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Controlled release of theophylline through semi-interpenetrating network microspheres of chitosan-(dextran-g-acrylamide)

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Abstract Semi-interpenetrating network microspheres of chitosan-(dextran-g-acrylamide) were prepared by emulsion-crosslinking method using glutaraldehyde (GA) as a crosslinking agent. Graft copolymerization of dextran with acrylamide (Dx-g-AAm) was carried out by aqueous free-radical polymerization using ceric ammonium nitrate (CAN) as initiator. The grafting efficiency was found to be 92%. Theophylline (TH), antiasthmatic drug, was successfully encapsulated into semi-INP microspheres by varying the ratio of Dx-g-AAm and amount of GA. The laser light scattering technique shows that the particles size increased with increasing amount of graft copolymer and decrease with increasing amount of GA. The % encapsulation efficiency was found to vary between 50 and 78. MPs were characterized by FTIR spectroscopy and differential scanning calorimetry (DSC) techniques to confirm the graft copolymer, formation of semi-IPN structure of MPs and molecular distribution of the drug molecules in the polymer matrix. In vitro release studies of TH from these matrices have been investigated at Ph 1.2 and 7.4 media and the slow release were extended up to 18 h at 37°C. The release rates were fitted to an empirical equation to estimate the diffusion exponent *n*, which indicated that the release from the MPs follows non-Fickian type.

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1 Introduction

The extent of drug concentration at the site of action in the human body is of central significance for the success of a pharmacotherapy. The too low drug levels lead to the failure of the medical treatment, whereas too high drug concentrations can lead to serious side effects. Using controlled drug delivery systems, the rate at which the drug appears at the target site can be adjusted and, thus, the effects of the pharmacotherapy can be optimized [1–5]. Moreover, as drug release can be controlled over prolonged periods of time, the frequency of drug administration can be reduced, for example once daily instead of two or three times per day. Hence, the life quality, patient compliance and convenience can be improved.

Theophylline (TH) is an antiasthmatic drug and recent studies indicate that it has anti-inflammatory effects [6, 7]. Unfortunately, since its short half-life (6 h), conventional dosage forms have to be administered 3–4 times a day in order to avoid large fluctuations in plasma concentrations, which lead to poor patient compliance [8]. Encapsulation of TH in various synthetic and natural polymeric microsphers for use as sustained release dosage forms has been estimated [9–13]. The need for using biocompatible and biodegradable carriers for this purpose leads to the use of natural polymers as the materials for the preparation of drug delivery systems. As reported in literature [14–18], polysaccharides such as chitosan or dextran have been introduced as the base materials to obtain microcapsules and microparticles with encapsulated different active agents for pharmaceutical and medical purposes.

Chitosan (Cs), a polyaminosaccharide, is a partially deacetylated polymer of *N*-acetyl glucosamine and is usually prepared from chitin. Chitosan and chitin are natural polysaccharides found in a wide range of natural sources

such as crustaceans, fungi, and insects [19]. For handling in health care or biomedical purpose, a chitosan containing substance is thermally stable due to its intramolecular hydrogen bonds between hydroxyl and amino groups. Nevertheless, chitosan is still difficult to make in bulk form because of low mechanical strength [20, 21]. Dextran (Dx) is a high-molecular-weight polymer of D-glucose, produced by different bacterial strains. Dx and its derivatives are used as plasma expanders [22], blood substitutes [23], bone healing promoters [24], and also for dermal and subcutaneous augmentation [25] and for drug delivery [26].The major disadvantage of hydrogels of hydrophilic polymeric matrix is their low mechanical strength due to their high water content, particularly after swelling. To alleviate like this problem, attempts have been carried out to improve the physicochemical and mechanical properties of hydrogels by crosslinking, blending and grafting methods [27–31].

Chemical modification of polysaccharides is very interesting to introduce new functionalities on natural polymers [32]. Grafting of poly vinylic and poly acrylic synthetic materials on the polysaccharides are mainly achieved by radical polymerization. Graft copolymer was prepared by first generating free radicals on the biopolymer backbone using a ceric ion redox initiating system and then allowing these radicals to serve as macroinitiators for the vinyl (or acrylic) monomer [33]. The mechanism of initiation for dextran is believed to begin with a complex formation of the Ce^{4+} ion with the hydroxyl groups at the C-2 and C-3 position, based on work conducted with model compounds. The present study is aimed at developing novel type of semi-IPN microspheres of Cs with Dx-g-AAm for the CR of TH. The IPN are a combination of two or more polymers in network form, at least one of which is synthesized and/or cross-linked independently in the immediate presence of the other [34]. The networks are held by topological bonds, essentially without covalent bonds between them. The IPN based systems have gained good potential to develop the CR systems. The microspheres formed have been characterized by variety of techniques. In vitro release studies have been performed by dissolution experiments. Release data have been discussed in terms of Fickian equation.

