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Gelatin/starch orally disintegrating films as a promising system for vitamin C delivery

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ABSTRACT

Orally disintegrating films (ODFs) may disintegrate rapidly or slowly when in contact with saliva, acting as carriers of different compounds. The objective of this work was the production of gelatin and starch ODFs as vehicles of vitamin C obtained via a spray-drying method from camu-camu powder. ODFs were produced by mixing gelatin and/or starch as main components, sorbitol as plasticizer, and the powder from camu-camu as an active compound. The ODFs were characterized regarding their visual qualities, mechanical properties, contact angle, surface pH, disintegration time (*in vitro* and *in vivo*), ascorbic acid degradation, antioxidant activity stability and sensory attributes. The ODFs were homogeneous and easy to handle. An increased starch concentration in the ODF promoted a significant increase of hydrophilicity and thus, the decrease of *in vitro* disintegration time. The ODFs also showed a fast *in vivo* disintegration time. Moreover, the evaluation of the sensory attributes demonstrated that ODF consumption was palatable to the panelists. Therefore, ODFs with camu-camu extract can be used as an efficient and natural supplementary source of vitamin C and as a potential carrier of antioxidant compounds.

1. Introduction

Several compound delivery systems have been studied. Among these, the development of fast-release vehicles has been highlighted. Ciper and Bodmeier (2005) listed new systems that are based on rapidly disintegrating dosage forms of freeze-dried tablets (Zydis®), compressed tablets (Orasolv®, Durasolv®, Wowtab®, FlashDose®) and fast-dissolving films (Listerine® Pocketpacks). One of the new systems is an oral strip or orally disintegrating film (ODF), which is a thin film that is prepared using hydrophilic polymers blended with a plasticizer (Cilurzo, Cupone, Minghetti, Selmin, & Montanari, 2008) that rapidly dissolves (disintegration time is approximately 60 s) on the tongue or within the buccal cavity (Mandeep, Rana, & Nimrata, 2013).

Several studies have demonstrated the use of different polymers to fabricate oral films that have pharmaceutical potential due to their dosage form (Adrover & Nobili, 2015; Azim, Nafee, Ramadan, & Khalafallah, 2015; Borges & Carvalho, 2015; Cilurzo et al., 2008; Kianfar, Chowdhry, Antonijevic, & Boateng, 2012). In all cases, contact with saliva promotes hydration of the films and, consequently, a disintegration and/or dissolving process. Among the polymers employed to fabricate ODFs, starch and gelatin have received special attention (Castro et al., 2015). Starch is readily available from renewable sources and has the ability to form transparent, tasteless, odorless and biodegradable films (Acosta, Jiménez, Cháfer, González-Martínez, & Chiralt, 2015). Moreover, modified starches form rapidly dissolving films. Otherwise, gelatin has a high film-forming ability with good mucoadhesive properties. Both polymers are considered to be non-toxic, non-irritant materials and are listed as generally recognized as safe (GRAS) and included in the FDA Inactive Ingredient Guide (Dixit & Puthli, 2009).

Water-soluble vitamins, such as vitamin C, represent a structurally and functionally diverse set of organic molecules that play crucial roles in maintaining metabolism, energy, differentiation and proliferation status of cells (Azim et al., 2015; Said, 2004). Vitamin C plays a potential role in minimizing the risk of several diseases (cancer, heart disease, cataracts), and its deficiency is associated with the disease known as scurvy (Padayatty et al., 2003). The human body is unable to synthesize this vitamin and cannot store

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it. Therefore, suitable amounts must be ingested, often through the diet or supplements (Nishikimi, Fukuyama, Minoshima, Shimizu, & Yagi, 1994; Nishikimi, Koshizaka, Ozawa, & Yagi, 1988).

The population consumes different sources of vitamin C daily, especially from fruits. Several studies have indicated that camu-camu (*Myrciaria dubia* McVaugh), an exotic fruit native to the Amazon rainforest in Brazil (Akter, Oh, Eun, & Ahmed, 2011), is a potential source of this important vitamin (Genovese, Pinto, Gonçalves, & Lajolo, 2008; Gonçalves, Lellis-Santos, Curi, Lajolo, & Genovese, 2014; Neves, Campos, Colombo, Roberto, & Cisneros-Zevallos, 2017; Rufino et al., 2010; Vidigal, Minim, Carvalho, Milagres, & Gonçalves, 2011; Zanatta, Cuevas, Bobbio, Winterhalter, & Mercadante, 2005). Camu-camu represents one of the richest sources of vitamin C, similar to acerola and cashew apple fruits, and is a promising source of various bioactive compounds, such as phenolic compounds and carotenoids (Genovese et al., 2008; Gonçalves et al., 2014; Zanatta et al., 2005). Therefore, the aim of this study was to develop an ODF using the natural polymers gelatin and starch supplemented with a camu-camu powder, a great source of vitamin C and active compounds.

2. Materials and methods

2.1. Materials

Pig skin gelatin type A (Gelita, Bloom 260 and mesh 40, Brazil), pregelatinized starch (AMIDOMAX 3600, Cargill Ltda., Brazil) and sorbitol (Vetec, Brazil) were used to produce films. Ascorbic acid (Synth, Brazil, 99% purity) and DPPH$^{\bullet}$ (2, 2-diphenyl-picrylhydrazyl, Sigma Aldrich, USA) were employed for the determination of the vitamin C content and antioxidant capacity. Camu-camu (*Myrciaria dubia*) fruits were kindly provided by the Brazilian Agricultural Research Corporation (EMBRAPA, Brazil), and maltodextrin (DE 12) was donated by Ingredion Products (Brazil).

