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Studies on encapsulation of Rifampicin and its release from chitosan-dextran sulfate capsules

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Abstract−Biodegradable capsules of size around 350 nm were prepared by layer-by-layer (L-b-L) assembly of oppositely charged chitosan and dextran sulfate on silica particles and the subsequent removal of template. The resulting capsules were loaded with rifampicin, an anti-tuberculosis drug under modest conditions, as demonstrated by scanning electron microscopy (SEM). Maximum encapsulation of rifampicin was found to be about 82 μg at 25 °C and pH of 3. Release studies were done in-vitro mode by semiautomatic release protocol, with different pH solutions in water and phosphate buffered saline (PBS). The microcapsules exhibited a slow and sustained release over 72 hours and maximum release was obtained at a pH of 1.2 in water and a pH of 7.4 in PBS. The size of silica particle was analyzed by dynamic light scattering method. Scanning electron microscopy (SEM) measurements showed the surface morphology of the hollow capsules. UV spectroscopy was employed to monitor the drug release processes in both solutions. The kinetics of drug release mechanism was studied using Ritger-Peppas and Higuchi models.

Keywords: Biodegradable Capsules, Chitosan, Dextran Sulfate, Drug Release, Encapsulation, Microcapsules, Rifampicin

INTRODUCTION

Controlled release technologies are becoming more popular due to minimum side effects, prolonged time of activity and protecting sensitive drugs from degradation in the gastrointestinal tract [1-3]. Polyelectrolyte capsules find applications in catalysis and the biomedical, pharmaceutical, and cosmetics areas and with tailored structures and properties due to their potential functions. Main constituents of the controlled drug delivery system are polystyrene sulfonate [4], polyallylamine hydrochloride [5], chitosan [6], and dextran sulfate [7]. In recent years, a novel microencapsulation technology based on the L-b-L assembly of oppositely charged polyelectrolytes onto colloidal particles followed by selective core removal has been established [8-11]. Main attractions of L-b-L technique are improved stability of core shell particles [12,13] and controlled release of encapsulated material [14-16]. By using L-b-L technique capsules with well-controlled size and shape, fine tuning of wall thickness and variable wall compositions can be obtained [17].

Alginate-chitosan microcapsule prepared by ionotropic gelation method was employed as a potential drug carrier for the slow and sustained release of rifampicin over a period of 72 hours for better management of tuberculosis [18]. Rifampicin loading and release studies were carried out using Poly (Vinyl Pyrrrolidone) and Poly (Methacrylic Acid) microcapsules of size around 4 microns. Release studies showed a burst kind of release and maximum release occurred at pH 7. Interaction studies with *Mycobacterium smegmatis* showed that the capsules were cytocompatible and the released drug functioned with the same efficacy as the free drug [19]. The burst release is due to the swelling of capsules at pH 6. Biodegradable nanoparticles composed of poly lactide-co-glycolides (PLGA) have been employed for the encapsulation of Rifampicin by solvent emulsification/diffusion process. The effect of the variation of amount of rifampicin, amount of surfactant and polymer composition with rifampicin encapsulation showed considerable improvement in antibacterial activity [20]. Recent studies on PLLA/rifampicin blend particles prepared by the freeze-drying method show that the release rate can be controlled to a great extent by tuning the size and porosity of the blend particles, both of which are varied by parameters such as the solution concentration and the method of freezing [21].

There has been a growing interest over the past few years in applications of biopolymers due to their renewable, sustainable and biodegradable properties [22]. Chitosan is a natural polyelectrolyte obtained by the deacetylation of chitin and has received a great deal of attention due to its appealing biocompatibility and non toxic nature for targeted drug delivery [23-27]. Due to its positive charges at physiological pH, chitosan is a bioadhesive, which increases retention time at site specific applications [27-34]. Polymeric materials are the most prominent material for biomedical and drug delivery applications. The advantage of having polymer in drug delivery is primarily because of the ease of processing, ability to control their physicochemical properties from molecular aspect, biocompatibility and biodegradability.

Drug encapsulation and release studies have been done mostly with Poly Styrene Sulfonate (PSS)/Poly Allyl amine Hydrochloride (PAH) system, whereas the other systems have been studied to a

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lesser extent [35,36]. The biodegradable and biocompatible nature of dextran sulfate has been used for the controlled release of basic drugs. The negatively charged sulfate groups of dextran sulfate bind with positively charged amino groups of chitosan to form polyelectrolyte complexes [37]. Biodegradability is one of the important requirements in biomedical applications.

