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Organized polysaccharide fibers as stable drug carriers

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ABSTRACT

Many challenges arise during the development of new drug carrier systems, and paramount among them are safety, solubility and controlled release requirements. Although synthetic polymers are effective, the possibility of side effects imposes restrictions on their acceptable use and dose limits. Thus, a new drug carrier system that is safe to handle and free from side effects is very much in need and food grade polysaccharides stand tall as worthy alternatives. Herein, we demonstrate for the first time the feasibility of sodium iota-carrageenan fibers and their distinctive water pockets to embed and release a wide variety of drug molecules. Structural analysis has revealed the existence of crystalline network in the fibers even after encapsulating the drug molecules, and iota-carrageenan maintains its characteristic and reproducible double helical structure suggesting that the composites thus produced are reminiscent of cocrystals. The melting properties of iota-carrageenan:drug complexes are distinctly different from those of either drug or iota-carrageenan fiber. The encapsulated drugs are released in a sustained manner from the fiber matrix. Overall, our research provides an elegant opportunity for developing effective drug carriers with stable network toward enhancing and/or controlling bioavailability and extending shelf-life of drug molecules using GRAS excipients, food polysaccharides, that are inexpensive and non–toxic.

1. Introduction

Drug discovery and development are challenging, laborious and expensive endeavors. High throughput screening processes continuously give rise to a gamut of new molecules; however, a majority of them fail as prospective drugs due to, in part, poor pharmacokinetics. If successful, the method by which the drugs are delivered to the target site has a controlling effect on their bioavailability and consequently on the therapeutic effectiveness. Drugs are most often administrated by the oral route. These traditional delivery approaches rely primarily on the dissolution and stability properties inherent to the API (active pharmaceutical ingredient) and modifications achievable through the incorporation of pharmaceutically inactive components, *i.e.* excipients. Thus, there is a recognized unfilled need for the design and deployment of new pharmaceutical materials, especially composites of known and reproducible structures made from API's and functional excipients.

Certain drugs have a narrow therapeutic index within which the maximum benefit can be derived and beyond the therapeutic window it is toxic if too high or ineffective if too low. In this regard, there is a growing interest to formulate delivery systems with predefined systemic exposure level, specific rate and time intervals. Such motivation, coupled with the complexity of newly developed drug molecules and associated elevated costs, necessitates the design and discovery of optimal delivery vehicles. Synthetic and biodegradable polymers readily serve the purpose (Langer & Tirrell, 2004; Langer, 1990). Nonetheless, the possible side effects and toxicity impose restrictions on acceptable dose formulations and warrants the search of new carrier systems that are safe and cost-effective. Bio-macromolecules are viable alternatives (Goldberg & Gomez-Orellana, 2003; Takakura & Hashida, 1996) but many of them lack organized networks and stable molecular architecture, which deter their widespread utilization. Herein, we demonstrate the feasibility of GRAS polysaccharides especially in their organized state, as in oriented fibers, to effectively encapsulate and release drug molecules. The type systems introduced here are crystalline API-polymer composites and to the best of our knowledge this is the first report on this subject.

Natural polysaccharides such as cellulose, chitin and starch acquire semi-crystalline organization during their biosynthesis. In contrast, polysaccharides routinely employed in food, pharmaceutical and medicinal applications as thickening and gelling agents (Stephen, 1995) do not possess ordered networks. However, they can be coaxed, under suitable experimental conditions, to form extended fibers having sturdy molecular and packing structures.

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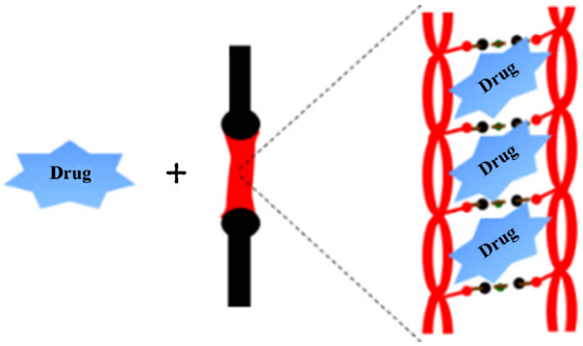

Fig. 1. Schematic encapsulation of drug molecules in the polysaccharide fibers. The drug molecules are securely encased between a pair of helices, viewed normal to helix-axis, and gain protection from external influences such as temperature, heat and moisture.

For example, systematic studies on iota-carrageenan, an anionic sulfated seaweed, has revealed that well-oriented and crystalline fibers can be prepared by judiciously selecting polysaccharide concentration, salt amount and relative humidity (Janaswamy & Chandrasekaran, 2001, 2002, 2005, 2006). Three-dimensional structure analysis reveals that it adopts a three-fold, parallel and fairly rigid double helical structure with pliable peripheral sulfate groups. The negative charges preclude iota-carrageenan association due to repulsion but cations promote inter-helical interactions. This process results in a well-orchestrated hexagonal network having 8–15 Å wide webs imbued with water molecules (Janaswamy & Chandrasekaran, 2001, 2002). These structural pockets are intrinsic feature of the crystalline iota-carrageenan fibers and are of similar dimensions of many drug molecules, and thus can be advantageously utilized as molecular cavities for entrapping molecules of interest, as illustrated in Fig. 1. Overall, our approach is about incorporation of host drug molecules into the crystalline biopolymer networks, and the resulting API-biopolymer composites are analogous to cocrystals observed in the case of small molecules.

