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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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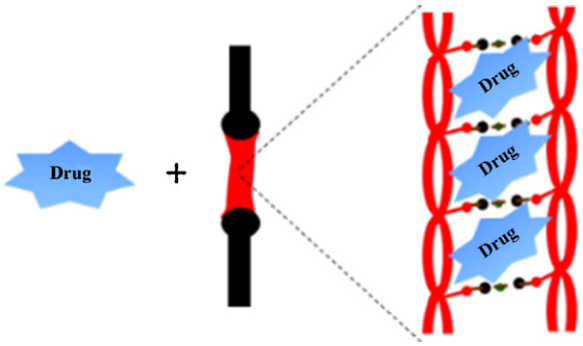

Fig. 1. Schematic encapsulation of drug molecules in the polysaccharide fibers. The drug molecules are securely encased between a pair of helices, viewed normal to helix-axis, and gain protection from external influences such as temperature, heat and moisture.

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.

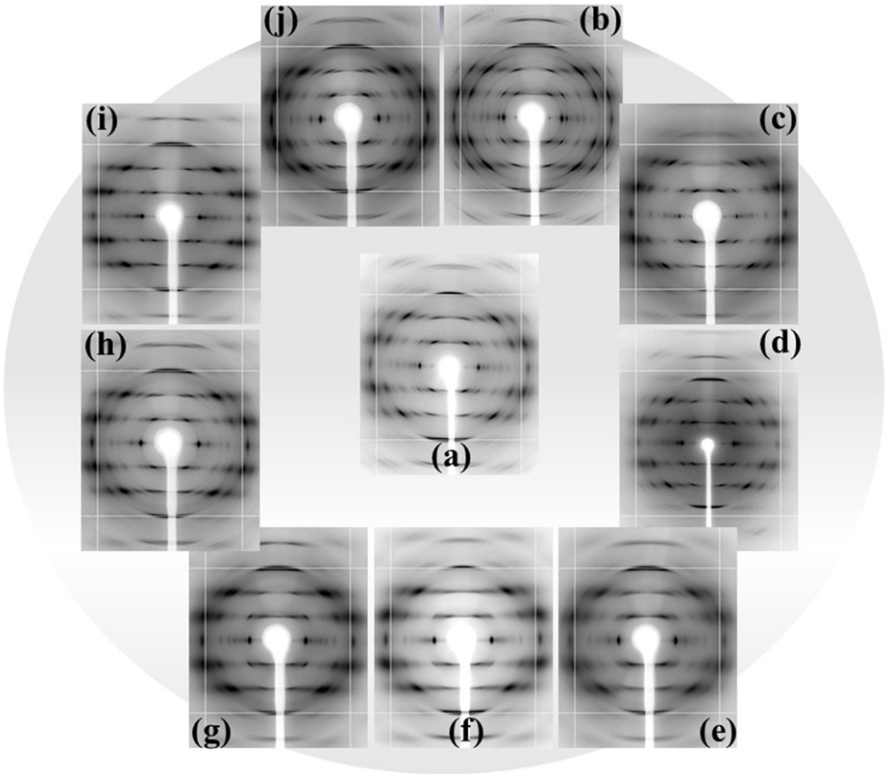

Fig. 2. X-ray diffraction patterns from well oriented and polycrystalline fibers of (a) iota-carrageenan, and iota-carrageenan:drug cocrystals (b) benzocaine, (c) furosemide, (d) griseofulvin, (e) hydrocortisone, (f) ibuprofen, (g) indomethacin, (h) phenylephrine HCl, (i) sulfapyridine and (j) thymol. The fibers are almost perpendicular to the incident X-ray beam. The first reflection on the meridian (meridian is an imaginary line in the north–south direction passing through the center) suggests the helix fold.