2 Materials and methods

Chitosan (Mn: 90–100 KDa with deacetylation degree 75–85%) and Theophylline were purchased from Sigma-Aldrich Chemicals. Dextran, (low molecular weight) was obtained from Acros Organics, New Jersey, USA. Analytical reagent grade samples of acrylamide, acetic acid, ceric ammonium nitrate (CAN), light liquid paraffin oil, *n*-hexane, glutaraldehyde (25% solution), ethanol, heptane and Tween-80 were purchased from LOBA Chemical, Mumbai, India. All the chemicals were used without further purification.

2.1 Synthesis of graft copolymer of dextran and acrylamide

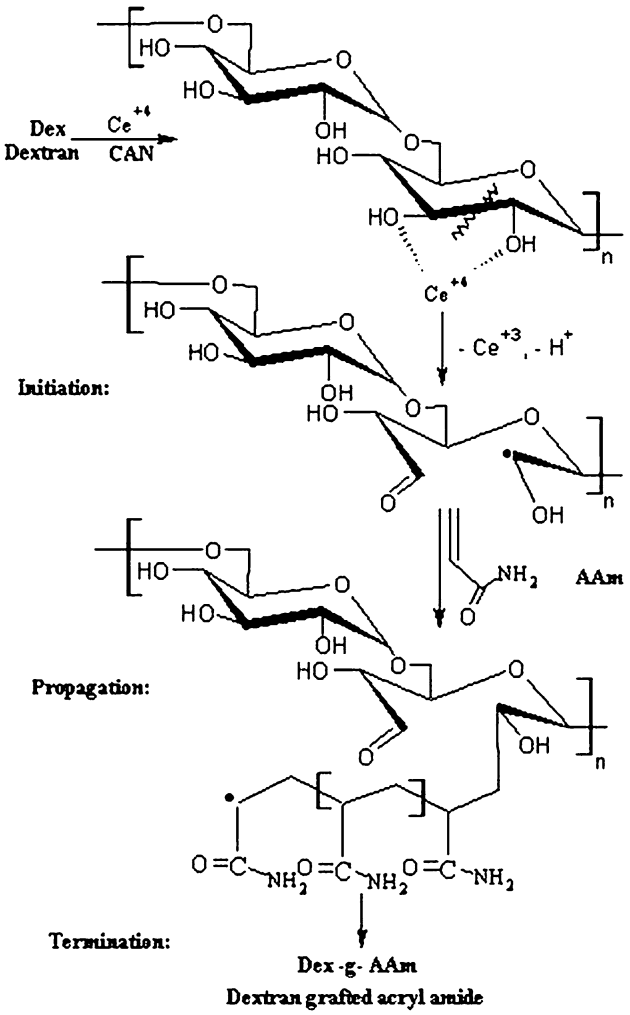
Dextran-grafted-acrylamide (Dx-g-AAm) copolymer was prepared by aqueous free-radical polymerization using CAN as redox initiator. Briefly, 2% aqueous solution of Dx was prepared by dissolving the polymer in distilled water under constant stirring in 250 ml three-necked round bottom flask for overnight. To this, a solution of 0.28 mol of acrylamide (AAm) was added and stirred for 1 h at 60°C. The initiator solution containing 4.47×10^{-4} mole of CAN was added drop wise to the above mixture. Polymerization was carried out under continuous purging of nitrogen gas with a constant stirring at 60°C for 5 h. The reaction mixture was then cooled and a pinch of hydroquinone was added to quench the reaction. The weight obtained was precipitated in sufficient amount of ethanol: heptanes (80:20) to remove the homopolymer formed. The solid copolymer was dried in an electrically controlled oven at 40°C before further use. The % grafting efficiency was calculated by the following equation:

$$\%\ \text{Grafting effciency} = \left(\frac{W_1 - W_0}{W_2}\right) \times 100 \qquad (1)$$

where W_0, W_1 and W_2 denote weights of hydroxyl ethyl cellulose, graft copolymer and monomer, respectively. The proposed reaction mechanism is presented in Scheme 1 [33, 35].

