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# Assessment of physicochemical properties, dissolution kinetics and storage stability of a novel strawberry confection designed for delivery of chemopreventive agents

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ARTICLE INFO

*Article history:*
Received 9 May 2013
Received in revised form
7 September 2013
Accepted 8 October 2013
Available online 17 October 2013

*Keywords:*
Confection
Strawberry
Physicochemical properties
Dissolution
Oral delivery

ABSTRACT

Oral diseases are a common health concern within the United States, and have been associated with increased risk of certain chronic disease and reduced overall quality of life. A unique starch-based confection containing freeze-dried strawberries was developed for sustained, targeted phytochemical release to the oral mucosa for use in future chemoprevention trials. Sensory evaluation was used to optimize the confectionery formulation for this investigation. Physicochemical properties, scanning electron microscopy and dissolution studies revealed the effects of 14-day storage on phytochemical release from the amorphous semisolid matrix. Upon storage, moisture content decreased 4% and water was more tightly bound. Rheological testing revealed Newtonian-like response to shear below 10 $s^{-1}$ and pseudoplastic behavior at higher shear. Changes in the food structure were observed with scanning electron microscopy. Total phenolics released in phosphate buffer (47.2 ± 2.7 mg GAE/L) or simulated saliva (66.7 ± 1.2 mg GAE/L) after 10 h from fresh confections was significantly ($p = 0.001$) greater compared to stored confections in phosphate buffer (39.0 ± 2.9 mg GAE/L) and simulated saliva (56.4 ± 1.0 mg GAE/L). Strawberry confections may be a novel strategy for localized delivery and sustained release of strawberry bioactive compounds.



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*Abbreviations:* SEM, scanning electron microscopy; OSU, The Ohio State University; ISO, International Organization for Standardization; JAR, Just About Right; TGA, thermogravimetric analysis; TPA, texture profile analysis; USP, The United States Pharmacopeial Convention; SPB, sodium phosphate buffer; GAE, gallic acid equivalents; SD, standard deviation; ANOVA, analysis of variance; DSC, differential scanning calorimetry; LSP, lyophilized strawberry powder; $T_g$, glass transition temperature.

2213-3291/$ – see front matter 
http://dx.doi.org/10.1016/j.foostr.2013.10.001

## 1. Introduction

Oral health has a significant effect on overall health and quality of life (Gift & Atchison, 1995; Petersen, Bourgeois, Ogawa, Estupinan-Day, & Ndiaye, 2005). Oral diseases are a common health concern in the United States, and studies have revealed that poor oral health may lead to increased risk of certain chronic diseases (Grossi et al., 1997; Meurman, Sanz, & Janket, 2004). Inflammation, dry mouth, tooth decay, and tooth loss consequently disrupts saliva production, mastication, swallowing, organoleptic perception, nutritional deficiencies (Chen, 2009; Gift & Atchison, 1995). Diets rich in fruit and vegetable have been implicated in promoting health (Kolonel et al., 2000; Winn, 1995). Specifically, fruit consumption has been associated with preventing maladies of the mouth, larynx, and esophagus. Fruit phenolics have been shown to elicit significant chemoprotective effects on oral mucosa when evaluated in animal models (Casto, Knobloch, & Weghorst, 2011; Seeram, 2008).

In particular, phytonutrients from strawberries (*Fragaria* × *ananassa*), such as ellagitannins, anthocyanins, flavonols, and catechins, confer known anti-inflammatory, anti-oxidant, and anti-carcinogenic properties that could improve associated oral maladies (Seeram, 2008; Zafra-Stone et al., 2007). Promising results from human clinical studies have shown that strawberry compounds, specifically anthocyanins are readily absorbed by oral epithelial cells and converted by salivary enzymes to bioactive aglycone forms within a relatively short contact time (Seeram, 2008). However, because of the relatively high moisture content in strawberries (~90%), lyophilizing strawberries is critical for concentration (~10-fold) of phytonutrients and fundamental for maximizing their delivery (Craig, Royall, Kett, & Hopton, 1999; Stoner, 2009). Moreover, selection of strawberry cultivars with high phytochemical content (Meyer et al., 2004; Meyers, Watkins, Pritts, & Liu, 2003) and control of post-harvest processing (Asami, Hong, Barrett, & Mitchell, 2003) collectively contribute to developing an optimized functional strawberry confection for clinical trials.