2.6. Rheology

Small angle oscillatory tests were performed on 2% aqueous solutions of IC and IC:drug cocrystals. The solutions were made at least 12 h before testing so as to ensure that the fibers were fully dissolved. A rheometer model AR-G2 from TA instruments (New Castle, DE) was used with 20 mm cone and plate geometry and a truncation gap size of 51 μm. About 80 μL of solution was used for each test. In order to minimize the water loss during experimentation, a small amount of water was placed near the sample and the testing area covered. Strain sweeps of the solutions were performed in the range 0.01–100% strain to determine the linear viscoelastic range. Change in the storage modulus G′ and loss modulus G″ as a function of frequency were measured from 0.01 to 100 Hz at 1% strain (linear region) and room temperature. Furthermore, temperature sweep in the range 5–80 °C was performed at 1% strain and 1 Hz. Average values from duplicate measurements are reported.

2.7. Drug release from iota-carrageenan:drug cocrystals and quantification

Concentration testing was performed using a Beckman Coulter DU 730 Life Science UV/vis Spectrophotometer. IPA was used as the solvent for generating the calibration curves of the pure drugs. Initially, a wavelength scan was performed in the range 200–600 nm for determining the optimum wavelength of absorbance. Subsequently, calibration curve of each drug molecule was generated by dissolving known amounts in IPA. Disposable UV cuvettes were used to hold the samples and generate time release profiles. Initially, spectrometer was zeroed with cuvette containing only water. Drug amounts were estimated using the calibration curve, and measurements from duplicate analysis are averaged and reported.

3. Results and discussion

3.1. Structural characterization

The diffraction patterns of IC and IC:drug cocrystals contain uniformly sharp Bragg reflections extending up to 2.8 Å indicating long-range ordering in the fibers (Fig. 2). The crystalline nature of all the patterns unambiguously suggests the resilient nature of IC network while accommodating a range of drugs, *i.e.* the formation of polymeric cocrystals. In all the patterns, the first meridional reflection is seen on the third layer line indicating the intact three-fold helical structure of IC. Nevertheless, size and intensity differences of Bragg reflections and changes in their positions hint structural differences among the complexes. Fig. 3 highlights the equatorial intensity distribution in all the diffraction patterns. In the case of IC, two strong reflections at 0.0910 and 0.2426 $Å^{-1}$ (ξ) are followed by weak reflections at 0.0505, 0.1029, 0.1165, 0.1358, 0.1569, 0.1788 and 0.2176 $Å^{-1}$. These positions and intensities change upon drug encapsulation. For example, in IC:benzocaine, reflections are observed at 0.0523, 0.0920, 0.1045, 0.1373, 0.1546, 0.1792 and 0.0.2410 $Å^{-1}$ but none at 0.1165 and 0.2176 $Å^{-1}$. Similar behavior is noticed in the rest of the cocrystals prepared in this study. All the diffraction patterns are indexable on the trigonal system (Table 1). The layer line spacing (c = half of the helix pitch of IC) is approximately the same but there are considerable changes in the basal net (a) dimensions. While the intact layer line separation indicates unperturbed IC molecular structure, variations in a unequivocally point out altered packing modes adapted by IC while accommodating the drug molecules in its lattice. In the IC:drug cocrystals with benzocaine, sulfapyridine, indomethacin, ibuprofen and griseofulvin, the cell edge a is maintained at 24 Å as in native IC. But, it becomes 37.3 Å after encasing furosemide molecules, 56.1 Å with phenylephrine HCl, 62.4 Å with thymol and the longest of