2.2 Preparation of semi-IPN MPs and drug loading

Semi-IPN microspheres of Cs and Dx-g-AAm, hereafter designed as Cs-(Dx-g-AAm) were prepared by emulsion-crosslinking method using glutaraldehyde (GA) as a crosslinking agent. In briefly, weighed amounts of Cs and Dx-g-AAm copolymer were dissolved in 20 ml of 2% aqueous acetic acid solution with continuous stirring until a homogeneous solution was obtained. Theophylline equivalent to 30% (w/w) of dry weight of the polymer was added to the above polymer solution and stirred for overnight. This solution was emulsified into light liquid paraffin in the presence of 1% Tween-80 using mechanical stirrer equipped with a 3 blade propeller at 500 rpm for 10 min. Then, a mixture of different quantities of GA and 1 ml of 5 N HCl was added slowly to this w/o emulsion, to harden the microspheres and stirring was continued for 2 h. The MPs thus produced were separated by filtration, washed repeatedly with *n*-hexane followed by water to remove the paraffin oil and excess of the crosslinking agent. Totally,



Scheme 1 Proposed reaction mechanism for grafting of poly acrylamide AAm into Dx using ceric ion initiation

nine (9) formulations were prepared by varying amount of graft copolymer and amount of crosslinking. To understand the variables, formulation codes are assigned as given in Table 1. For example the formulation codes, P-xy, refers to two variables viz., x-represents three amounts of Dx-g-AAm numbered as 1, 2 and 3 for 10, 20 and 30% based on dried Cs, y-represents three amount of crosslinking numbered as 4, 7 and 10 for 4 ml, 7 ml and 10 ml of GA added.

2.3 Drug content

The exact theophyllinne content loaded within the MPs was estimated by crushing 10 mg of the loaded-microspheres in 100 ml of phosphate buffer pH 7.4 at 50°C in order to extract the drug from the microspheres. The concentration of the solution was investigated spectrophotometericaly using the UV/Vis spectrophotometer (Shimidzu, Japan) at λ max of 274 nm. These data were collected in triplicate, but the average values were considered in calculating the % drug loading and encapsulation efficiency. These were calculated as follows:

$$\%\text{Drug loading} = \left(\frac{\text{Weight of drug in microspheres}}{\text{Weight of microspheres}}\right) \times 100 \quad (2)$$

$$\%\,\text{Encapsulat ion efficiency} = \left(\frac{\text{Actual drug loading}}{\text{Theoretical drug loading}}\right) \times 100 \quad (3)$$

These data for various formulations are presented in Table 1.

2.4 Swelling studies

Equilibrium water uptake by the microspheres was determined by measuring the extent of swelling of the matrix in water. To ensure complete equilibration, samples were allowed to swell for 24 h to obtain equilibrium at 37°C. Excess surface adhered liquid drops were removed by

Table 1 Formulation parameters used for the preparation of microspheres, results of % encapsulation efficiency, mean particle size and % equilibrium swelling (Q)

Formulation code[a]	% AAm-g-Dx per g of Cs	GA (in ml)	% Encapsulation efficiency	Main particle size (μm)	% Equilibrium swelling (Q)
P-14	10	4	50	325	335
P-17	10	7	54	276	270
P-110	10	10	60	270	160
P-24	20	4	61	362	320
P-27	20	7	66	320	250
P-210	20	10	70	280	140
P-34	30	4	65	395	303
P-37	30	7	72	350	230
P-310	30	10	78	317	130

[a] P-24 refers to Formulation with two parameters, three AAm amount and three crosslinking amount

blotting carefully (without pressing hard) and the swollen microspheres were weighed on an electronic microbalance. The hydrogel microspheres were then dried in an oven at 60°C for 5 h until there was no change in the weight of the dried mass of the samples. Swelling experiments were repeated thrice for each sample and the average values were used in data analysis. The standard deviations (SD) in all cases were <3%. The % equilibrium water uptake (Q) was calculated as:

$$Q = \left(\frac{W_\infty - W_0}{W_0}\right) \times 100 \quad (4)$$

where, W_∞ is the mass of swollen MPs and W_0 is the mass of dry MPs.

2.5 In vitro drug release study

In vitro drug release, known amounts of different formulations, Cs-(Dx-g-AAm) MPs contained 20% of the active ingredient were placed in 500 ml of the dissolution medium at pH of 2 and 7.4 using the USP apparatus dissolution tester (Dissotest, Lab India, Mumbai). The dissolution medium was stirred at 100-rpm speed at 37°C. Aliquots of dissolution medium (3 ml) were withdrawn and filtered through 0.45 mm millipore filters at the predetermined time intervals. After appropriate dilution, drug concentrations were analyzed by UV–Vis spectrophotometer (Shimidzu, Japan) at the λ_{max} value of 274 nm. Dissolution medium was maintained at a constant volume by replacing the samples with a fresh dissolution medium. The calibration curve was prepared using graduated dilutions of standard, which were assayed in the same way.