The health benefits of naturally occurring strawberry phytochemicals can be targeted to specific tissues by developing a food-based vehicle which contains relevant doses for bioactive response. Pharmaceutical dosing forms such as gums and troques can be effective vehicles for delivery of active ingredients to the oral mucosa, but unlike a starch-based functional confection have limited palatability and require mechanical stress to liberate the active ingredient which can pose a challenge to individuals with significant oral maladies (Madhav, Shakya, Shakya, & Singh, 2009). Therefore developing a soft confection consisting of fruit phytochemical from which bioactive compounds can be easily liberated from its starch matrix without mastication may be a desirable strategy for delivery of bioactive ingredients to the oral mucosa. Moreover, starch-based, confection systems provide an environment suitable to support the stability of fruit phytochemicals and provide the structure for their sustained localized delivery. Many fruit bioactives can readily undergo chemical transformation or degrade within a food system during processing but in this novel confectionary system, pH, moisture content, and solute concentration were carefully examined and formulation was developed to prolong exposure of fruit phytochemicals to the oral mucosa (Klopotek, Otto, & Böhm, 2005; Sadilova, Carle, & Stintzing, 2007).

A unique starch-based confection containing freeze-dried strawberries was developed to provide sustained, targeted release of phytochemicals to the oral mucosa to promote oral health in future phase I/II clinical trials. In this study, an optimized strawberry confection was selected to assess if sugars and starch recrystallization in an amorphous solid during storage affects the release of phytochemicals under physiologic conditions of the oral cavity.

Starch-based confections are amorphous semisolids that offer many advantages over traditional crystalline preparations including increased solubility, improved rate of release, recovery upon compression, and can be readily formulated from low-cost biopolymers (Leuner & Dressman, 2000; Yu, 2001). While amorphous solids offer advantages over crystalline forms, they are heterogeneous in nature and therefore not as stable. Characterization of amorphous forms unlike crystalline forms is not simple. Food amorphous forms require a multifaceted approach to their characterization because they are a composite of multiple food components and inherently are prone to changes particularly during storage (Yu, 2001). For instance, water absorption in the proximate environment of the confection affects relaxation of the confection matrix and crystallization of the food ingredients. Moreover, water becomes a plasticizer and facilitates the release of phytochemicals when low moisture, amorphous, functional confections when placed in the oral cavity (Roos & Karel, 1991). Dissolution tests used commonly in pharmaceutics is an ideal tool to measure the release of active ingredients from solids under physiologic conditions (Abdou, 1990). Thus this method can be employed as a novel approach to assess the role of structure on entrapment and controlled release of phytochemicals in a functional confection (Hao & Heng, 2003).

The delivery and deposition of phytochemical in the oral cavity are critical in directing functional confection design; however, the functional confection must retain its identity as a pleasant tasting food. Therefore, sensory evaluation was used to select for an optimized formulation. Physicochemical characterization of time-dependent effects on confectionery gel structure was conducted from a macroscopic perspective using textural analyses and scanning electron microscopy (SEM) and from a molecular perspective using rheometry (small amplitude oscillatory testing) and thermal analysis.

Therefore the objective of this study was to compare physicochemical properties of the confection with *in vitro* dissolution studies to determine the feasibility of the confection to sustain phytochemical release in the oral cavity and to quantify time-dependent changes in the confection upon storage.

## 2. Materials and methods

### 2.1. *Strawberry preparation*

Three strawberry varieties (Albion, Wel-Pict, and Driscoll proprietary variety) were provided by the California Strawberry Commission (Watsonville, CA). They were hand-picked