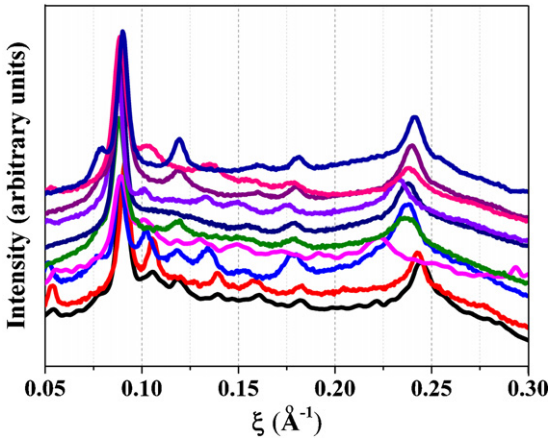

Fig. 3. Intensity distribution on the equator in iota-carrageenan (bottom most) and its binary complexes with benzocaine, furosemide, griseofulvin, hydrocortisone, ibuprofen, indomethacin, phenylphenine HCl, sulfapyridine and thymol (from bottom to top).

76.5 Å with hydrocortisone so as to accommodate a greater number of IC helices and drug molecules while modulating the packing schemes. The changes in the unit cell dimensions are convincing proof of encapsulation of drugs in the IC fibers, and it appears that the number of drug molecules and IC helices involved in the network formation in each complex is not conserved. The preservation of crystalline networks by IC fibers even after encapsulation is the most notable outcome of this study. The expansion of the unit cell dimensions indicates the distinctive attribute of IC in producing adjustable but with well-organized networks that are capable of holding host of molecules. These are significant results considering that IC:drug cocrystals thus obtained can be termed as inclusion complexes, *e.g.* cyclodextrins (Del Valle, 2004; Szejtli, 1994; van de Manakker, Vermonden, van Nostrum, & Hennink, 2009). Cyclodextrins are characterized with immutable cavity sizes. In contrast, cavity dimensions in the IC network (referred as pockets in this article) are adjustable, which in-turn results in incorporation of drugs of various sizes without obliteration of the underlying crystalline network.

3.2. Modulated DSC (MDSC)

To assess the effect of encapsulation on the thermal and melting properties, IC fibers, pure drug molecules (benzocaine, furosemide, griseofulvin, ibuprofen, indomethacin and sulfapyridine) and IC:drug cocrystals have been subjected to MDSC analysis. Table 2 summarizes the measured glass transition temperature, crystallization and melting behaviors. Fig. 4 depicts the total heat signal of the MDSC, which in general corresponds to the thermogram obtainable using conventional DSC. Pure ibuprofen melts

Table 1
Unit cell dimensions (trigonal lattice: $a = b \neq c$, $\gamma = 120^\circ$) of iota-carrageenan (IC) and its complexes with drug molecules.

Sample	a (Å)	c (Å)
IC	24.02	12.93
IC:benzocaine	21.15	13.19
IC:griseofulvin	21.32	13.21
IC:sulfapyridine	21.38	13.16
IC:indomethacin	22.16	13.27
IC:ibuprofen	24.57	13.13
IC:furosemide	37.31	13.05
IC:phenylephrine HCl	56.05	13.23
IC:thymol	62.44	13.32
IC:hydrocortisone	76.49	13.15

Table 2
The crystallization and melting temperatures (°C) of iota-carrageenan (IC) and its complex with drug molecules.

Sample	Crystallization	Melting	
		Pure drug	Complex
IC	180.4 ± 0.1	186.1 ± 0.1	
IC:benzocaine	170.9 ± 2.1	089.6 ± 0.4	171.9 ± 0.5
IC:furosemide	170.4 ± 0.4	206.0 ± 0.1	179.2 ± 11.5
IC:griseofulvin	179.9 ± 1.4	219.9 ± 0.1	187.1 ± 0.6
IC:ibuprofen	169.0 ± 1.1	075.9 ± 0.5	169.0 ± 1.0
IC:indomethacin	172.6 ± 0.2	160.8 ± 0.3	172.7 ± 0.1
IC:sulfapyridine	174.3 ± 0.9	191.9 ± 0.2	176.4 ± 5.1