We chose a therapeutic drug, rifampicin, for the encapsulation and release from chitosan - dextran sulfate capsules. This therapeutic drug is recommended against *Mycobacterium* infections such as, *Mycobacterium Tuberculosis* and leprosy. No major study has been done so far on encapsulation and kinetic release studies of rifampicin from chitosan - dextran sulfate microcapsules using the Peppas and Higuchi models.

EXPERIMENTAL SECTION

1. Materials

Chitosan (Mw 650 kDa, degree of deacetylation >75%) and Dextran sulfate (Mw 500 kDa), were obtained from Sigma Aldrich, India. Rifampicin (Mw 823) was purchased from Merck, India. Monodisperse colloidal silica particles of size 320 nm were employed as template. TEOS (Tetra Ethyl Ortho Silicate), NH_4OH, C_2H_5OH, NaCl, HCl and HF were obtained from Merck, India. Millipore water (18.2 MΩ resistivity) was used in all experiments. To ensure the accuracy, reliability and reproducibility of the collected data, all batch experiments were carried out in triplicate and the mean values of three data sets are presented.

2. Synthesis of Silica Templates

Monodisperse spherical solid core silica particles were synthesized based on the Stöber protocol [38-40]. The synthesized silica particle was purified by centrifugation and the resulting particles were redispersed in ethanol. The overall reaction in the synthesis of silica particles is

$$Si(OR)_4+2H_2O \rightarrow SiO_2+ROH \tag{1}$$

The mean diameter and particle size distribution of synthesised silica particles were measured by dynamic light scattering (DLS) using a Brookhaven B1 9000AT analyzer (Brookhaven Instruments Corporation, USA). Surface morphology of the silica particle was analyzed by SEM (FEI-Sirion, Eindhoven, The Netherlands).

3. Hollow Capsules Preparation

Capsules were prepared by the L-b-L technique [41] with chitosan as the first layer. Silica particles used for capsule preparation were etched in 25% NH_3, 30% H_2O_2 and water in the ratio 1 : 1:5 for 20 minutes to ensure a better attachment of chitosan to the bare silica surface and thoroughly washed with water. The adsorption of polyelectrolytes (1 mg/ml) was conducted in 1 M NaCl solution for 15 minutes followed by three washings in water. Then the respective oppositely charged polyelectrolytes were adsorbed. After five bilayers were adsorbed, the coated particles were subjected to treatment with 1 M HF to remove silica cores. The products of core decomposition and the excess HF were washed off in pure water and centrifuged five times at 2,000 rpm to remove traces of HF. The resulting capsules were characterized by SEM at an operating voltage of 3 keV. The samples for SEM analysis were prepared by placing a drop of capsule suspension on a pre-cleaned silicon wafer, dried under a nitrogen stream followed by gold sputtering.

4. Encapsulation of Rifampicin

The deposition method employed was by switching the capsule shell permeability through change in environmental conditions [42]. Capsule suspension and the drug solution to be encapsulated were mixed in the volume ratio 1 : 8. The drug loading was studied at different pH, initial concentration and time. For encapsulation, a drug feeding concentration ranging from 10 μg/ml to 100 μg/ml at 27 °C and a pH of 3 was maintained. The capsule-drug suspensions were incubated at the same temperature for 30 hours, followed by centrifugation at 2,000 rpm for 5 minutes. A 100 μl of supernatant was diluted over hundreds of times with Di Methyl Sulfoxide (DMSO). Quantitative deposition of rifampicin as a function of drug feeding concentration and time was monitored by UV-visible spectrophotometer (ND-1000, Nanodrop Technologies Inc, USA). The drug loaded capsules were washed thoroughly with water and centrifuged at 2,000 rpm to remove the entire free drug. The amount of drug encapsulation was calculated using the equation

$$\%\ \text{Drug encapsulation} = \frac{C_0 - C_1}{C_0} \times 100 \tag{2}$$

where C_0=Initial concentration of drug in μg/ml, C_1=final concentration of drug in μg/ml

5. Rifampicin Release Studies

The in vitro drug release in water and PBS was performed at 37 °C and a speed of 100 rpm was maintained. Rifampicin loaded capsules were transferred in different release media such as water and phosphate buffered saline and the release study was performed up to 72 hours. The pH of the release medium was adjusted with 0.1 N HCl and 0.1 N NaOH. Aliquots (5 ml) of sample were withdrawn at fixed time intervals and replaced with same amount of fresh solvent. The withdrawn samples were analyzed using UV spectroscopy for rifampicin concentration at 475 nm. The amount of drug released at various time intervals was calculated and plotted against time.

