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Development and characterization of natural polyelectrolyte capsules for drug delivery applications

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Nanotechnology has provided numerous cutting-edge applications in drug delivery, biosensors, nanorobots, biomedical devices and nanocarriers. Polyelectrolyte mediated nanocapsules contributes a significant development as drug carriers for more than a decade. Majority of the nanocapsules employed in the drug delivery system are fabricated using synthetic materials leading to many health complications. In this research, natural polyelectrolyte capsules are prepared using carboxy methyl cellulose (CMC) and chitosan by dip coating technique. The capsules are used for the delivery of antibacterial drug by encapsulating ciprofloxacin hydrochloride into the capsule interiors. The drug release study has been carried out by altering the permeability of the capsule shell. The optimal *p*H for the drug encapsulation has been established at 2.3 *p*H and 381 µg of drug is loaded in 60 min. The drug release study is performed at three different *p*H conditions of 2.0 *p*H, 6.0 *p*H, and 7.2 *p*H respectively and the release media chosen is water and PBS. Maximum amount of drug release (367 µg) is achieved at *p*H 2.0 within 48 hours. The study demonstrates an easy and effective delivery of antibacterial drug from natural polyelectrolyte capsules.

Keywords: Antibacterial drug, Carboxy methyl cellulose, Chitosan, Colloidal particles, Drug delivery

Modernizations in materials science and nanotechnology have promoted the development of efficient drug carriers[1,2]. Novel nano materials play a key role in the design and fabrication of natural degradable, biocompatible, non-toxic, and site specific drug carriers. Design and targeting of nano scale drug delivery systems are of vital importance in the medicine and pharmaceutical area[3,4]. Innovative drug delivery systems derived from polymeric materials are receiving considerable attention in controlled release applications. Significant advances have been made in the development of nanostructured materials utilizing different types of polymers for drug targeting[5]. The processing techniques of such types of polymers are very crucial due to the release kinetics behaviour, easy handling and the capacity of the researchers to readily control the chemical and physical properties[6]. The delivery of drug at targeted site increases the bioavailability and allows the consumption of limited amount of drugs and thus releasing the side effects. Nanotechnology can aid the size control, geometry and multi-functionality of the drug carrier[7].

Owing to the smaller size, nanocapsules possess superior qualities which are well appreciated in recent times due to the fine tuning of wall thickness and exceptional reproducibility. The fabrication technique of nano capsules mainly depends on their application in bio pharmaceutics and engineered drug delivery systems[8]. These nano capsules own both scientific and technological attention due to their prospective applications such as novel drug carrier systems, detection and identification of diseases, and micro reactors. The improved delivery of bioactive molecules offers numerous challenges and opportunities in the future advancement of innovative and improved therapies[9,10]. Formulation of improved drug delivery systems is an importance area of concern in healthcare sector during the last few decades. The well-organized loading and release of drug from carrier systems are prevalent due to extended passage of drugs with reduced side effects. Nano particles and capsules have been suggested for augmented bio availability and controlled release applications, which has enormous prospective for multidrug delivery devices[11]. Natural degradable polymers are considered to be a promising capsule wall material for a wide range of applications in drug targeting, paramedical and cosmetics[12-14]. Most of the drug delivery vehicles are prepared from synthetic

materials, which limit the biocompatibility and biodegradability leading to severe health complications[15-18]. Those issues can be addressed by choosing natural degradable polymers as drug carriers thereby minimize the side effects. Carrageenan and chitosan are the commonly employed natural polymers in controlled release of drug due to their attractive properties of biocompatibility and biodegradability[19-21]. Biodegradable polyelectrolyte capsules would be preferred to non-degradable ones due to their biodegradation; multi functionality; tunable wall thickness; biocompatibility and non-toxicity during administration[22-24].

The limited permeability to small molecules and capsule shell wall are of micron size, which restricts the wider applications of such capsules in drug delivery. Still persistent research efforts are in place to resolve the permeability issues. Though, considerable progress has been made during the recent years for the fabrication of polymeric capsules, the sustained release is still a serious concern for pharmaceutical researchers[25,26]. However, at present the study of nanoscale innovations in medical field is lacking. Considerable attention has been devoted in the preparation of biopolymer based capsules for drug delivery applications[27]. Advanced studies are needed to fabricate natural degradable capsules with fine tuning of the loading and release of drugs. The main objective of the study was to develop an efficient drug delivery system using natural degradable nanocapsules and to study the capability of these capsules in controlled release applications. In this work, a feasible and environmentally friendly approach for the encapsulation and release of ciprofloxacin hydrochloride from carboxy methyl cellulose (CMC) and chitosan nano capsules was reported.