2.6 Fourier transform infrared (FTIR) spectra

FTIR spectral measurements were performed using Shimadzu-1800S spectrophotometer (Japan), to confirm the graft copolymer and formation of semi-IPN structure of Cs-(Dx-g-AAm)MPs. All the samples were crushed with potassium bromide and pellets were obtained by applying a pressure of 600 kg/cm^2 using FTIR pellet maker. Spectral scanning was done at 2 cm^{-1} resolution with 64 scans over the spectral range from 4,000 to 400 cm^{-1}.

2.7 Differential scanning calorimetric (DSC)

For DSC measurements, a Perkin-Elmer DSC-7, operating in a dynamic mode was employed. Nitrogen gas was used as an inert gas at a flow rate of 20 ml/min. Each sample (80 mg) of (a) plain TH, (b) placebo microspheres and (c) drug loaded microspheres was placed in aluminum pan. An empty aluminum pan was used as a reference and the analysis was performed by heating/cooling the samples at the rate of 10°C/min with scan ranges between 0 and 350°C.

2.8 Scanning electron microscopic (SEM)

SEM micrographs of the microspheres were measured using a JEOL model JSM-840A scanning electron microscope (Japan) and micrographs were taken at the required magnification. A working distance of 33.5 mm was maintained and the acceleration voltage used was 10 kV with the secondary electron image (SEI) as a detector.

2.9 Particle size measurements

Particle size of the MPs was measured by laser light diffraction technique (Mastersizer-2000, Malvern Instruments, UK). About 200 mg of MPs were dispersed into 100 ml of methanol and stirred under sonication for 2 min to avoid agglomeration of MPs before measurements. For measurement of sizes of different formulations, the sample holder was cleaned with distilled water followed by acetone to prevent cross contamination.

3 Results and discussion

3.1 Synthesis of Dx-grafted-acrylamide

Graft copolymerization of Dx with AAm was carried out by CAN ion catalyzed free radical polymerization. The complex formed with the –OH groups of Dx at the C-2 and C-3 position decomposes to generate the free radical site, facilitating the grafting to occur at the active site of Dx with the incoming acrylamide monomer. The monomer concentrations of 0.28 mol was used, which resulted in percentage of grafting efficiency of 92. The reaction was carried out at 60°C for 6 h. The proposed reaction mechanism is shown in Scheme 1.

3.2 Preparation and characterization of microspheres

The theophyllinne-loaded semi-IPN microspheres of Cs and Dx-g-AAm copolymers were prepared by emulsion-crosslinking using GA as crosslinker. By this method, % encapsulation efficiency ranged between 50 and 78. However, % encapsulation efficiency showed a dependence on the amount of crosslinking agent and also on the ratio of the graft copolymer to chitosan employed when formulating the microspheres. These data presented in Table 1.

The % encapsulation efficiency was increased with increasing amount of Dx-g-AAm in the microspheres. For microspheres containing 10, 20 and 30 wt% of Dx-g-AAm, keeping TH (30 wt%) and GA (7 ml) constant,

Table 2 The values of characteristic parameters, k and n, correlation coefficient, r and diffusion coefficient, D using power law equation

Formulation code	n	k	r^2	$D \times 10^6$ (cm^2/s)
P-24	0.510	0.291	0.984	14.8
P-27	0.495	0.273	0.979	14.0
P-210	0.472	0.263	0.986	12.5
P-17	0.531	0.286	0.985	16.8
P-27	0.514	0.265	0.977	16.1
P-37	0.484	0.246	0.989	14.3

encapsulation efficiencies were 54%, 66% and 72% for formulations, (P-17, P-27 and P-37), respectively. In case of the microspheres crosslinked with 4, 7 and 10 ml of GA, encapsulation efficiencies are, 61%, 66% and 70%, for formulations, (P-24, P-27 and P-210), respectively, see Table 1. Such as an increase in % encapsulation efficiencies is due to increasing crosslinking density and poor solubility of TH during encapsulation.

The size of particles (Table 2) depends on the amount of % Dx-g-AAm content and extent of GA used for crosslinking. In general, the size of particles ranged from 270 to 400 μm. The particle size was increased with increasing amount of Dx-g-AAm in the microspheres. For instance, as the amount of Dx-g-AAm increases from 10 to 30 wt% and 30 wt% TH with 7 ml GA, particle size has increased from 276 to 350 μm. This can be explained to the fact that at higher amounts of Dx-g-AAm, the viscosity of polymer solution increased, thereby producing bigger droplets during emulsification that were later hardened in the presence of GA. However, amount of crosslinking was a significant effected on the particle size, see Table 1. For instance, the MPs containing 30% drug and 30% Dx-g-AAm, with increasing crosslinking, by adding 4–10 ml of GA, the particle size decreased from 395 to 317 μm for formulations P-34 to P-310. This is attributed to the fact that with increasing amount of GA in the semi-IPN matrix, the shrinkage of particles has taken place, thereby reducing their sizes.