Three different pH solutions were used as the release medium with pH 1.2, 5 and 7.4. A semi-automatic release protocol was adopted. In short, 900 μl of the supernatant was taken out each time from the encapsulated rifampicin system, while supplementing the same volume of release medium to keep the total volume constant at 1 ml. The cumulative amount of drug release was measured from each measurement, with concentrations determined from a standard calibration curve.

6. Kinetics of Drug Release

To understand the mechanism and kinetics of drug release, the results of the in vitro drug release studies were fitted with the Peppas [43] model:

$$\frac{M_t}{M_\infty} = k_1 t^n \tag{3}$$

where M_t, the amount of drug released at time t and t_∞ is the amount of drug released after an infinite time.

M_t/M_∞, the fractional drug release, n is the diffusion order and k_1 is the release rate constant. A plot of $\ln(M_t/M_\infty)$ with ln(t) gives a linear graph with slope n and intercept $\ln(k_1)$.

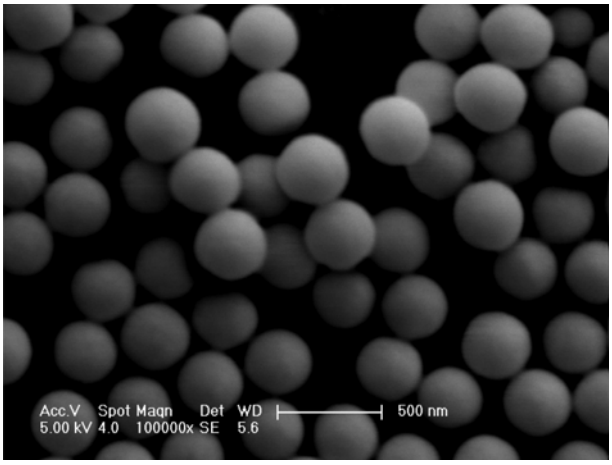

Fig. 1. SEM image of silica particles.

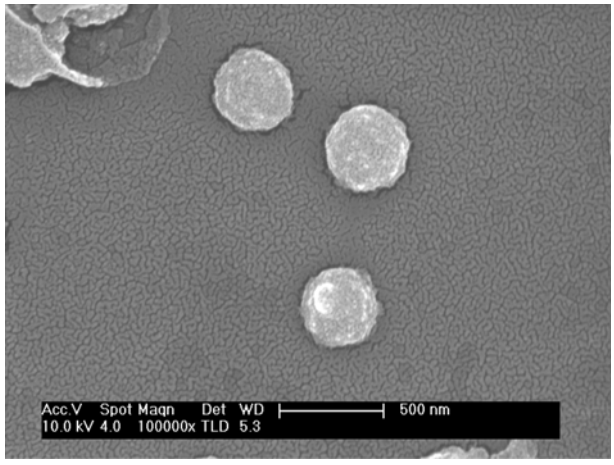

Fig. 3. Chitosan-dextran sulfate microcapsules observed under SEM.

For comparison purposes, the data was also analyzed using the Higuchi model [44].

$$\frac{M_t}{M_\infty} = k_2 t^{0.5} \tag{4}$$

Eq. (4) represents the release data which are dependent on the square root of time and will give a straight line release profile, with k_2 presented as a root time dissolution rate constant.

RESULTS AND DISCUSSION

Silica particles were synthesized by the Stöber protocol. The scanning electron micrograph as shown in Fig. 1 illustrates the particles are spherical, well dispersed and of uniform size. Particle size analysis shown in Fig. 2 demonstrates a narrow size distribution with an average size of 320 nm. All analyses were repeated six times and the results were averaged. DLS measurements were done with a laser wavelength of 658.0 nm and at 27 °C. Five bilayers of polyelectrolytes were deposited on silica template followed by core dissolution. The capsules were rinsed five times with water before use. Fig. 3 shows the micrograph of hollow capsules after core dissolution. The capsules showed good integrity and a high yield with diameter around 350 nm. The capsule wall appears thick due to the high molecular weight of the polyelectrolyte used. No aggregation of capsules has been observed, which is critical from application point of view.