around 76 °C, while pure IC fibers display an exothermic event at 180 °C immediately followed by endothermic one at 186 °C. The exothermic peak in the IC fibers is assigned to crystallization of the amorphous content present in the fibers and the endothermic event is assigned to the melting of the junction zones in the crystalline network of the fibers. Encapsulation of the drug molecules results in two significant changes in the thermograms. The first difference is directly noticeable from the total DSC heat flow: IC:ibuprofen cocrystals do not display melting arising from either the ibuprofen molecules or IC fibers. Another one is the endothermic baseline shift observed prior to the exothermic peak in Fig. 4a and c. The baseline shift in the pure IC (Fig. 4a) is comparably smaller than that in the IC:ibuprofen cocrystals (Fig. 4c). The corresponding temperature ranges are also different: ~140–150 °C in IC (Fig. 4a) *vs.* ~120–160 °C in IC:ibuprofen cocrystals (Fig. 4c). Though the peak shapes are somewhat similar, the results clearly suggest that these two profiles might represent different melting events. In order to better understand these occurrences, reversing and non-reversing thermal components of IC and IC:ibuprofen cocrystals have been analyzed. Fig. 5 depicts the MDSC heat flow components of the pure IC (Fig. 5a) and the IC:ibuprofen cocrystals (Fig. 5b). The endothermic baseline shift in Fig. 5a is entirely reflected in the reversing heat flow signal. This is the MDSC signature of a glass transition and it is consistent with the presence of amorphous content in the complex. Conversely, Fig. 5b shows that the endothermic shift is entirely reflected in the non-reversing component

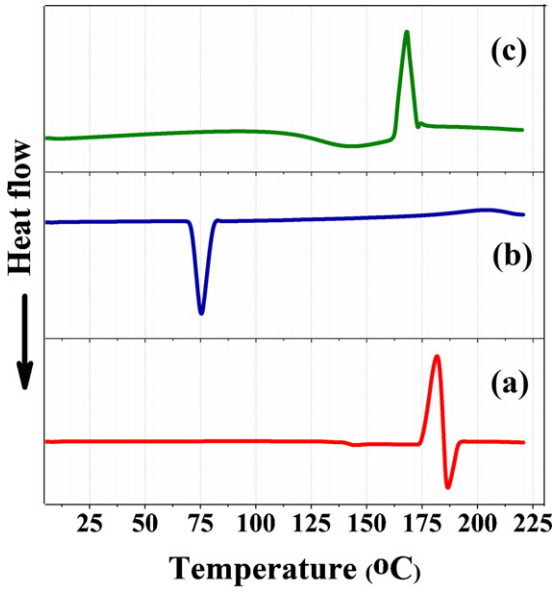

Fig. 4. Modulated differential scanning calorimetry (MDSC) profiles confirm the thermal protection of the drug molecules from the iota-carrageenan network after encapsulation. (a) iota-carrageenan, (b) ibuprofen, and (c) iota-carrageenan:ibuprofen cocrystal.

