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Ultrasound-Triggered Release of Ibuprofen from a Chitosan-Mesoporous Silica Composite - a Novel Approach for Controlled Drug Release

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Summary: In this work, an attempt was made to synthesize a novel Chitosan-Mesoporous silica (CS-MS) hybrid composite to design a drug delivery system based on ultrasound triggered stimuli-responsive smart release. The in-vitro drug release properties of both the Mesoporous Silica (MS) and Chitosan (CS) hybrids were investigated. Ibuprofen (Ibu) was used as a model drug. The results from powder X-Ray diffraction (XRD) patterns, and BET N_2 adsorption isotherms exhibited that MS can accommodate drug molecules into the lumen of the channels and pores. Drug release, stimulated by temperature and pH of the release media was also investigated. We studied the Ultrasound (US) triggered release of Ibu in a simulated body fluid (pH 7.4). The results exhibited that US can be used as a non-invasive technique for drug release from polymeric materials. The enhancing effect of ultrasound on drug release is due to the Cavitation effect, without causing any significant destruction on the polymer morphology.

Keywords: chitosan; drug delivery systems; ibuprofen; mesoporous silica; ultrasound

Introduction

Chitosan (CS) is the deacetylated product of chitin, a pH dependent biopolymer found in the cell wall of fungi and microorganisms. Due to its biocompatibility, biodegradability, high mechanical strength, hydrophilicity, good adhesion, and non-toxicity, CS has been used in many biomedical applications[1] and acts as a promising encapsulating agent in drug delivery systems.[2-8] Ibuprofen (Ibu) is a non-steroidal anti-inflammatory (NSAID) drug used for the relief of rheumatoid arthritis and osteoarthritis. Due to frequent side effects, its therapeutic use is often limited.[9] This problem could be reduced by a formulation able to control the drug release. As matrices to prepare a controlled release formulation, we have taken into account the use of porous materials. The idea was to store the drug in the channels of a porous inorganic host and allow the drug release as a consequence of a de-intercalation and/or diffusion process. Recently, there has been increased concern in Mesoporous silica (MS) materials for use as carriers in controlled drug release.[10] Mesoporous silica has been investigated as a sustained release carrier agent because of its biocompatibility, non-toxic nature, adjustable pore-diameter, and very high specific surface area.[11-17] For a successful drug-delivery system, it is desirable that drug-delivery pattern is optimized to a pulsatile behavior in which the drug molecules are naturally released at the targeted site from the implant body. Release systems that are susceptible to external impulses such as oscillating magnetic fields,[18] thermal,[19] ultrasound,[20]

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or electric fields[21] at the target site have therefore been investigated to achieve on-demand drug regulation. In connection to this, US is considered as the most potential technique of external trigger for pulsatile delivery in which the release rate of the incorporated drug can be adjusted by applying ultrasound irradiation. Advantages of therapeutic ultrasound arise from the fact that it is relatively a noninvasive technique, broadly applicable to a variety of cells, can penetrate deep into the interior of the implant body, and it can be carefully controlled through a number of parameters including frequency, power density, duty cycles, and time of application. Although US irradiation technique is at its early stage of development, still a high-intensity US has found many biological applications.[22,23] So in this work US was used as an external trigger for the smart release of the incorporated drug. In contrast with the unidirectional channels present in the most commonly used MS, SBA-15 have attracted much attention due to their unique penetrating and bicontinuous channel network which is very useful for applications requiring easy molecular accessibility and fast molecular transport.[24] Of particular relevance to this study, during the release process, the loaded drug, Ibuprofen (Ibu), diffuses subsequently through the channels of MS and the CS molecular chains into the release medium. That is, the drug release is doubly controlled by the mesoporous shell and the biopolymer matrix. For Ibu loaded MS, only the MS shells control drug diffusion, which results in the sustained-release behavior alone.