Experimental Section

The reagents ethanol, ammonium hydroxide, tetra ethyl ortho silicate (TEOS) and the model antibacterial drug ciprofloxacin hydrochloride are procured from Knowledge foundation, Oman. The biopolymers carboxy methyl cellulose (CMC) and chitosan used for the fabrication of capsules are purchased from sigma Aldrich. The loading and release of drug was done by adjusting the pH of the solution. The characterization techniques employed are Scanning Electron Microscopy (FEI Sirion, Eindhoren, The Netherlands), X-Ray diffraction (XRD–P Analytical), Fourier Transform Infrared Spectroscopy (FTIR – Schimadzu, Japan), and UV-Visible Spectroscopy (Nanodrop ND - 1000, Nanodrop Technologies Inc., USA).

Template synthesis

The colloidal templates are synthesized by stober's protocol[26]. The synthesized colloidal particles are used for the surface morphological characterization using SEM, X-Ray diffraction (XRD) measurement, and characteristic functional groups using FTIR analysis.

Preparation of coated particles and hollow capsules

The coating process was carried out by depositing cationic and anionic polymers on a colloidal template using dip coating technique by sequential deposition of chitosan and carboxy methyl cellulose. The coating process was continued until five bilayers of the polymers are deposited on the surface of colloidal particles. The templates are removed by treating the polymer coated particles with 0.1 M HF for one hour and then centrifuged at 4000 RPM for 5 min to form hollow capsules. The resulting hollow capsules are washed with Millipore water and then characterized using SEM, EDS and FTIR analysis.

Drug encapsulation and release study

The loading and release studies of the antibacterial drug from the capsules are investigated by changing the capsule wall permeability. 100 µL of capsule suspension was mixed with 900 µL of drug solution and incubated at room temperature for 24 h under slow stirring. The supernatant was collected at specific time intervals and the actual amount of drug load was quantified using UV spectroscopy. The drug encapsulation was quantified using the Equation (1).

$$\% \text{ Drug encapsulation} = \frac{x - y}{x} \times 100 \qquad \ldots(1)$$

where '**x**' is the initial drug concentration in ppm, '**y**' is the final drug concentration in ppm. The capsules after drug load was subjected to drug release in water and PBS maintained at three different pH conditions (*p*H 2.4, *p*H 6.0 and *p*H 7.0). The extent of drug release was monitored at definite time intervals and the aggregate amount of drug release was calculated.

Results and Discussion

Template synthesis and its characterization

The surface morphological characterizations of the colloidal particles are performed using SEM. Figure 1 depicts the micro structural features of the colloidal

particles captured using SEM operated at 15 kV and a magnification of 20,000 X. The SEM image endorses the synthesized templates are well dispersed, spherical geometry and free from any aggregation with average an particle size of 300 nm. The SEM image shown in Fig. 1 indicates the distribution of the particles showing a smooth surface topography.

X-Ray diffraction analysis

The X - Ray diffraction patterns of the colloidal templates are presented in Fig. 2. The XRD spectra exhibit a single peak corresponding to a diffraction angle 15° endorses the successful synthesis of colloidal nanoparticles.

Fourier transform infrared spectroscopy (FTIR)

The infrared spectroscopic analysis of the sample was analyzed using FTIR as shown in Fig. 3. The broad spectrum at 2945 cm^{-1} can be attributed to the hydroxyl groups (O-H) in stretching mode. The asymmetric vibrations observed at 1090 cm^{-1} represents Si–O bond stretching, 950 cm^{-1} corresponding to Si–OH stretching and wave number analogous to 795 cm^{-1} exhibited the Si–O bonding.

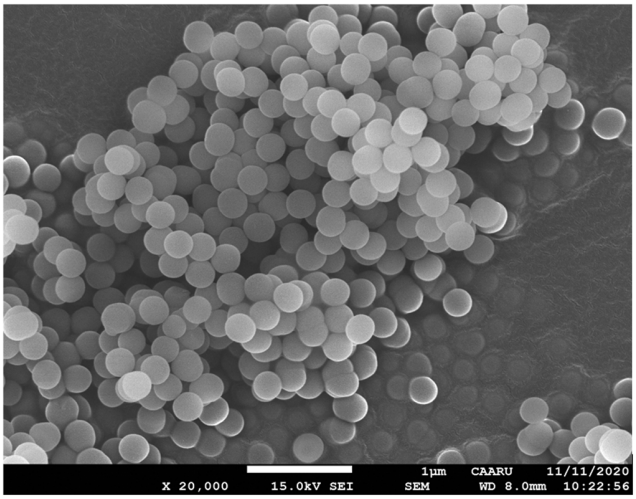

Fig. 1 — SEM micrograph of colloidal particles.