Encapsulation of rifampicin into chitosan-dextran sulfate capsules was studied as a function of time and initial concentration. The capsule concentration was kept constant (150 μg/ml) and all experiments were performed at 27 °C. 850 μl of drug solution at different initial concentration was mixed with 150 μg of capsule suspension. Fig. 4 illustrates the relationship between rifampicin loading and time. It is clearly seen that maximum amount of drug loading occurred at 30 hr. For a given capsule concentration, the amount of rifampicin encapsulation increased with initial concentration from 10 μg/ml to100 μg/ml, above which there is no significant amount of loading. Fig. 5 shows a nonlinear increase of drug concentration in the interior of the capsule as compared to

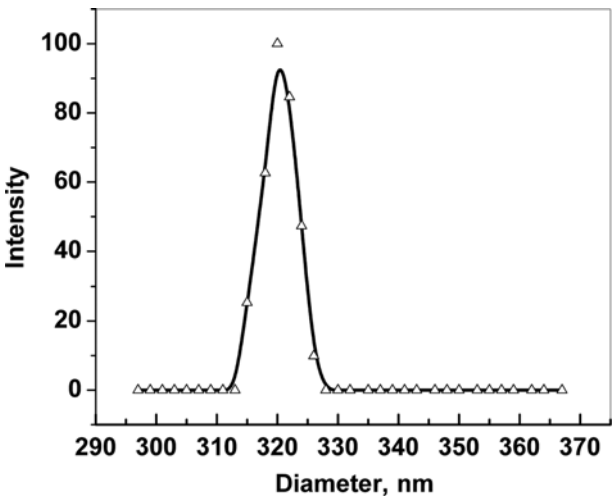

Fig. 2. Size distribution of silica particles.

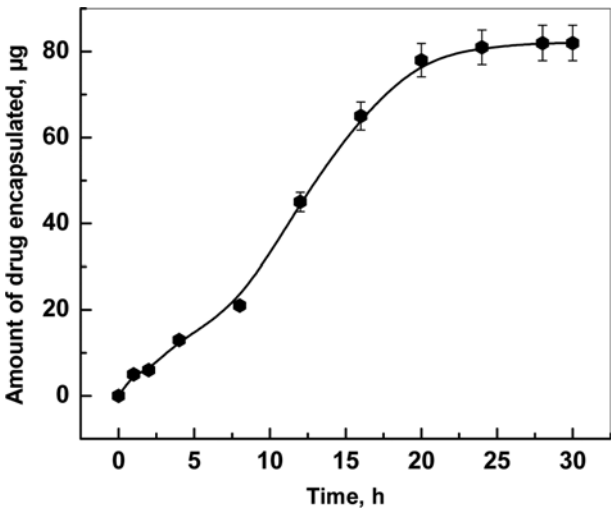

Fig. 4. Rifampicin loading kinetics at pH 3.

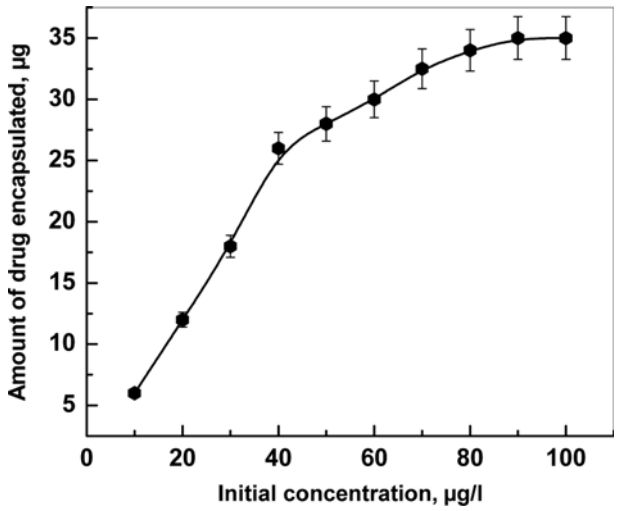

Fig. 5. Effect of initial concentration at a loading pH of 3 and 30 hours.