Materials and Methods

Preparation of Mesoporous Silica (SBA-15)

SBA-15 was prepared by the method already reported by Stucky et al.[25] In short, SBA-15 was prepared using tetraethyl orthosilicate (TEOS, Aldrich Co.) as silica source, Pluronic P123 (poly (ethylene glycol)-block-poly (propylene glycol)-block-poly (ethylene glycol), $EO_{20}PO_{70}EO_{20}$; average molecular weight = 5800, Aldrich Co.) as template and HCl as pH controlling agent. In a typical synthesis, 10 g of P123 was dispersed in 75 ml of water and 300 ml of 2 M HCl solution while stirring. To it, 22 g of TEOS was added over 45 min. The gel formed was continuously stirred at 40 °C for 24 h and aged at 100 °C, for 48 h. Then, the solid product was separated by filtration, washed with deionized water, and dried, first, at 25 °C, and then, at 80 °C. The material was finally calcined in air at 550 °C for 6 h to decompose P123 and to obtain a white powder, SBA-15.

Preparation of Ibu Loaded CS and CS-MS Hybrids

For the preparation of drug loaded samples and release experiments, Ibu was used as the model drug. Ibu was completely dissolved in hexane (30 mg/ml). To prepare Ibu loaded MS (MI-1); MS was dispersed in Ibu solution and stirred for 24 h. The drug-loaded powder was washed carefully with hexane to remove Ibu, which is physically adsorbed or bound on the exterior surface of the prepared MI-1, and finally dried at 60 °C in air oven. The amount of Ibu in the MI-1 was determined by thermogravimetry (TGA), and found to be around 15 weight %. Similar washing procedure of Ibu from hexane from the surface of MS was also followed by Zhu and coworkers [26]. However, from environmental concerns, pentane can also be used to wash the unadsorbed drug molecules. For preparation of CS-MS composite (CMI-1), Ibu-loaded MS was mixed with an aqueous solution of CS. The drug-loaded MS powder was dispersed and stirred vigorously in the CS solution with the ratio of 1:10 (MS/CS). The final solution was poured on a glass Petri plate, and vacuum dried at 37 °C for 48 h and cured at 60 °C for 24 h. Drug-loaded CS (CI-1) film sample was also prepared for control experiments. For this, Ibu was dispersed in a CS solution of 10:90 (Ibu/CS). The drying and curing procedures were the same as for the CMI-1 system.

Characterization

Small angle X-ray diffractograms (SXRD) were recorded on an X'Pert Pro (Philips) diffractometer using Cu Kα radiation and a proportional counter as detector. The Wide Angle X-ray Diffractometer (WXRD) patterns of the samples were obtained by Rigaku (Japan) X-Ray diffractometer with Cu-Kα radiation at 50 kV between the scan ranges of 2θ from 2–30 ° by the scan rate of 2°/min. The d- spacing was calculated by Bragg's formula where the λ was 0.154 nm. SBA-15 was characterized by type IV nitrogen adsorption-desorption isotherms. The Fourier-transform infrared (FTIR) spectra were obtained from the sample on a Perkin-Elmer Spectrum GX. Powder samples were molded in KBr pellets and analyzed at a resolution of 2 cm^{-1}. To demonstrate the in-vitro biocompatibility of Ibu loaded CS-MS composites, growth studies were performed for HeLa and CHO cells. Two series of experiments were designed for both types of cells: one series studies the natural cells growth on pristine CS (control) and the other was studied on the prepared CS-MS composites. To ensure enough space and media for cell growth, the cells were seeded in T-25 flasks. After allowing 24 hours for cell adhesion, the cells were analyzed everyday (3 flasks per day) for 6 days. The relative cell-growth compared to control cells containing cell culture medium without CS was calculated by $[A]_{test}/[A]_{control}$. For this, after every 24 h, 100 µl of the cell culture was incubated for MTT assay and the absorbance was taken at 490 nm wavelength in Spectrophotometer Plate Reader. All the in-vitro tests were done in triplicate and the results were reported as an average value. The in-vitro drug-release study was carried out by immersion of around 1.5 cm × 1.5 cm films of CMI-1 and CI-1 into 25 ml of simulated body fluid (SBF) (pH 7.4). For comparative studies, the release experiments were done in silent and ultrasound conditions. To study the effect of ultrasound on drug release and pulsatile release, the drug loaded sample flask was immersed in the ultrasound bath (frequency 33 kHz) and was continuously irradiated for ultrasound at 37 °C and the resultant release medium (5.0 ml) was removed for analysis at given time intervals, and replaced with fresh release media (SBF). The in-vitro medium thus collected was filtered through a 0.5-µm Millipore filter. The concentration of Ibu released was determined by UV-VIS spectrometer at λ 264 nm. Release studies were further performed by varying the temperature and pH of the release medium under silent conditions, i.e. without ultrasound. The temperature of the release media was kept constant by continuous addition of ice to the ultrasound bath. All the release experiments were run in a triplicate and the average values obtained are given.