3.3 Fourier transform infrared (FTIR) spectra

The FTIR spectra of (a) plain Dx and (b) Dx-g-AAm are presented in Fig. 1a and b. As can be seen, in the spectrum of AAm-g-Dx, as compared to the pure Dx, the additional absorption, a new shoulder band apparel at ~3,150 cm^{-1} and a sharp peak around ~1,665 cm^{-1} correspond to –NH and C=O stretching vibration, respectively thereby confirmed grafting reaction. The appearance of relative intensity band at 2,925 cm^{-1} corresponds to aliphatic –CH stretching in the graft copolymer confirms the grafting of acrylamide on Dx. The new peak at ~1,565 cm^{-1}

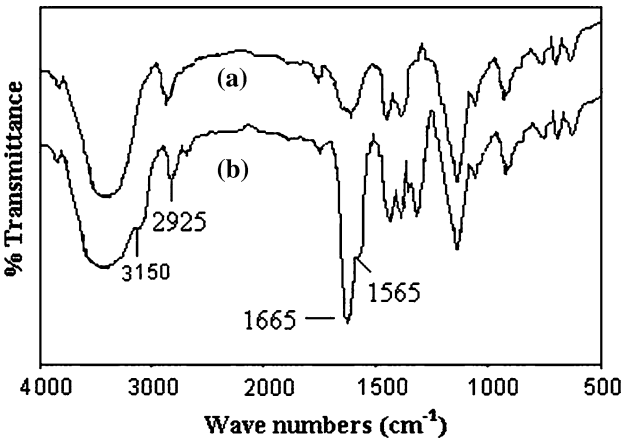


Fig. 1 FTIR spectra of (a) plain Dx and (b) Dx-g-AAm

corresponding to C–N bending vibration further support the grafting reaction.

Figure 2 shows the FTIR spectra of (a) plain Cs, (b) Cs-(Dx-g-AAm) uncrosslinked and (c) Cs-(Dx-g-AAm) crosslinked. In case of plain Cs, a broad band appeared at 3,450 cm^{-1} due to the overlapping of the stretching vibrations of hydroxyl O–H and amine N–H_2 groups. Another broad band appearing around ~1,073 cm^{-1} indicates the C–O stretching vibration of chitosan. Three bands observed at 1,650, 1,594 and 1,379 cm^{-1} indicate amide-I, amide-II and amide-III, respectively. Peaks

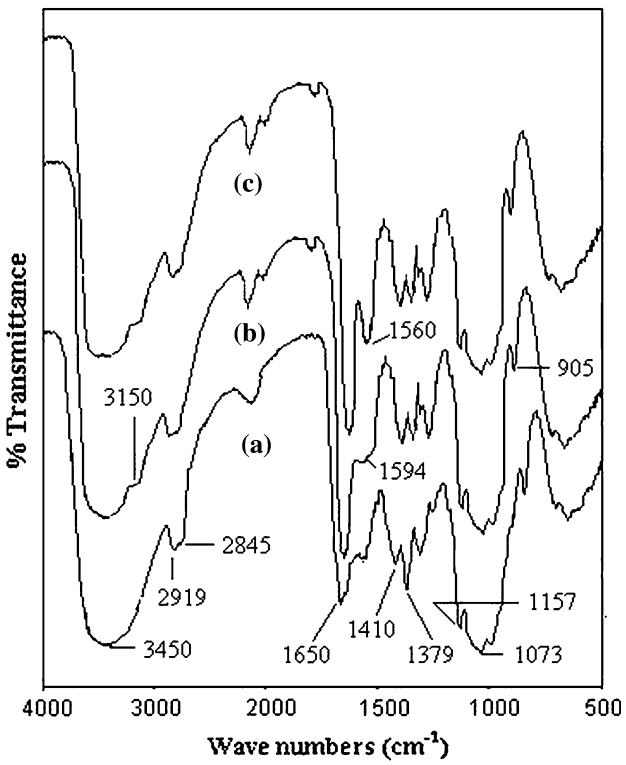
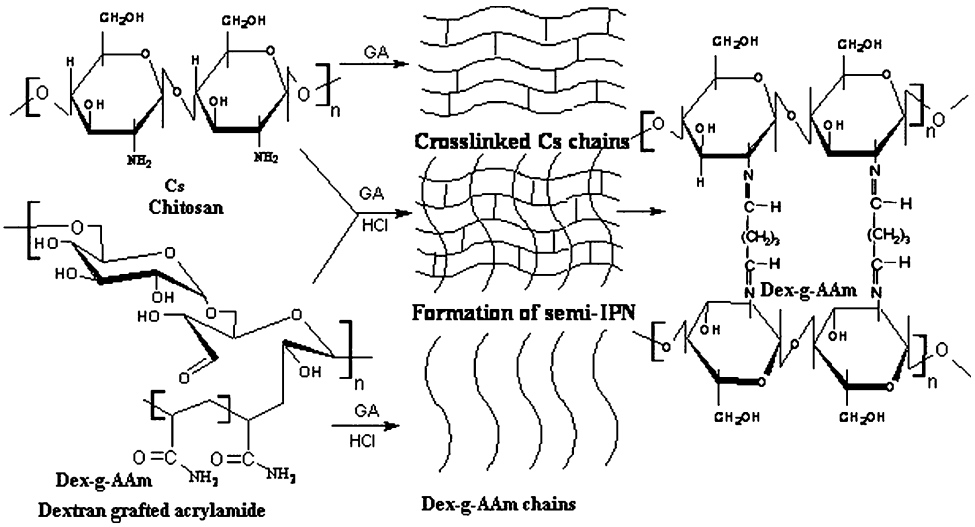


