zinc load, low water activity and moisture content and good flowability and compressibility. Besides, the co-crystallized products led to compressed tablets with suitable hardness, fast-oral disintegration times and optimal sensory perception. The developed products constitute a very feasible way to prevent zinc nutritional deficiency.

Acknowledgements

The authors would like to thank the Argentinean National Research Council (CONICET). In memoriam Dra. Miriam Martino (1958-2014).

6. References


7. TABLES AND FIGURES

![Morphological aspect and superficial mapping of the zinc sulfate on the co-crystallized products, performed by SEM–EDX](image-url)

**Figure 1.** Morphological aspect and superficial mapping of the zinc sulfate on the co-crystallized products, performed by SEM–EDX
**Figure 2.** DSC thermograms of raw zinc sulfate, control samples (without zinc) and co-crystallized products with zinc

**Figure 3.** FTIR spectra of control samples (without zinc) and co-crystallized products with zinc
**Table 1.** Flowability parameters of raw materials, control samples and co-crystallized products with zinc

<table>
<thead>
<tr>
<th>Samples</th>
<th>Dynamic repose angle</th>
<th>Hausner Index</th>
<th>Carr compressibility index (%)</th>
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<tbody>
<tr>
<td>Raw zinc sulfate</td>
<td>49.1 ± 0.5</td>
<td>1.1 ± 0.05</td>
<td>12.8 ± 3.2</td>
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<tr>
<td>Raw sucrose</td>
<td>41.9 ± 2.6</td>
<td>1.1 ± 0.01</td>
<td>9.1 ± 1.1</td>
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<tr>
<td>Control product</td>
<td>41.8 ± 4.7</td>
<td>1.0 ± 0.04</td>
<td>7.05 ± 0.5</td>
</tr>
<tr>
<td>Co-crystallized product with zinc</td>
<td>47.1 ± 5.9</td>
<td>1.2 ± 0.07</td>
<td>12.5 ± 2.9</td>
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</tbody>
</table>

**Table 2.** Physical properties and sensorial evaluation of the tablets

<table>
<thead>
<tr>
<th>Physical properties</th>
<th>Sensory evaluation</th>
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<tbody>
<tr>
<td></td>
<td>Average weight (mg)</td>
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<td>344± 12</td>
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*9-points hedonic scale: 1: dislike very much; 5: neither like nor dislike; 9: like very much