Results and Discussions

The small angle X-ray diffraction (SXRD) pattern of MS (SBA-15) and MI-1 is given in Figure 1. As compared with MS, there is a remarkable decrease in the intensity of the peaks of MI-1, which corresponds to (100), (111) and (200) planes based on the hexagonal unidirectional structure. The peak positions were shifted to higher 2θ value because of the inclusion of drug molecules to the inter-pore region of MS. This observation is similar with the reported result [27], in which the authors

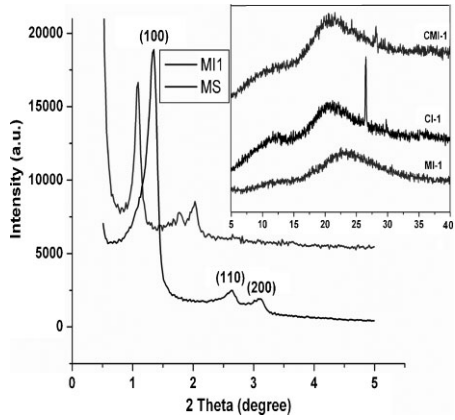

Figure 1.
Low and Wide Angle XRD patterns (INSET) of the prepared composites.

demonstrated that this behavior is attributed to the filling of surfactant into MS pores.

The d_{100} spacing and unit-cell size (a_0) for MI-1 measured to be 40.30 Å and 45.42 Å, respectively. As a_0 represents the repeated distance between two pore centers in the hexagonal array, the pore diameter can be calculated from a_0 by subtracting 10 Å, which is an approximate value of the pore-wall thickness.[28] Therefore, a pore diameter of 35.42 Å is obtained, which means that the pore size of MS is large enough to allow access to the large internal surface area to accommodate Ibu molecules.[29] The wide angle X-ray diffraction (WXRD) patterns of CMI-1 and CI-1 are given in the INSET of Figure 1. All the samples show a characteristic peak at around 21°, which confirms the presence of crystalline CS in the composites. MS (SBA-15) and MI-1 were characterized by type IV nitrogen adsorption-desorption isotherms. MS has a Brumauer-Emmet-Teller (BET) surface area and pore volume of 900 m^2/g and 0.92 cm^3/g, respectively. On the other hand, MI-1 has a BET surface area of 335 m^2/g and pore volume of 0.31 cm^3/g. In addition, the pore size distributions of the MS and MI-1 are centered at 2.9 and 2.1 nm, respectively. The obtained results suggest that the impregnation of Ibu in the mesoporous channels leads to a decrease in the pore diameter, BET surface area, and pore volume. This observation confirms that Ibu molecules have been successfully retained inside the pore channels of mesoporous host. Figure 2 shows the FT-IR spectra of pristine Ibu and drug loaded MS samples. As compare to the pristine Ibu, the band corresponding to a free carboxylic acid (1718 cm^{-1}) in Ibu, has changed to a carboxylate one (1461 and 1634 cm^{-1}) in MI-1, which suggests the interactions between -COOH group of Ibu and Si-OH group of the MS host. Typical υ (CH) stretching vibrations of Ibu are observed at 2958, 2927, and 2871 cm^{-1} for pristine Ibu as well as for MI-1. In addition to that, Si-OH vibration band at 965 cm^{-1}