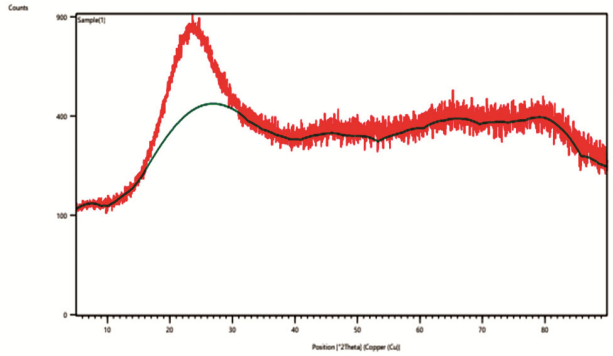

Fig. 2 — X - Ray diffraction patterns of colloidal template.

Also, a sharp peak observed at 650 cm^{-1} is characterized by the O-Si-O stretching and bending vibrations.

Preparation of coated particles and hollow capsules: The SEM image shows that coated particle exhibits larger size compared to the template size and the diameters of the coated particle was nearly 320 nm, which indicates the effective deposition of the polymers on the template surface. The surface morphology of the coated particles is shown in Fig. 4. The chemical bond and functional groups are identified using the FTIR spectra as demonstrated in Fig.5. The highest peak corresponding to the wave number 2400 cm^{-1}. 2000 cm^{-1} endorses the deposition of polymer layers on the surface of the templates. The SEM image shown in the Fig. 5 indicate the particles are well dispersed with uniform size and scattered distribution, which is crucial in drug delivery applications.

Hollow capsule preparation

The core dissolution was carried out using 0.1 M HF and the ensuing hollow capsules were analyzed by SEM at 20kV and 20000X magnification as shown in Fig. 6. The SEM micrograph reveals that the capsules are intact and evenly distributed without rupturing the wall material, which demonstrates the successful formation of the hollow capsules. The surface of the

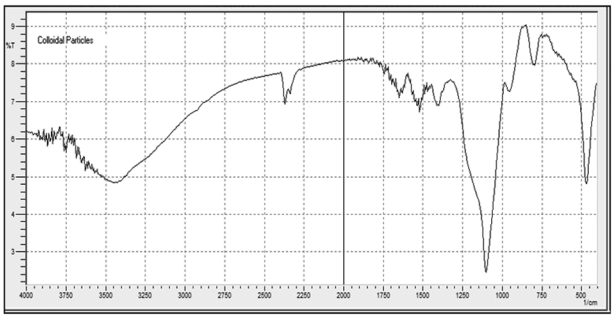

Fig. 3 — FTIR Spectra of colloidal particles.

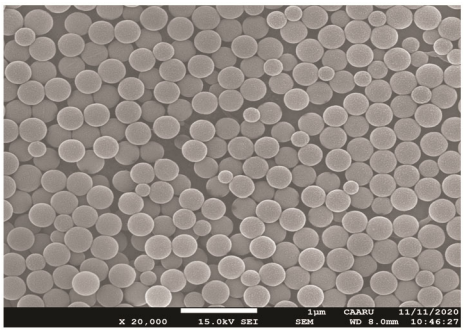

Fig. 4 — SEM micrograph of carboxy methyl cellulose - chitosan coated particles.

hollow capsule became rough due to the dissolution of silica particles and its release due to the high osmotic pressure exerted by the interiors of the coated particles.

Drug encapsulation and release study

The extent of drug loading was studied as a function of time by encapsulating the drug into the hollow capsules. A desired quantity (900 µL) of drug solution was mixed with 100 µL of capsule and incubated at room temperature and 2.3 *p*H. Figure 7

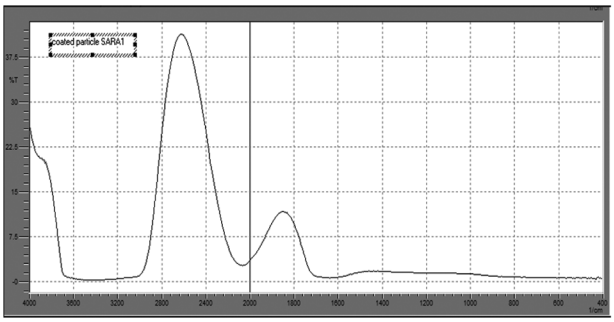

Fig. 5 — FTIR spectra of carboxy methyl cellulose - chitosan particles.