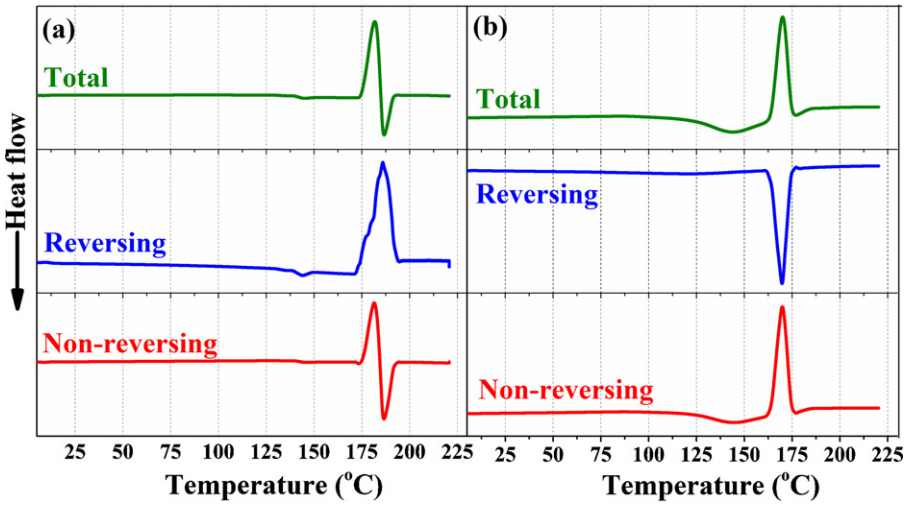

Fig. 5. Modulated DSC heat flow component signals of (a) pure iota-carrageenan fibers and (b) iota-carrageenan:ibuprofen cocrystal fibers.

indicating that the sample does not exhibit a glass transition event. The endothermic (non-reversing) shift in this case is actually a broad peak, most likely reflecting the thermally induced dissociation of the IC:ibuprofen cocrystals.

Upon encapsulation melting from neither ibuprofen nor IC is detected, instead crystallization takes place at 169 °C, around 11 °C lower than for the pure IC. The ibuprofen molecules present in the binary complex are responsible for the crystallization of amorphous phase at lower temperatures. It is noteworthy that the absence of endothermic event (melt) in IC:ibuprofen cocrystals (Fig. 4c) is only apparent. Its reversing signal (Fig. 5b) shows a clear endothermic peak, suggesting that while the melt of pure IC follows immediately after the crystallization (Fig. 4a), in the cocrystal the melting event actually overlaps with the crystallization (Fig. 5b). Similar results are observed with benzocaine encapsulation (results not shown). In the complex, absence of ibuprofen melting indicates non-existence of its crystals, and a close examination of the three-dimensional structure of IC provides the necessary details. Though the number of ibuprofen molecules encapsulated in any water pocket in the network is yet to be determined, one molecule is likely in successive pockets, they are separated laterally by IC helices and vertically by the chemical repeat of IC (two sugar units). Consequently, formation of ibuprofen crystallites is unlikely and hence inter-molecular associations that are necessary to trigger the melting during DSC heating are absent.

In the case of high melting point drugs furosemide, griseofulvin and sulfapyridine, the complex decomposition temperature increases by about 8 °C. Subsequent heating results in the melting of the drug but at a lower temperature of 12–35 °C. For example, griseofulvin melts at 220 °C and the melting temperature decreases by 33 °C after encapsulation. Similarly, sulfapyridine melts at 192 °C and the corresponding drop is about 16 °C. The temperature reduction appears to be correlated to the melting point of the pure drug (Fig. S1, Supporting Information) but this relationship needs further verification with more examples. Decrease in melting generally results in higher aqueous solubility, and thus drug encapsulation in the polysaccharide fibers will be useful for enhancing their solubility during formulations.

3.3. Solution properties

In order to gain insights about the solution behavior after encapsulation, viscoelastic properties of benzocaine and ibuprofen embedded in the IC fibers have been subjected to rheological measurements. The frequency sweep results of 2% solutions (Fig. 6) suggest that in IC the storage (G′) and loss (G″) moduli are close to each other confirming a weak gelling behavior. Similar trend is exhibited by the complexes too; however, benzocaine and ibuprofen encapsulation results in elastic and viscous solutions, respectively. Temperature sweep indicates the elastic nature for IC in the range 5–20 °C followed by transition to a solution state (Fig. S2, Supporting Information). On the other hand, the IC:benzocaine cocrystal has a viscous behavior throughout the temperature range, while IC:ibuprofen exhibits a moderate elastic state below 35 °C. The differences in viscoelastic properties are presumably due to the solubility variations of benzocaine and ibuprofen; the aqueous solubility of benzocaine (0.4 g/L) is much higher than that of ibuprofen (1.6×10^{-4} g/L). Thus, IC:benzocaine might be