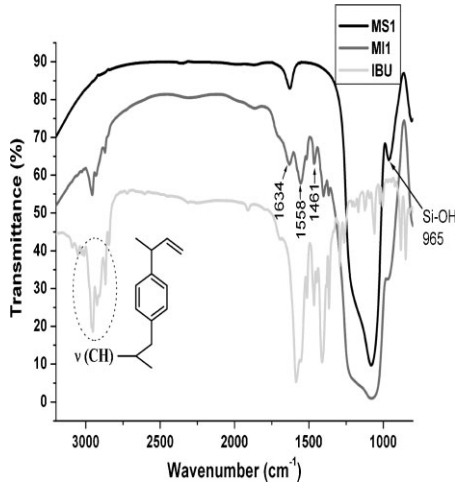

Figure 2.
FT-IR spectra of the prepared composites.

present in MS,[30] almost disappears after Ibu loading, which suggests that the –H bond has been formed between the –COOH group of Ibu and the Si-OH of the MS host.[31] Moreover, the FT-IR spectra of the prepared composites confirm that the structural integrity of the drug molecules is preserved upon intercalation with the MS pores with a structure and geometry similar to that of the drug molecule outside the MS pores. The prepared samples were subjected to the cell-growth studies and the results are shown in Figure 3. On the basis of the results, we predict that the incorporation of MS may

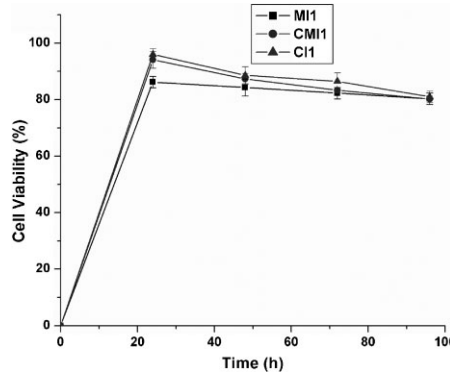

Figure 3.
Results from the Cell-growth studies of the prepared composites.

significantly enhance the interactions between biopolymer matrix and cells.

The results indicated that the cell growth for blank and CS-MS hybrid system were very similar indicating that the increase in numbers of cells was not hindered by the presence of either CS or MS. Also, the Si-OH groups of MS may develop London-Vander Valls forces and -H bonding with the cells. Suspended together with MS, the biopolymer matrix was surrounded and/ or adsorbed by the inorganic host, which acts as a bio-adhesive between the polymer and the cells. The developed London- Vander Valls forces and H-bonding may be mainly responsible for the increased polymer-cells interactions. In addition to that the mesoporous structure of the inorganic silica host may allow enhanced cell invasion in the matrix. Although cell-growth studies shown that the samples does not affect the normal growth of cells, still in-vivo testing should be done to provide a better insight on its biological suitability. So, in-vivo analyses of the CS-MS samples are under progress and will be a part of our next communication. We have studied the stimuli-responsive investigation of the effect of temperature on the drug release of CS-MS system. The results are given in Figure 4a and it depicts that the range of temperature over which the transition takes place is quite broad (30–40 °C), which is due to the steric hindrance of CS chains with the silica host, and a transition is detected at 35 °C for CMI samples. In other words, CS can respond to thermal stimulation of the release media. At low temperature, the drug molecules are restrained in the porous MS channels, and along with CS molecular chains, Ibu molecules takes part in the formation of -H bonding between CS and Ibu molecules. CS has a high water retention capacity, and it absorbs enormous amount of water. So, when the Ibu loaded CS-MS samples immersed in the aqueous release media, the films absorbs enough water, eventually taking the form of a hydrogel. However, at low temperature this water is in the form of a bound state, and as the temperature increases these bound-water molecules gains an enthalpy and changes from a bound state to a free state, with subsequent release of the incorporated drug molecules from the matrix. Moreover, MS is not a thermo-sensitive material, so we may predict that as the temperature increases, the biopolymer chains swells within the MS pore network resulting in the disruption of weak -H-bonds, accelerating the drug molecules from the pores. The obtained results reflect a situation similar to that obtained by Li et. al. [32] Consequently, this implies that the swelling of the polymer chains, as a consequence of temperature, can be used for controlled and thermally-stimulated drug release.