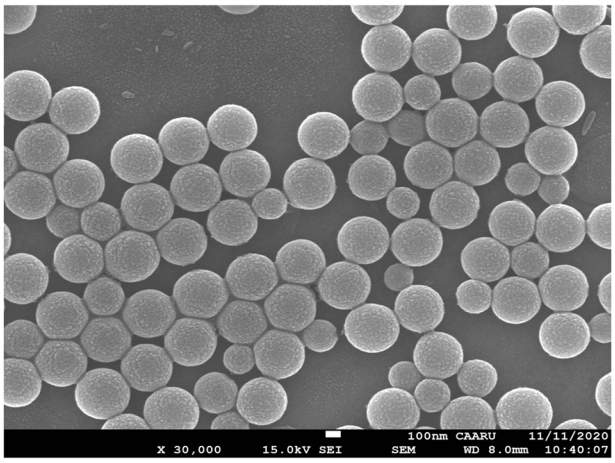

Fig. 6 — SEM Micrograph of hollow capsules after core removal.

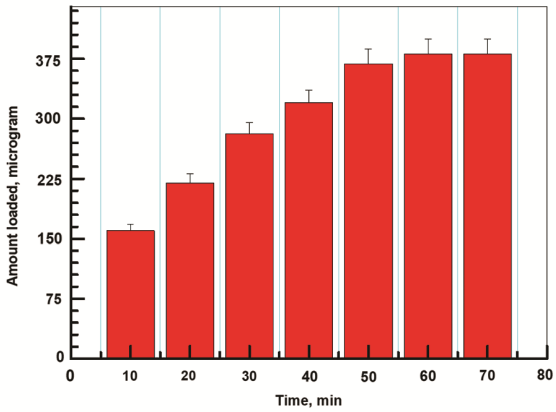

Fig. 7 — Amount of drug loading with respect to time (loading *p*H 2.3)

illustrates the kinetics of ciprofloxacin hydrochloride loading at 2.3 *p*H. The drug encapsulation process was continued for a period of 90 minutes. The drug loading profile shown in Fig. 7 indicates that the amount of drug load increased with increase in contact time and maximum loading occurred at 60 minutes. The surface morphological characterization of the drug after loading is shown in Fig. 8. From the SEM image, it is observed that there is a slight increase in the capsule size after the drug encapsulation process and also the capsule surface become smooth unlike the hollow capsules.

The *in vitro* drug release studies were performed in water and PBS at 37°C Fig. 9(a) and (b). The drug loaded capsules were submerged in the release media at *p*H 2.0, 6.0 and 7.2. A specified quantity of supernatant (10 µL) was removed from the release medium at different time intervals and the drug concentration was determined by assessing the absorbance value at 276 nm using UV-Vis Spectroscopy. The aggregate drug release was quantified from each measurement using a standard calibration curve. The release profile in water at different *p*H conditions are shown in Figure. 9(a). From the 381 µg of the encapsulated drug, 367 µg of drug was released (96%) at *p*H 2.0. The maximum drug release was observed at *p*H 2.0, which is due to the active electrostatic interaction between the capsule surface and bulk solution. The smallest amount of drug was released at *p*H 6.0. This is due to weak electrostatic interaction and hence minimum release rate. The similar trend was followed in the case of PBS Fig. 9(b). However, the maximum release was seen at *p*H 7.2 in PBS as illustrated in Fig. 10.

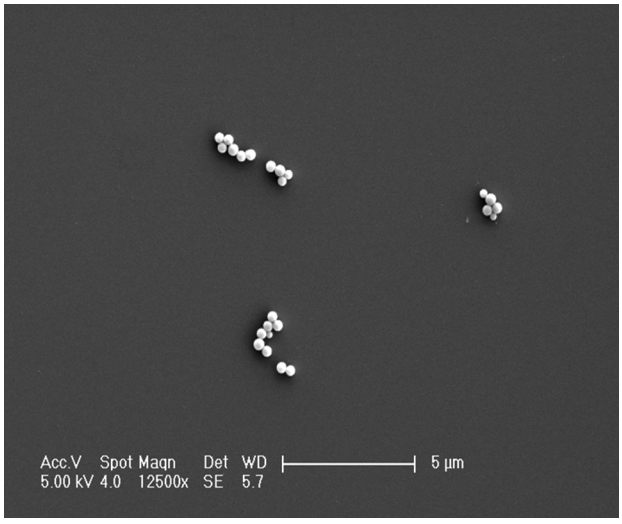

Fig. 8 — SEM image of drug loaded capsules.