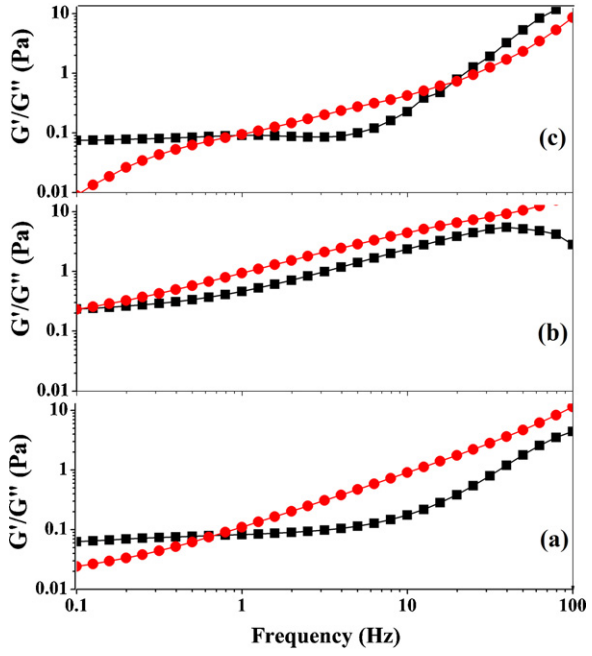

Fig. 6. Variation in the viscoelastic properties G′ (black filled squares) and G″ (red filled circles) of (a) sodium iota-carrageenan, (b) iota-carrageenan:ibuprofen cocrystal and (c) iota-carrageenan:benzocaine cocrystal as a function of frequency at 25 °C and 1% strain (linear region). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

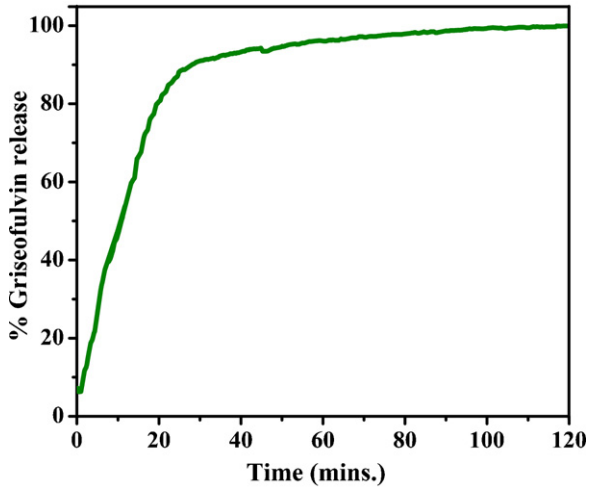

Fig. 7. Release rate of griseofulvin, measured at room temperature, from the iota-carrageenan:griseofulvin cocrystal.

forming heavily loaded network while ibuprofen disperses in the IC matrix leading to IC like gels.

3.4. Drug quantification and release profile

IC:griseofulvin has been selected as a model system for estimating the drug load in the IC fibers and understanding the drug release characteristics. The wavelength scan of griseofulvin yielded 291 nm as the optimum for highest absorbance. Subsequently, a calibration curve has been generated by measuring the griseofulvin absorbance from known concentrations. Duplicate absorption values are averaged and a linear regression is used to fit the data ($y = 71.2x - 0.1$: y represents the absorbance and x stands for the drug concentration, and $r^2 = 0.99$; Fig. S3, Supporting Information, portrays the corresponding calibration curve). Dissolution testing is performed by placing 3 mg of complex in 600 μL of distilled deionized water in a disposable cuvette, at room temperature and pH 7.0. The absorbance has been recorded every 2 min while shaking the cuvette every 60 s. The percent of griseofulvin released *vs.* time is shown in Fig. 7. The complex displays faster release within the first 30 min and a plateau is reached after 2 h. At 2 h, around 1.8 μg of griseofulvin per mg of IC has been released. In the case of benzocaine, the extent of release is significantly smaller (0.28 μg/mg) and takes considerably longer (>2 h, Fig. S4, Supporting Information). The strength of association and interaction between the encapsulated drug molecules and IC helices control the observed differences in the overall load amounts and release patterns of griseofulvin and benzocaine. The benzocaine molecules appear to be held strongly in the IC pockets though more favorable hydrogen bonds and van der Waals interactions. Tertiary structure analysis of IC:drug cocrystals is necessary to elucidate the molecular interactions responsible for these variations.