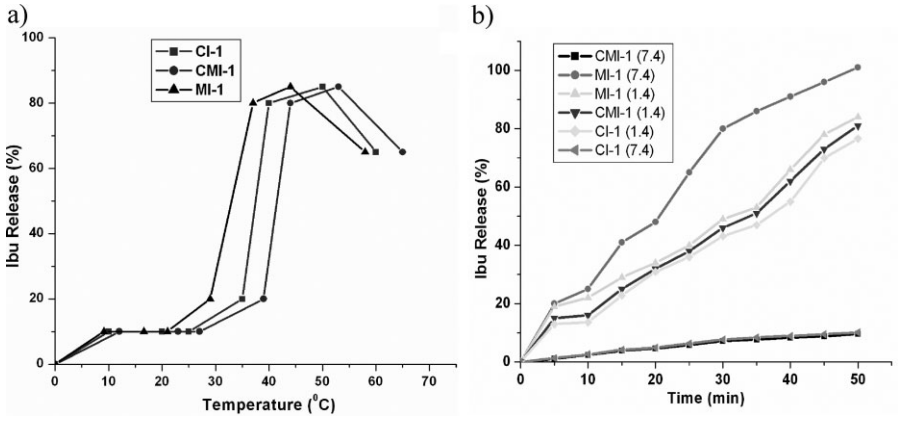

Figure 4.
Effect of (a) temperature variation, and (b) Effect of pH on drug release.

Since Ibu is mainly adsorbed in the stomach and proximal intestine, the release profiles of Ibu loaded samples were determined in simulated gastric fluid (pH 1.4) and simulated body fluid (pH 7.4). It is evident from Figure 4b that the release profile of all the systems (MI-1, CI-1 and CMI-1) are very similar in the medium of pH 1.4, where the amount of drug released reaches >75% in 50 h. This behavior shows that all the systems display sustained release, and the possible explanation is, at this low acidic pH, the $-NH_2$ groups of CS gets protonated, leading to the dissociation of the H-bonds involving the CS $-NH_2$ groups with the -COOH groups of the Ibu molecules. Hence, we can say that at this low pH, CS matrix could not cap the openings of the MS channels. Therefore, the drug molecules can easily diffuse out from the MS pores into the release medium. On the other hand, the release profile in the medium of pH 7.4 is apparently different. We observed that MI-1 also exhibits the sustained release property and the amount released reaches 90% in 50 h, i.e. the release rate in the pH 7.4-release medium is higher than that in the pH 1.4 medium. This dramatic difference in release rates should mainly be attributed to the unusual solubility of Ibu in release media of different pH values. Ibu is sparingly soluble in low-pH solutions (pH < 7) but is readily soluble in high pH (>7) solutions. The obtained results find similarity with the findings of Donath and coworkers.[33] For CMI system, the release rate is very low, and the released amount reaches 12% over a period of 50 h. This finding indicates the good storage space of MS and sealing effect of the CS chains at pH 7.4 solution; i.e. the CS chains are compact with MS, which leads in decreased permeability at the higher pH value, and the CS chains could easily cap the openings of the MS channels. It can be concluded that the CMI system has a much better controlled release than MI, and CMI can achieve a stimulated pH-responsive delivery profile by changing the pH value of the release medium. This kinetic profile offers a great interest for pharmaceutical applications in order to achieve better therapeutic efficacy and rapid delivery profile of poorly water-soluble drugs like Ibuprofen. Figure 5a and 5b shows the release profiles of Ibu from MI-1, CI-1, and CMI-1 under silent condition and subsequent release profile for CI-1 and CMI-1 samples under ultrasound irradiation, respectively. As shown in figure 5a, under silent condition, the release of Ibu stored in MS occurs only after the release medium has penetrated among the MS channels and subsequent dissolution of Ibu in the aqueous media. Remarkably, MI-1 showed very fast release within