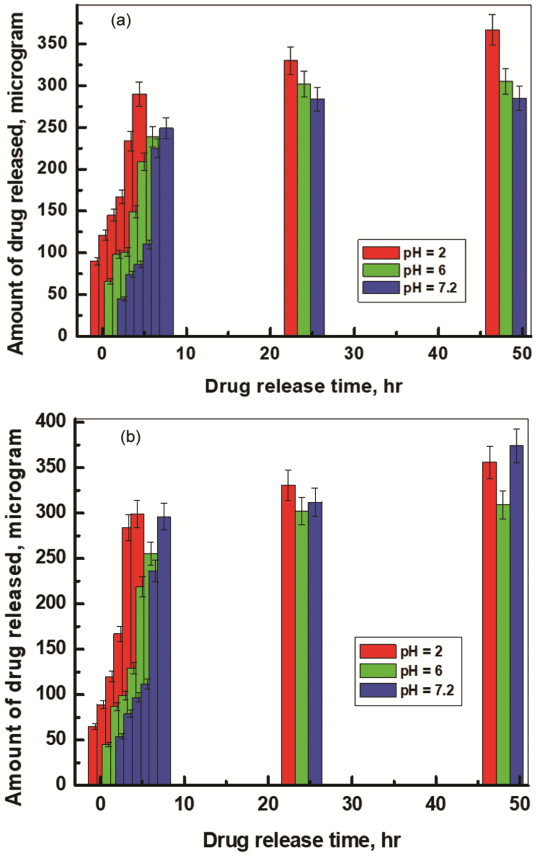

Fig. 9 — Release profile of drug from the capsules at different *p*H water (*p*H 2.0, *p*H 6.0, *p*H 7.2) & release profile of drug from the capsules at different *p*H PBS (*p*H 2.0, *p*H 6.0, *p*H 7.2).

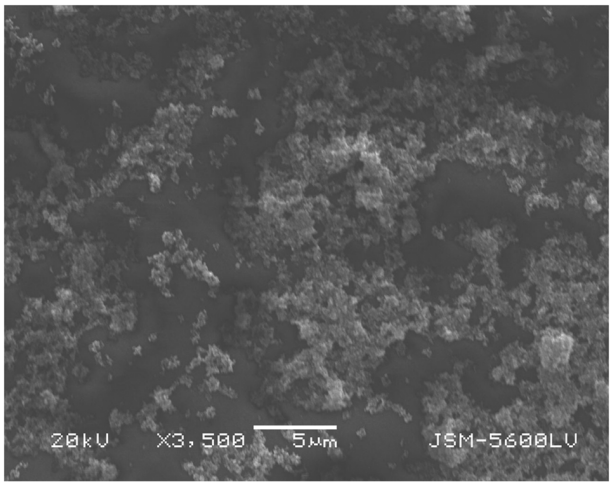

Fig. 10 — SEM micrograph of capsules after drug release.

After 48 hours of drug release, the capsules are visualized through SEM to know the surface morphological changes. The SEM image shown in Fig. 10 designates the capsules are broken showing the lesser wall thickness and stability as the original capsules. A fractional degradation of the capsules are seen after *in vitro* drug release.

Conclusion

In this work, natural degradable nano capsules are prepared using carboxy methyl cellulose – chitosan for the effective delivery of antibacterial drug. A total amount of 381 μg drug is encapsulated into the capsules at *p*H 2.3. The *in vitro* drug release has been performed in water and PBS at *p*H 2.0, 4.0 and 7.2. The drug release profile in water show a sustained release up to 48 h with a partial degradation of the capsule walls. The maximum release is obtained at a *p*H of 2.0 in water. The highest release in PBS was obtained at *p*H 7.2 and the release profile is similar to that of water. The release study demonstrates that carboxy methyl cellulose - chitosan capsules could substantially prolong the release time of the encapsulated drug. This research offers a facile approach in fabricating carboxy methyl cellulose (CMC) - chitosan nano capsules for the successful delivery of antibacterial drug.

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