Fig. 2 FTIR spectra of (a) plain Cs, (b) Cs-(Dx-g-AAm) uncrosslinked, and (c) Cs-(Dx-g-AAm) crosslinked

Scheme 2 Schematic representation structure of synthesis of semi-IPN



observed at ~2,845 and ~2,919 cm^{-1} are typical of C–H stretching vibrations. The peaks around 905 and 1,157 cm^{-1} are corresponding to saccharide structure. The observed peaks at ~1,410 cm^{-1} is assigned to CH_3 symmetrical deformation mode [36, 37].

In case of Cs-(Dx-g-AAm) crosslinked, all the bands of both Cs and Dx-g-AAm were observed in addition to a new band observed at 1,560 cm^{-1}, due to imine bonds (C=N) was formed as a result of crosslinking reaction between amino groups in Cs and aldehyde groups in GA [38, 39]. A reaction leading to the formation of crosslinking is depicted in Scheme 2.

3.4 Differential scanning calorimetry (DSC)

DSC thermograms of (a) plain TH, (b) placebo microspheres and (c) drug loaded microspheres are displayed in Fig. 3. The DSC thermogram of TH showed a sharp peak at 280°C, indicating the melting of the drug. In case of placebo microspheres, two small sharp peaks and a broad peak were observed at 68, 96 and 202°C, respectively, due to endothermic transition of the polymer matrix. In case of drug-loaded microspheres, three peaks were noticed at 75, 102 and 202°C due to endothermic transitions. However, there was no characteristic peak of TH in the drug-loaded microspheres, indicating that drug is molecularly dispersed in the polymer matrix.

3.5 Scanning electron microscopy (SEM)

SEM micrograph of theophylline-loaded chitosan and modified dextran blend microspheres taken at 40 magnification are shown in Fig. 4. The microspheres almost are spherical in nature with smooth surfaces. However, the polymeric debris is seen around some of the particles could be due to the preparation methods.

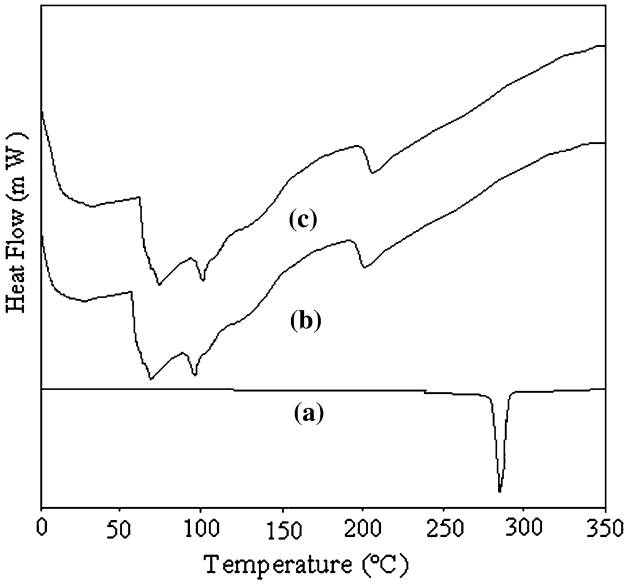


Fig. 3 DSC thermograms of (a) plain TH, (b) placebo microspheres and (c) drug loaded microspheres