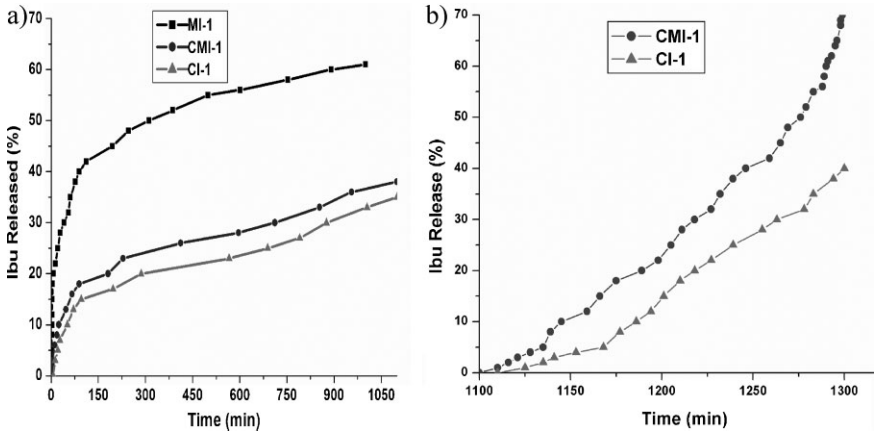

Figure 5.
Cumulative release (a), and (b) The effect of ultrasound on the drug release behavior of the prepared composites.

first 100 min, while the subsequent release rate was quite low as compare to the initial rate. Similar release pattern was also observed by Linden et al.,[34] while according to Xue et al.[35] this behavior of drug release could be ascribed to favorable physical hosting of the drug inside the inter-pore network of MS and ionic interactions of –Si-OH groups of MS and –COOH groups of Ibu molecules. For a successful controlled release of a drug, the initial burst from the inorganic host framework of MS should be controlled. As shown in Figure 5a, the initial drug release rate of CMI-1 was substantially reduced. The Ibu release profile of CMI-1 was quite similar to that of CI-1. Conceivably, this similar release rate could be attributed to a strong dipolar interaction and H bonding between the abundant Si-OH groups of MS, -NH_2 of CS and –COOH groups of Ibu. The release profile was found to be a two step. In the initial stage a small amount of drug was continuously released for about the first 250 minutes, which may be due to the release of excessive drug molecules which were weakly entrapped inside the pores or located at the external MS surface. The second stage shows extremely slow liberation of Ibu, which could be due to the physical blocking of the entrapped drug molecules inside the solvent filled channels of MS, along with CS chains. To understand the effect of US on the drug release profile of CI-1 and CMI-1, the samples were exposed to US for another 200 minutes to increases the release rates after 1100 minutes of release experiment under silent condition. For this the samples were immersed in the release media, and kept in an US bath, maintained at a constant temperature by continuous addition of ice. During the course of ultrasonic irradiation, it was observed that Ibu was continuously released from both CI-1 and CMI-1, while US was found to have an apparent effect to enhance the drug release kinetics of both the systems. It has been well documented that US could increase the drug-release rate in polymeric systems[36] while, Kost[37] reported the enhanced release kinetics in a nondegradable polymer, exposed to ultrasound. In addition to that, US has already been used to alter polymer membrane permeability to stimulate the release of polymer encapsulated drugs.[38] This release effect can be ascribed to the enhancing effect of US irradiation which is capable of reversibly losing the rigid packing of the hydrocarbon chains[39] which results in increase the permeability of water and drug through the polymer. These effects can generally be explained by an important phenomenon called cavitation which is generated by ultrasonic irradiation. Cavitation is a well-known effect of US[40] in which the burst of bubble takes place in an adiabatic fashion, which leads to concentrate the acoustic energy of the release system and creates conditions of temperature and pressure [41]. Moreover, the release effect of drug molecules from the CS-MS system is a combination of mechanical actions imposed by ultrasonically induced air pockets in the matrix, which may include (1) the disorganization of the biopolymer film, and (2) subsequent formation of transport channels in the inter-pore network of MS. To investigate the effect of US on the pulsatile release of the drug from CI-1 and CMI-1, the specimens were given an US dose of 10 minutes for around 120 min.