2.2. Methods

2.2.1. Production of camu-camu powder

Camu-camu fruits were washed in running water and pulped using horizontal equipment for the extraction of fruit pulp (Compacta, Brazil) with a strainer diameter of 1 mm. The pulp was packed in low-density polyethylene bags (approximately 800 g) and frozen at −18 °C until use. A pasteurization process was performed according to Bastos, Ladeira, Rogez, and Pena (2008) at 90 °C for 60 s. Subsequently, maltodextrin (15%), a carrier agent (Dib Taxi, Menezes, Santos, & Grosso, 2003), was added to the pulp under mechanical agitation (IKA, RW20 model, USA) at 500 rpm and room temperature (25 ± 2 °C) for 30 min. Camu-camu powder was prepared using a spray dryer according to the methodology proposed by Dib Taxi et al. (2003), with a flow rate that was fixed at 20 mL/min and an inlet temperature that was set at 150 °C. The outlet air temperature was 95 ± 3 °C.

2.2.2. Production of orally disintegrating films (ODFs)

ODFs were produced by casting technique using different gelatin:starch ratios, 100:0 (gelatin-ODF), 80:20, 60:40, 40:60, 20:80, 0:100 (starch-ODF). The polymer concentration (gelatin and pregelatinized starch) was kept constant at 2 g of polymers/100 g filmogenic solution. The concentration of plasticizer (sorbitol) used in all formulations was 20 g/100 g of polymer. Gelatin was hydrated (30 min) in distilled water at room temperature (25 ± 2 °C), and then, the dispersion was solubilized at 90 °C (10 min) using a thermostatic bath (Marconi, MA 127 model, Brazil). Starch was dispersed in distilled water at room temperature (25 ± 2 °C) and maintained under magnetic stirring for 30 min; following dispersion, the starch was solubilized using a thermostatic bath (Marconi, MA 127 model, Brazil) at 90 °C (10 min).

The gelatin and starch solutions were homogenized under magnetic stirring (IKA, Big squid, USA) for 3 min and were kept at 90 °C in thermostatic baths (Marconi, MA 127 model, Brazil) for 10 min. In this new solution, sorbitol, previously dissolved in distilled water, was added and homogenized using magnetic stirring (IKA, Big squid model, USA). The solution was cooled to 30 °C (room temperature), and then, the camu-camu powder was added under magnetic stirring (IKA, Big squid model, USA) at a concentration of 4 g of powder/100 g of the filmogenic solution. The solution was placed into acrylic plates (12 cm × 12 cm) for drying in an air circulation oven (Marconi, MA 035 model, Brazil) at 30 °C for 24 h. The film thickness was controlled as a function of the mass of the filmogenic solution (24 g) in the plates and was determined by using a digital micrometer (0.001 mm, IP − 65 model, Mitutoyo, Japan) through the arithmetic average of 10 random measurements of the film surface. Before characterization (color parameters and opacity, mechanical properties, contact angle, surface pH and disintegration time *in vitro* and *in vivo*) films were stored in desiccators containing a saturated NaBr solution for controlling the relative humidity (58%) at 25 ± 3 °C for 5 days. Analyses were performed in a climate-controlled room at 25 ± 2 °C (relative humidity of 50–60%).

2.2.3. Visual aspect

Visual analyses of the ODFs were performed based on the following parameters: homogeneity (uniform color and absence of insoluble particles), capacity for film formation (absence of discontinuous zones after the drying process), and manageability (the ability to remove the ODFs from the plates).

2.2.4. Color parameters and opacity

The determination of the color parameters (luminosity, chroma a* and chroma b*) was performed according to Gennadios, Weller, Hanna, and Froning (1996), using a Miniscan XE (HunterLab) colorimeter with a CIE Lab system (Comisson Internationale de Eclairage). The opacity was determined using the equipment software, which calculated the relation between the opacity of the superimposed film on the black pattern (Pblack) and that on the white pattern (Pwhite) according to Sobral (2000).

2.2.5. Mechanical properties

The tensile strength (TS) and elongation at break (EB) of the ODFs were determined by tensile tests according to the ASTM method D882-10 (ASTM, 2010) using a TA.XT2 plus texturometer (Stable Microsystems SMD, England). ODF samples were cut into 70 mm × 25 mm strips. The initial separation distance was kept at 50 mm, and the test speed was 50 mm/min. The TS and EB were obtained directly from the tension vs. elongation curves, and the elastic modulus was determined by using the angular coefficient in the linear part of the curve. Each treatment was analyzed with fifteen replicates.

2.2.6. Contact angle measurements

The contact angle was measured at room temperature (25 ± 2 °C) using a tensiometer Attension Theta Lite (KSV Instruments, USA). For all formulations, the contact angle was determined for the side that remained in contact with the air during the drying step of the film fabrication. Digital pictures were analyzed by Attension Theta Lite software version 4.1.9.8 (NIH, USA) for angle determination. ODF samples were fixed with equipment support, and a deionized water droplet (5.0 μL) was deposited onto the film surface. Digital pictures were captured after 10 s of deposition, and the images were used to calculate the contact angle. Five replicates were taken at different positions of the ODF.