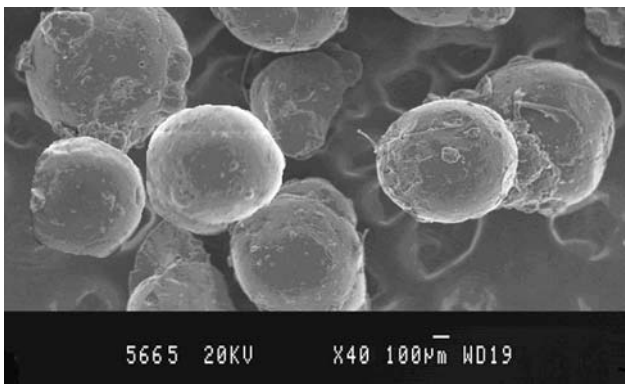


Fig. 4 SEM Micrograph of group of TH loaded microspheres

3.6 Swelling studies

MPs produced with different extent of crosslinking and graft copolymer ratio were subjected to dynamic swelling studies in water. These data are displayed in Table 1. T he equilibrium swelling is dependent upon the extent of crosslinking agent and graft copolymer ratio in the semi-IPN matrix. For instance, % equilibrium swelling decreased from 335 to 160 with increasing amount of GA from 4 to 10 ml (formulations, P-14 to P-110). This is due to increased crosslink density and decreased pore volume of the semi-IPN matrix with increasing amount of GA in the matrix. Also, the % water uptake of the semi-IPN matrix has decreased by increasing the graft copolymer ratio of Dx-g-AAm: CS in the semi-IPN matrix. For instance, % water uptake of the semi-IPN matrix containing 10, 20 and 30% wt/wt of Dx-g-AAm are 335, 320 and 303 for formulations, P-14, P-24 and P-34 respectively. Decreased equilibrium swelling of the microspheres at higher ratio of the graft copolymer can be explained as a result of decrease in the amount of chitosan of the network. In fact, the polyelectrolyte nature of chitosan induces a high osmotic pressure and thus, a high swelling occurs due to increase in the translational entropy of counterions.

3.7 In vitro drug release

In vitro release of TH from Cs-(Dx-g-AAm) MPs were carried out in gastrointestinal pH conditions. The MPs were first left for 2 h at pH 2, and then changed to pH 7.4 for 16 h. Figures 5 and 6 show the release profile of TH from Cs-(Dx-g-AAm)MPs. The release of TH was somewhat fast in the initial stages, but subsequent release was slow and continues up to 18 h. The fast release during initial

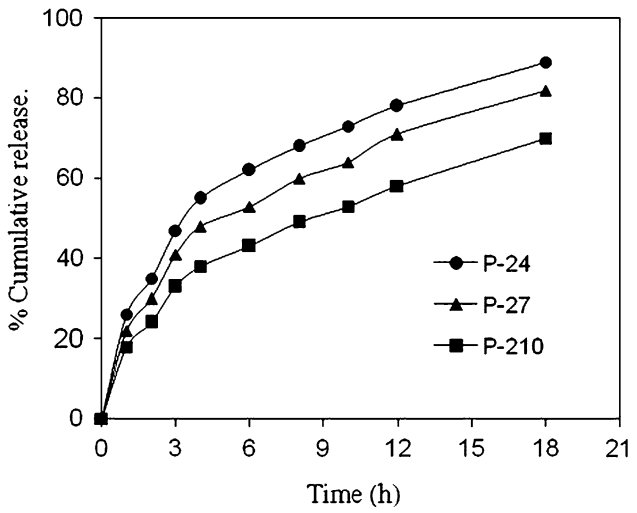


Fig. 5 Effect of crosslinking on in vitro theophlline release profiles of formulations, P-24, P-27 and P-210

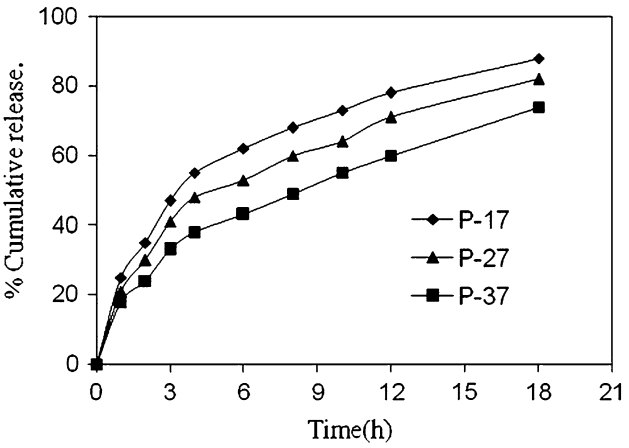


Fig. 6 Effect of polymer ratio on in vitro theophlline release profiles of formulations, P-17, P-27 and P-37