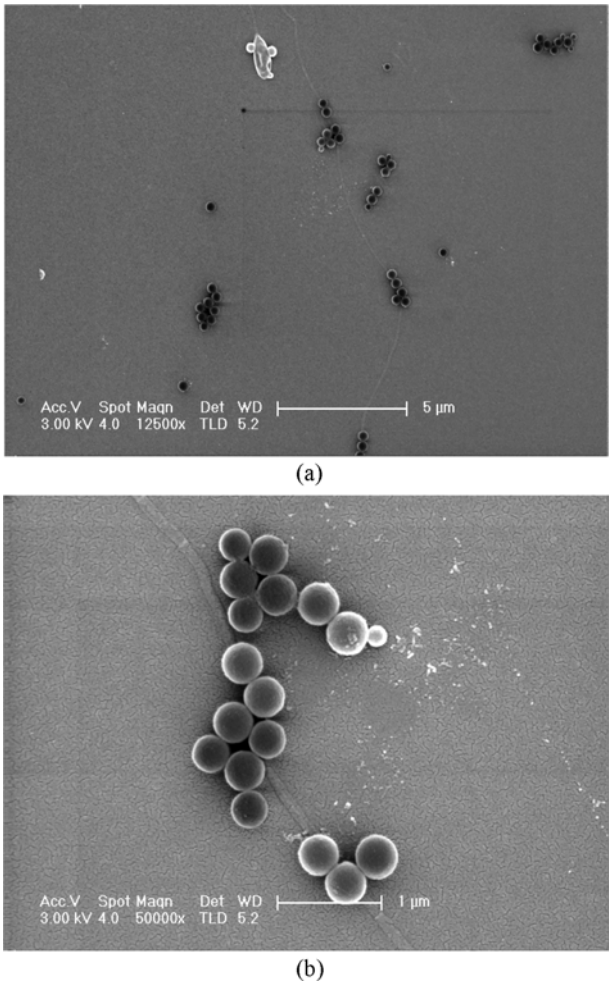

Fig. 6. (a) & (b) Scanning electron micrograph of drug loaded capsules @ 82 μg drug load.

the bulk solution. These observations are in agreement with the previous investigations [45,46]. Fig. 6(a) and 6(b) show the scanning electron micrograph (SEM) of drug loaded capsules. Dark shadows were observed at the centers of the drug loaded capsules, revealing the successful loading. The filled capsules do not collapse, which confirms the successful encapsulation of rifampicin. Further, the encapsulated capsules are larger as compared to hollow capsules as shown in Fig. 7.

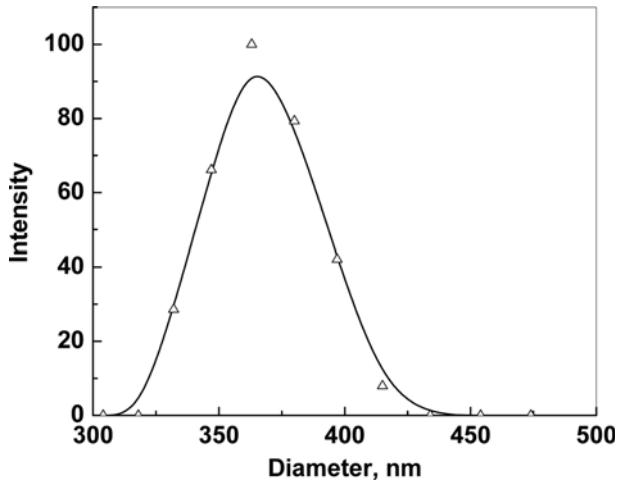

Fig. 7. Size distribution of drug loaded capsules.

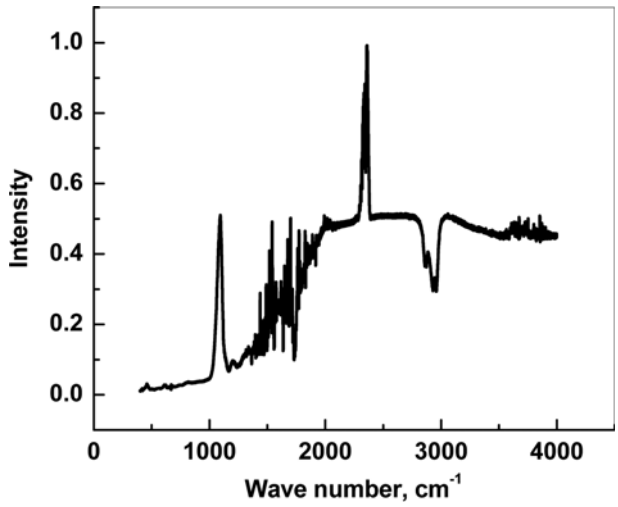

Fig. 8. FTIR spectra of drug loaded capsules.