4. Conclusions

We have demonstrated for the first time the feasibility of cradling drug molecules in the well-orchestrated iota-carrageenan network and releasing in a controlled manner. The existence of ordered network in the complexes clearly suggests that they can indeed be similar to well-known cocrystals. Cocrystal is defined as a crystalline structure made up of two or more compounds in a definite stoichiometric ratio (Blagden et al., 2008; Bond, 2007; Schultheiss & Newman, 2009; Shan & Zaworotko, 2008; Vishweshwar, McMahon, Bis, & Zaworotko, 2006). These structures exhibit long-range ordering and their individual components interact *via* non-covalent interactions such as hydrogen bonds, ionic interactions, van der Waals interactions and π-interactions. In the binary complexes reported in this study, one is a crystalline biopolymer fiber with well-defined molecular and packing structure comprised of long polymer chains, and another a crystalline small molecule drug; thus we strongly believe that a more realistic way of representing our complexes could be to address them as "Polymeric Cocrystals". Further studies are needed to fully characterize this type of API-polymer composites.

The continuing quest for novel drug delivery agents led to the design and development of biopolymers (Goldberg & Gomez-Orellana, 2003; Langer & Tirrell, 2004; Takakura & Hashida, 1996), synthetic polymers (Duncan & Kopecek, 1984; Edlund & Albertsson, 2002; Patri, Majoros, & Baker, 2002; Sheridan, Shea, Peters, & Mooney, 2000), biodegradable polymers (Jeong, Choi, Bae, Zentner, & Kim, 1999; Pillai & Panchagnula, 2001; Winzenburg, Schmidt, Fuchs, & Kissel, 2004), hydrogels (Coviello, Matricardi, Marianecci, & Alhaique, 2007; Hoare & Kohane, 2008; Peppas, 1997) and lipids (Wissing, Kayser, & Muller, 2004; Zasadzinski, 1997) based carriers, to name a few. Their outstanding physical and biological properties satisfy a number of scientific drug delivery needs, but their low stability, arising from non-rigid frameworks, during actual delivery is an important drawback. In order to address this primary concern, the novel approach presented here capitalizes on the well-organized and crystalline polysaccharide fibers and their innate water pockets to encapsulate sparingly soluble drug molecules toward the development of stable drug delivery vehicles. The polysaccharide network is not only capable of protecting the encapsulated drugs from external influences, especially over prolonged storage, GI track transition and targeted delivery, but also acts as stable platform for timely delivery. We strongly believe that the aforementioned results with iota-carrageenan as a model system will hold good for other FDA approved polysaccharides such as kappa-carrageenan, lambda-carrageenan and xanthan. The charge balancing cations (*e.g.* Na^+, K^+, $Ca^{2+}$and Fe^{3+}) on these anionic polysaccharides will indeed provide a range of structural geometries for hosting drug molecules with variable release rates, and thus offer elegant opportunities for tailoring the release kinetics and dosage of drug carriers. The GRAS status of food grade polysaccharides and their compatibility with the human digestive system coupled with their low cost readily attest to the large scale production of polysaccharide-based stable and effective drug carriers. Though the direct application of our current research appears to be in the area of modified release of drugs, the notable property of crystalline polysaccharide fibers to cradle small molecules will be equally suitable for various bioactive compounds and health promoting molecules, *e.g.* nutraceuticals (Janaswamy & Youngren, 2012). Further research is necessary to take full advantage of the proposed methodology.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.carbpol.2013.01.008.

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