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Polysaccharide hydrogel particles for enhanced delivery of hesperidin: Fabrication, characterization and *in vitro* evaluation

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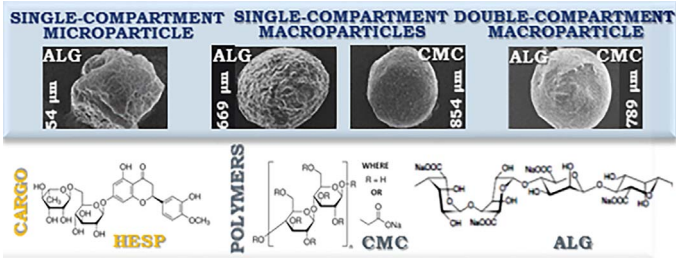
GRAPHICAL ABSTRACT



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ABSTRACT

In the present contribution we focus on the fabrication and characterization of targeted delivery systems suitable for encapsulation of hesperidin (HESP) – a natural health-promoting flavonoid glycoside. We fabricated and extensively studied pH-responsive, biodegradable double-compartment hydrogel carriers composed of sodium carboxymethyl cellulose particles (ACP) filled with hesperidin-loaded sodium alginate microparticles (AMP). Additionally, hesperidin was encapsulated directly in sodium alginate or sodium carboxymethyl cellulose particles (AP or CP, respectively). The obtained carriers were characterized in respect to their morphology and size by using scanning electron microscopy (SEM). The cargo encapsulation was confirmed by spectroscopic analysis (FTIR), while the process efficacies were derived spectrophotometrically (UV–vis). The effect of different pH on the stability of the beads has been assessed. The *in vitro* release kinetics of the fabricated HESP-loaded particles was studied in simulated gastric and intestinal environments. The fabrication processes yielded stable particles of desired properties. Comparing the results obtained for both single- and double-compartment systems, makes it possible to conclude that the latter is superior in regard to prolonged delivery of hesperidin to the place of action under simulated intestinal conditions.

1. Introduction

The encapsulation approach is an emerging technology in which various types of micro-vesicles are designed in order to seal or entrap inside or within their structure a variety of chemically sensitive materials [1]. In the recent years extrusion and emulsification processes were the most frequently utilized methodologies for encapsulation of functional ingredients, such as drugs, bioactive compounds, as well as nutritional and food additives. These techniques can provide various gastroenteric delivery systems, usually based on hydrocolloids. It should be noted, however, that there are several challenges in fabrication of the desired carriers for site-specific targeting and tailored (controlled, sustained) release of the encapsulated cargo. The main objective of using colloid-based microparticles designed for oral administration is to ensure stability of the payload during processing, storage and transfer through the human gastric tract [2]. To improve a