The FTIR spectra of the drug loaded capsules are shown in Fig. 8. The samples were scanned in the spectral range 4,000 cm^{-1}-400 cm^{-1}, with a resolution of 4 cm^{-1}. The characterestic peaks of chitosan appear at 1,092 cm^{-1} of C-O-C and 1,550 cm^{-1} of -NH_2. Dextran sulfate presented sulfyl peaks near 1,150 cm^{-1} due to asymmetric SOO^- vibrations. The peaks specific to rifampicin at 3,300 cm^{-1} were not observed in the spectrum, which indicated absence of rifampicin on the surface of the capsule. FTIR spectra reveal that there was no rifampicin present on the surface of the capsules, which confirmed the drug molecules were encapsulated in the interior of the capsule rather than on to the surface. Apparently, there is no interaction between drug molecules and the wall material of the capsule.

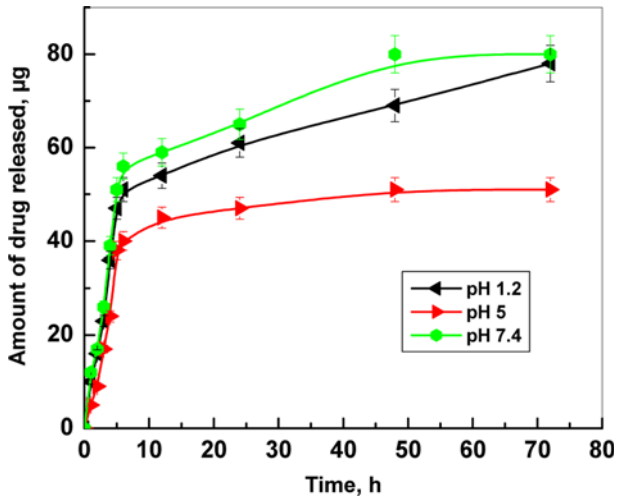

Fig. 9. Release profile of Rifampicin capsules at different pH water @ 82 µg drug load.

The in-vitro release of rifampicin from the chitosan-dextran sulfate capsules was studied as a function of time and pH. Release studies were carried out in both plain water and phosphate buffered saline medium. Fig. 9 shows the release kinetics of rifampicin in plain water at different pH values. The initial drug encapsulated was 82 µg/ml. It is seen from Fig. 9 that there is a sustained release of the drug up to 72 hours. The amount of drug released is dependent on the pH value of the release medium. The least amount of drug was released at pH 5. Maximum amount of drug release was at pH 7.4, where nearly 80 µg was released after 72 hours. The higher release rate was due to higher solubility of the drug and also due to electrostatic repulsion between the drug molecules and capsule surface. About 51 µg was released at pH 5 and 78 µg drug released at 1.2 pH. At pH 5, the drug release was appreciably low due to decreased capsule wall permeability. The amounts of drug release in the case of PBS at 1.2 pH, 5 pH and 7.4 pH are 70 µg, 49 µg and 68 µg, respectively. This demonstrates that pH has a major role to play in the release of encapsulated rifampicin.

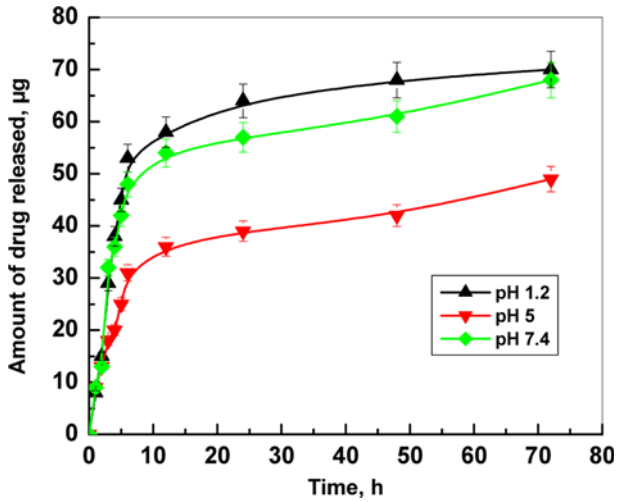

Fig. 10. Release profile of Rifampicin capsules at different pH buffer @ 82 µg drug load.

