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Natural fibre envelope for cross-linked and non-cross-linked hydrogel-drug conjugates: Innovative design for oral drug delivery

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ABSTRACT

Recent years have witnessed growing demand for cost-effective natural bioproducts for therapeutic applications. In this work, cardamom husk was processed and turned into a protective shield for the hydrogel-drug conjugate. The seedless cardamom husk comprises of crude fibers and offers effective protection to the encapsulated hydrogel-drug matrix against degradation. Sodium alginate (SA) and gelatin were the biodegradable polymers utilized, while naproxen sodium (hydrophilic) and piperine (hydrophobic) were used as model drugs. The polymer-drug blend encased in this husk was engineered to give a long hour, zero-order release kinetics for both types of drugs. The hydrogel-drug conjugate was carefully optimized to achieve a controlled release with minimal or no use of cross-linkers. The viscosity of sodium alginate was used in such a way that the synthesis of a cross-linker free hydrogel-drug blend can be a reality. The husk was also found to be stable near sterilization temperatures. This research not only focusses on an available resource in nature but also showcases the role of modern methodology to convert this resource (cardamom husk) into a protective shield for a polymeric blend carrying drug molecules.

1. Introduction

Drug delivery applications have commonly used biodegradable polymers like gelatin [1,2], sodium alginate [3,4], chitosan [5], etc. These polymers have been remodeled into 3D hydrogels [6–8], thin films [9], micelles [10,11], and transdermal patches [12]. In general, few common imperfections hinder the acceptance of these vehicles. These are mainly associated with the vehicle design i.e. its degradability, stability in the presence of enzymes, use of toxic cross-linkers like glutaraldehyde (GTA) [13] and high initial release of drugs that cross the therapeutic window. Apart from this, the cost of processing these biodegradable polymers to build drug eluting vehicles is usually high. To overcome these drawbacks, we had earlier worked on biodegradable hydrogels [6] and soya nuggets [14]. Still few of the shortcomings like nonuniform drug distribution in hydrogels and lower loading efficiency (10–15 mg) in soya nuggets were unattended.

This work involves the precise incision of cardamom and removal of its seeds. Cardamom is an Indian spice (by origin, but consumed throughout the world) that is widely used as a flavoring agent in foods [15]. Moreover, it has limitless medicinal properties and has been utilized in the treatment of digestive problems. The past and current research on cardamom focus on its seeds which are rich in essential oils [16,17]. In this work, the cardamom husk has been taken into an advantage that has a very low oil content and is rich in crude fibers (31%) [18]. Cardamom husk is the protective polymer casing around its seeds. The precise removal of the seeds leaves us with the empty husk, which has been effectively modified as a drug carrier in this research. The empty husk (after seed removal) was used as a carrier to encapsulate hydrogel-drug conjugates. Sodium alginate (SA) (Low viscosity (LV) and High viscosity (HV)) and gelatin were used as the biodegradable polymers while naproxen sodium (hydrophilic) and piperine (hydrophobic) were used as the model drugs. The polymer-drug ratios were optimized to achieve a balance between the drug release and polymer degradation. Initially, the hydrogel-drug conjugates were optimized using crosslinkers like GTA, genipin (GEN), and $CaCl_2$ but later it was realized that the viscosity of SA was instrumental in controlling the conjugate degradation and zero order release could be achieved without any cross-linker. The research shows a way to achieve cross-linker free vehicle and describes a less complicated protocol to remodel cardamom husk into a protective envelope that shields the hydrogel-drug matrix with realistic drug loading for oral delivery. The biopolymers used in this research are FDA approved (SA/G) including cardamom husk, which itself is consumed throughout the world. Thus, a natural resource (cardamom

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husk) is introduced, which when coupled with the modern procedures, transforms itself into a highly potential low-cost envelope that can preserve the hydrogel-drug matrix in harsh conditions (pH 1.2). This is the first use of cardamom husk as a hydrogel-drug carrier.

2. Materials and methods

2.1. Materials

Natural cardamom was purchased from Life Style Foods, Private Limited, Haryana, India. Sodium alginate: high viscosity (HV) (1000–1500 cps, 1% in water) and low viscosity (LV) (40–90 cps, 1% in water), gelatin, β cyclodextrin, naproxen sodium, piperine (98%), glutaraldehyde (GTA) (25% v/v Aqueous solution), calcium chloride ($CaCl_2$) and phosphate buffer saline (PBS, pH 7.4) were purchased from Alfa Aesar (Thermo Fisher) while genipin (GEN) and tween 20 were purchased from Sigma-Aldrich.

2.2. Preparation of hydrogel-drug conjugate and its encapsulation

The process of transforming cardamom husk into a carrier for the hydrogel-drug matrix can be seen in Fig. 1. A variety of polymer-drug mixtures were used like Gelatin/Naproxen, SA/Naproxen, Gelatin/SA/Naproxen and Gelatin/SA/Piperine. (Fig. 1**c**). Two different varieties of SA i.e. LVSA (40–90 cps, 1% in water) and HVSA (1000–1500 cps, 1% in water) were used in this work. This polymer/drug mixture was then allowed to form a blend (hydrogel-drug conjugate) inside the cardamom husk. GTA, Calcium chloride ($CaCl_2$) and GEN solutions were used for cross-linked cases while only deionized water was used to form non-cross-linked blends inside the husk. (Fig. 1**d**). The exact compositions of polymers (SA/G) and cross-linkers used to prepare the hydrogel-drug conjugate can be seen in Table 1.