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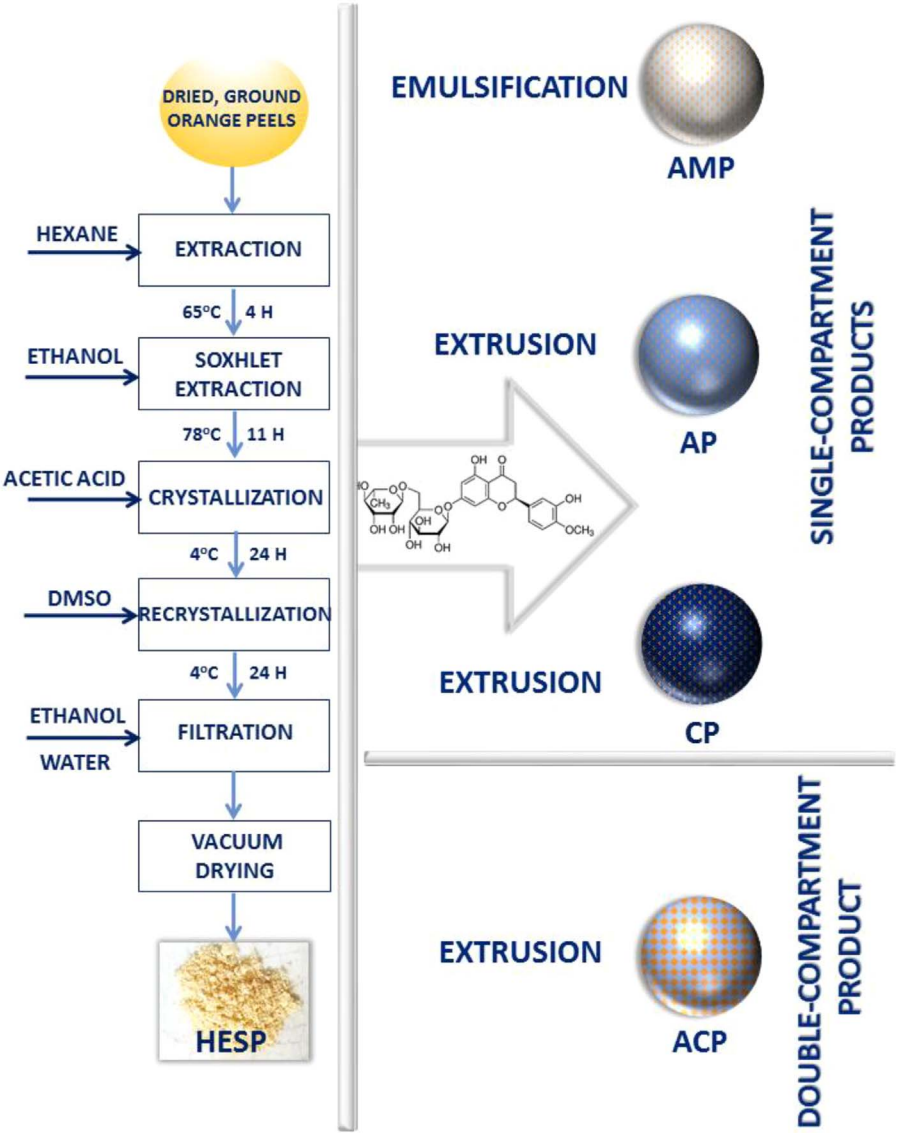

Scheme 1. Schematic illustrations of procedure of isolation of hesperidin and procedures of fabrication of hydrogel particles. For details see descriptions in Sections 2.2 and 2.3 respectively.

release mode of the cargo and to promote its sustained release, as well as to increase its gastric residence time, several novel encapsulation approaches have been introduced that are intended to enhance the uptake and the therapeutic effect of the bioactive compounds [3–6]. Among a variety of key factors, the nature of the materials used exerts a great influence on the physicochemical properties of the formulated systems [2]. Alginic acid sodium salt (ALG), a water soluble polysaccharide composed of D-mannuronic and L-guluronic acid residues, is an abundantly available biopolymer extensively used for formation of encapsulating systems [7], as it easily forms stable gels [8]. The gelation process occurs when divalent ions and the guluronic residues crosslink and form three-dimensional networks. Alginate micro-delivery systems exhibit some limitations – the matrices formed are porous, thus precise control of the release rate of the payload is impeded. Therefore, a combination of biopolymers is widely used to overcome this drawback and to reinforce the appropriate performance properties of the hydrogel particles [8]. Carboxymethyl cellulose sodium salt (CMC), one of the most extensively utilized hydrophilic cellulose derivatives, formed of linear cellulose chains with carboxymethyl groups attached to gluco-pyranose monomers, is another carbohydrate polymer that has regularly been applied in the encapsulation approaches for fabrication of micro-delivery systems [9]. These selected carbohydrates are preferred as building biomaterials for the hydrogel structures. Apart from any economic advantages (inexpensiveness and easy availability), both ALG and CMC demonstrate an important benefit, as they may be solidified by ionotropic gelation in the presence of multivalent cations [1]. This unique property enables them to form fully functional and effective delivery systems involving a single-step procedure that holds a considerable potential for successfull entrapment of different molecules inside the carriers. Moreover, since these materials are considered to be safe and biocompatible, they can be used to fabricate orally administrated vesicles. Although the fabricated distribution microsystems usually stay intact in acidic environment, in alkaline environment both polymers exhibit negative charges, therefore, under intestinal conditions they demonstrate enhanced mucoadhesive properties [8].

Recently, numerous plant-derived bioactive compounds have been used as functional foods, nutraceuticals and in treatments of various diseases. However, the phytochemicals are often sensitive to light, temperature, moisture or oxygen, therefore their effectiveness may be reduced in adverse environmental conditions [10], including human gut. Any systems designed for protection and delivery of those molecules require formulations that would ensure maintenance of their biological activity until they reach the targeted site within the organism [10]. According to literature reports, the encapsulation process of phenolic compounds may improve their stability and bioavailability,