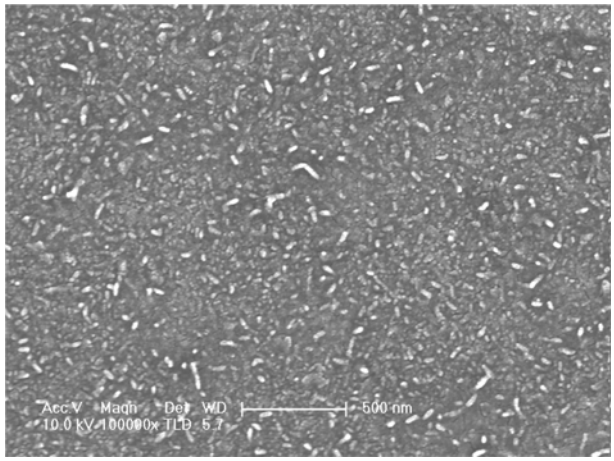

Fig. 11. Scanning electron micrograph of capsules after drug release in water.

The effect of phosphate buffered saline on release of rifampicin is shown in Fig. 10. Rifampicin release was highest at pH 1.2 and the least amount of drug release occurred at 5 pH. At 1.2 pH, the amino groups in chitosan are protonated and the sulfate group of dextran sulfate are ionized (pKa>1). This leads to swelling of capsules and hence higher release rate. The scanning electron micrograph of chitosan-dextran sulfate capsules observed after 72 hours of release studies is shown in Fig. 11. It indicates that the capsules were ruptured and did not have the same wall thickness and stability as the original capsules. A partial degradation of capsules was observed in this *in vitro* study with both water and PBS solute.

To investigate the drug release kinetics from capsules, the results were analyzed according to the Ritger-Peppas and Higuchi models. Using these models the drug release kinetic constant, order and correlation coefficient are obtained.

According to the Ritger-Peppas model, the R^2 value was greater than 0.9 and n was greater than 0.5. The Higuchi square root model describes the kinetics of drug release, and the rate of release is related to the rate of diffusion. Using the Higuchi model R^2 value was greater than 0.8 in all cases as shown in Table 1. This indicates that the drug

Table 1. Rifampicin release data for chitosan-dextran sulfate capsules obtained from fitting drug release experiment data to Higuchi and Ritge-Peppas models (n, diffusion exponent, k_1 and k_2 are kinetic constants, and R^2 correlation coefficient)

Release medium	Higuchi model		Ritger-Peppas model		
	R^2	k_2 [$con^{1-n}\cdot t^{-1}$]	n	k_1 [$con^{1-n}\cdot t^{-1}$]	R^2
1.2 pH Water	0.820	0.175	0.772	0.130	0.91
5 pH Water	0.781	0.160	1.061	0.060	0.916
7.4 pH Water	0.817	0.227	0.743	0.150	0.906
1.2 pH PBS	0.841	0.216	0.871	0.116	0.911
5 pH PBS	0.937	0.137	0.637	0.104	0.967
7.4 pH PBS	0.844	0.204	0.846	0.114	0.882

release kinetics is due to Fickian diffusion. The rifampicin release from the microcapsules is controlled by a drug diffusion process.

CONCLUSION

Chitosan-dextran sulfate hollow capsules of size about 350 nm were prepared by the layer-by-layer technique using silica template. We successfully encapsulated an anti-tuberculosis drug, rifampicin, into these capsules.

The encapsulated drug was released in in-vitro mode. Release kinetics in both plain water and PBS followed a similar trend. There was a sustained release up to 72 hours in both the release media. The rate constant and regression coefficient calculated from Ritger-Peppas and Higuchi models indicated that both models can be fitted for the rifampicin release from chitosan-dextran sulfate capsules. The chitosan-dextran sulfate capsules can substantially prolong the release time of the encapsulated drug molecules. This work presents an easy and versatile encapsulation method with a high potential for application of chitosan dextran sulfate capsules as drug carrier systems in various fields.

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SYMBOLS USED

M_t : amount of drug is released at time t [$\mu g \cdot l^{-1}$]
M_∞ : amount of drug released after an infinite time [$\mu g \cdot l^{-1}$]
M_t/M_∞ : fractional drug release [-]
n : diffusion order [-]
k : release rate constant [$(\mu g \cdot l^{-1})^{1-n} t^{-1}$]

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