Once the gel was formed the tip of the husk was sealed using a solution of gelatin/β-cyclodextrin (4:1 in 20 ml of water), as it forms a very sticky solution that seals the tip (Fig. 1**e**). The sealed husk was then dried for 24 h. To further strengthen the sealed tip, the loaded husk was further cross-linked using either GTA or GEN solutions for 10 min and again dried (Fig. 1**f,g**). This step (Fig. 1**f**) is not required for non-cross-linked cases as the cargo can be used after sealing with Gelatin/β-Cyclodextrin solution (Fig. 1**e**). Hence for cross-linked conjugates, the methodology involves two-step cross-linking i.e. the blend **(B)** and the tip **(T)**.

2.3. Drug release study

The drug release study for naproxen was done in 500 ml of PBS (pH 7.4) and 0.1N HCl (pH 1.2), mimicking the biological fluids. 3 ml of aliquots were collected at fixed time intervals and were quantified using UV–vis spectroscopy. The protocol for drug release study of piperine was different when compared to that of naproxen. 100 ml of PBS with 5% Tween 20 was used for release study at pH 7.4, while 100 ml of 0.1N HCl with 5% Tween 20 was employed at pH 1.2. Tween 20 was added to enhance the solubility of piperine in PBS as well as in HCl. These samples were replaced after every 2 h with the fresh ones to ensure the sink conditions for the hydrophobic drug. The analysis was performed using UV–vis spectroscopy (Perkin Elmer Lambda 35) at 272 nm (λ_{max}, naproxen) and 342 nm (λ_{max}, piperine). All the experiments were carried out in triplicates and the standard deviations were calculated to ensure the reproducibility.

2.4. Scanning electron microscopy

The morphology of the cardamom husk was studied using a tabletop SEM (Phenom world, Pro X). The husk was gold sputtered to reduce the charging effect and was analyzed at an acceleration voltage of 15 kV.

2.5. FTIR-ATR analysis

Cardamom husk was analyzed using Fourier transform infrared spectrophotometer (Bruker Alpha P). Attenuated total reflectance (ATR) method was used without any pre-treatment of the cardamom husk. Spectra were obtained between 400 and 5000 cm^{-1} which were further processed using the OPUS software.

2.6. Thermal studies

The thermogravimetric analysis was performed using a Perkin Elmer Pyris 1 TGA (Thermogravimetric Analyzer). 10 mg of cardamom husk was placed in a platinum pan and was heated from 30 °C to 1000 °C in an argon atmosphere at the rate of 10 °C/min.

3. Results and discussion

3.1. Drug release study

The sealed husk, carrying the polymer drug conjugate in its shell was tested for drug release at pH 7.4 and 1.2. It was expected that naproxen sodium would form a homogenous blend with gelatin due to its high solubility in water. The study began with the case, where 50 mg gelatin and 70 mg naproxen were encapsulated in the shell (husk) and allowed to form a gel inside using GTA (0.1% B, 0.02%T).

A release of 20 mg was observed for the first 24 h which increased to 33 mg in 36 h and 49.5 mg in 48 h (Fig. 2**a**). To further enhance the rate of drug release, GTA concentration used to cross-link the tip was reduced (also reduces potential toxicity) to 0.01% (T) (Fig. 2**a**). The loading amount of naproxen was also increased to 80 mg which resulted in a proportionate increase in its release (Fig. 2**b**).

The drug release was promising and the reason for this release at pH 7.4 was the ionization of carboxyl groups present in gelatin and naproxen into carboxylate ions. This ionization induces repulsions in the gelatin matrix that results in its swelling, which forces the drug out, into the solution due to increased osmotic pressure. As pH 1.2 never induces such ionization of carboxyl groups, only 10 mg naproxen release was observed in 36 h at pH 1.2, which was promising as the major drug release is intended in pH 7.4 i.e. the region of the intestine where the maximum absorption of the drug occurs (Fig. 2**c**). The standout feature of this release study was that the release kinetics was found to be zero order in all the cases for 48 h (Table 2, r^2 values: 0.98/0.99 for all the cases). But, the major concern here was the potential toxicity of GTA that could affect the acceptability of this vehicle on a large scale. To overcome this drawback, GTA was first replaced with GEN (biodegradable, non-toxic cross-linker though with prohibitively high cost) (Fig. 2**d**). To again overcome this stumbling block, gelatin was also replaced by sodium alginate (LVSA), where 5% $CaCl_2$ (nontoxic & low cost) was used as a cross-linker for the blend (B), while 0.02% GEN was used only for the tip(T) (Fig. 2**e**). Zero-order release kinetics was observed for both the cases (Table 2).

Since the husk offers a hard, rigid protective shell to the encapsulated hydrogel-drug matrix, it was thought that a controlled release of naproxen could be achieved without any cross-linker. To achieve this, two cases were studied, **(i)** 70 mg naproxen mixed with 50 mg HV SA **(ii)** 70 mg naproxen mixed with 25 mg HV SA

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