The results were shown in Figure 6, where the release of Ibu was observed to

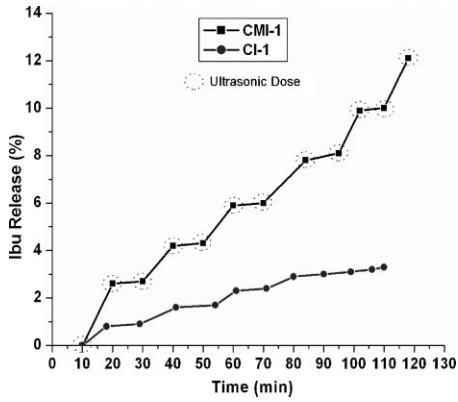

Figure 6.
Ultrasound-triggered pulsatile release of Ibu from CS and CMI composites.

start immediately for CMI-1, and sustained until the US irradiation was discontinued, while in the case of CI-1, the amount of released Ibu continuously decreased after a second irradiation. On the other hand, for CMI-1 regular pattern was displayed with repeated ultrasonic dose and the amount of Ibu released in each step was nearly the same each time, and was higher than that of CI-1 release profile. Since, the extent of Ibu loading for both the systems was same at around $15\,mg\,g^{-1}$, this difference does not originate from the amount of Ibu present in the matrix. It suggests that CMI-1 released the Ibu more effectively than CI-1, and it is believed that the hydrophilicity, high permeability, and subsequent high ultrasonic susceptibility of CMI-1, makes it possible for ultrasound to be transferred deep into the biopolymer matrix, hence promoting the regularity of the pulsatile release of the drug from the CMI-1 system. This may allow repeated operation for a continuously controlled release of a drug into a patient's body to maintain a therapeutically effective dose for a longer period of time to efficiently treat the disease. Polymeric materials can be predicted to undergo mechanical damage or surface rupture after the release experiment due to the cavitation created by high-power ultrasound.

However, as expected, the sample films were intact and we could not observe any microholes or cracks on scanning electron microscope (SEM) images after the ultrasonic irradiation (results not shown). Consequently, US could be applied to enhance the drug-release kinetics in a nondestructive fashion. Apart from increasing the interaction with Ibu, the extended polymer chains of CS would act as a holder to retain the drugs inside the pores as verified by the nitrogen isotherms showing the complete filling of the pores after adsorption. We envision that CS-MS system could serve as a novel biocompatible sustained release drug carrier, and allows us to think about new potential applications in medical sciences, and more specifically, in biomaterials and tissue engineering applications.

Conclusions

In conclusion, we have designed a novel stimuli-responsive controlled drug-release system where ultrasonic irradiation was used as an external trigger for smart drug release to obtain optimal therapeutic effects. The overall system was composed of MS as a drug storage device and CS as an implantable body. This system is efficient for storage and release of drug, further controlled by temperature and pH at will. CS successfully suppressed the initial burst of Ibu from the MS. Besides; the ultrasound was effective to improve the release kinetics of CS-MS system in a nondestructive manner. We envision that this novel system, which combines the advantages of both high drug storage capacity and the property of stimuli-responsive controlled release, could play a significant role in the development of new generation, site specific, and smart drug release.

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