In the present study, we tested the ability of iota-carrageenan (IC) fibers to entrap a range of drug molecules. The model drugs used include benzocaine, furosemide, griseofulvin, hydrocortisone, ibuprofen, indomethacin, phenylephrine HCl, sulfapyridine and thymol. These compounds cover a range of structural variety and therapeutic indications. The reason for choosing a series of chemically unrelated drugs is to demonstrate the viability of our methodology to encapsulate and deliver a wide variety of molecules with low aqueous solubility. This article reports the formation and structure of IC:drug cocrystals and the thermal protection of the drugs offered by these systems as well as the drug release properties. Our results suggest that upon encapsulation, IC fibers maintain crystalline network, protect the embedded drug molecules from thermal degradation and release in a controlled manner.

2. Experimental

2.1. Materials

Sodium iota-carrageenan (IC) was donated by FMC Corporation, USA and was used as received. Analytical grade benzocaine, furosemide, griseofulvin, hydrocortisone, ibuprofen, indomethacin, phenylephrine HCl, sulfapyridine, thymol and NaCl were purchased from Sigma–Aldrich. Reagent grade isopropyl alcohol and double distilled water were used as necessary.

2.2. Preparation of iota-carrageenan fibers

In a vial, 15 mg of IC was homogeneously dispersed in 1 mL of distilled deionized water with periodic vortexing, followed by subsequent addition of 6 mg of NaCl. The polysaccharide and salt concentrations were based on previous reports (Janaswamy & Chandrasekaran, 2001, 2006), and the excess salt amount was to enhance the crystallinity in the fibers. The vial was placed in a hot water bath for 30 min at 90 °C with intermediate vortexing and later cooled to room temperature. Approximately 20 μL of solution was suspended between two glass rods held at 1/8″ apart in a fiber puller at 75% relative humidity. The solution was then allowed to partially dry over a 4–6 h time period. During semisolid state, fibers were stretched incrementally to 2–3 times their original length. They were then dried in the fiber puller for 24 h before being cut from the glass rods for further analysis.

2.3. Preparation of iota-carrageenan:drug cocrystals

Isopropyl alcohol (IPA) was used as the solvent for solubilizing drug molecules. Solutions containing 0.1% of the drug were prepared by dissolving 20 mg of drug in 19 mL of IPA followed by an additional 1 mL of distilled water. The excess water was intended to loosen the fiber network and to facilitate drug diffusion during cocrystal formation. IC fibers were immersed in the drug:IPA:water mixture for 2 weeks after which they were taken out and equilibrated at 75% relative humidity. A control sample was formed by immersing the carrageenan fibers in the IPA:water solution but with no drug added.

2.4. X-ray fiber diffraction patterns and unit cell dimensions

Structural organization of IC and IC:drug cocrystals was analyzed using X-ray fiber diffraction principles. Synchrotron intensities were collected at 14-BMC beamline, BioCARS, Argonne National Laboratory, Chicago, IL. The wavelength of X-ray beam was 0.979 Å and the data were recorded on a CCD with 2 s exposure. Fiber to detector distance was accurately estimated by dusting the fibers with calcite power (3.035 Å characteristic spacing). FiberFix (Rajkumar, Al-Khayat, Eakins, Knupp, & Squire, 2007) from CCP13 suite of programs was used to process the images and to estimate the pattern center, detector to fiber distance, fiber tilt and rotation. Reflection positions in each quadrant were measured and the corresponding ρ (the distance between the origin and reflection point in the reciprocal space) was estimated. The relationship between ρ, and the cylindrical radius (ξ) and vertical component (ζ) is given by: $\rho^2 = \xi^2 + \zeta^2$, where $\xi = a^*(h^2 + hk + k^2)^{1/2}$ for the trigonal system ($a = b \neq c$, $\gamma = 120^\circ$) and $\zeta = lc^*$. The reciprocal unit cell dimensions, a^* and c^*, as well as Miller indices (h, k, l) for each reflection were estimated and the unit cell parameters, a and c, were calculated using in-house programs.

2.5. Modulated differential scanning calorimetry (MDSC)

MDSC was performed using a DSC Q2000 from TA instruments (New Castle, DE). The equipment was calibrated with a NIST traceable Indium disk. Sample sizes of 2.0 ± 0.1 mg were sealed in Tzero aluminum hermetic pans and were analyzed under a nitrogen gas flow of 50 mL/min. The temperature was ramped from 0–230 °C at a rate of 5 °C per minute with a modulation of ±1 °C every 60 s. Pure drug samples were also analyzed in the same manner with the exception that the ending temperature was 10 °C above their melting point. Samples were tested in duplicate and average values are reported.