stages is attributed to swelling ability or polymer relaxation. Furthermore, due to basic nature of TH (pKa 8.8), the release rate is expected to be higher under acidic conditions, while under the alkaline conditions, solubility becomes minimal, which might be reflected in the reduce dissolution of the dispersed drug particles and consequently decreased the release rate [40]. The results of percent drug release versus time show an effect of the matrices crosslinking on drug release for all formulations. Figure 5 shows the release of TH from MPs crosslinked with different amounts of GA containing 20 wt% of Dx-g-AAm and a fixed amount of drug (30 wt%) for formulations P-24, P-27 and P-210. Drug release rate is higher in case of MPs crosslinked with 4 ml GA, P-24 (89%), and the least % release rate is observed with MPs crosslinked with 10 ml GA, P-210 (70%). This could be due to the fact that at higher crosslinking, free volume of the matrix will decrease, thereby hindering the transport of drug molecules through the matrix as the amount of crosslinking agent was increased from 4 to 10 ml. The % cumulative release versus time curves for microspheres prepared by using different ratios of graft copolymer: chitosan matrices are presented in Fig. 6 for formulations P-17, P-27 and P-37. Drug release rates are higher for microspheres having lower amount of graft copolymer compared to those having higher amount of graft copolymer. The observed decrease can be attributed to the fact that with increasing number of graft copolymer chains in the MPs matrix, the density of the network increases, which results in relaxation of polymer chains. This clearly retards the diffusion of entrapped drug molecules into the release medium and thus gives rise to lower amount of released TH. From Fig. 6, one can visualize that drug release is faster for formulation P-17 (88%) as compared to P-27 (82%), which contains higher amount of the graft copolymer at the same extent of cross linking (7 ml) and the same drug loading (30 wt%).

Similar trends can be seen between formulations P-27 (82%) and P-37 (74%).

3.8 Drug release kinetics

Drug release kinetics was investigated by fitting the cumulative fraction release data, M_t/M_∞, to the power law equation [41]:

$$\frac{M_t}{M_\infty} = kt^n \tag{5}$$

Here, M_t and M_∞ represent the amount of DS released at time t and at infinite time, k is a constant characteristic of the drug-polymer system and n is the diffusional exponent which suggests the nature of the release mechanism. The release parameters k and n were computed by applying the least-squares estimation method to the release data at 95% confidential limit. These data along with the values of correlation coefficient, r are presented in Table 2. A value of $n = 0.5$ indicates Fickian transport; $n = 1.0$ indicates the presence of Case-II (zero order) transport. Values of n ranging between 0.5 ± 1.0 are attributed to the presence of anomalous transport. The values of k and n have shown a dependence on the extent of cross-linking and grafting ratio, (i.e., composition of the copolymer).Values of k decreased with increasing crosslink agent as well as with increasing the grafting ratio in the semi-IPN matrix. The k-values range between 0.247 and 0.291, indicating lesser interactions between the drug and the polymer matrices. Also, we observed that the n values were decreased with increasing crosslink agent as well as with increasing the grafting ratio in the semi-IPN matrix. These values ranged between 0.531 and 0.472, indicating that the drug release from the MPs shifted from non-Fickian or anomalous to Fickian trends. In other words, the release mechanism shifted from relaxation controlled to diffusion controlled.

The diffusion coefficient (D) of water within the MPs was calculated according the following equation [42]:

$$\frac{M_t}{M_\infty} = 6\sqrt{\frac{Dt}{\pi r^2}} - \frac{3Dt}{r^2} \tag{6}$$

The above equation is valid for the initial drug release (i.e., $0 \prec M_t/M_\infty \prec 0.4$).

At short times, Eq. 6 can be approximated as:

$$\frac{M_t}{M_\infty} = 6\left(\frac{Dt}{\pi r^2}\right)^{\frac{1}{2}} \tag{7}$$

The diffusion coefficient (D) of water absorption or drug release through microspheres can then be computed by using equation (8):

$$D = \left(\frac{r\phi}{6}\right)^2 \pi \tag{8}$$

Here, ϕ is slope of the linear portion of the plot of M_t/M_∞ versus $t^{1/2}$, r initial radius of the microspheres and M_∞ is maximum equilibrium swelling value. Diffusion coefficients were investigated by assuming the Fickian diffusion transport and the results presented in Table 2. The Diffusion coefficients fall in the range of $(12.5-16.8) \times 10^{-6}$ cm^2/s and decrease systematically with increasing amount of the crosslinking agent as well as with increasing the graft copolymer ratio in the semi-IPN matrix. The observed decrease can be attributed to the fact that with increasing amount of GA, the free volume of the matrix will decrease which could be hinder, the transfer of small molecule through MPs matrix. Also, with increasing number of graft copolymer chains in the semi-IPN MPs, the density of the network increased, which results in relaxation of polymer chains. This clearly retards the diffusion of water or entrapped drug molecules.

4 Conclusion

Dextran was successfully modified by grafting with acrylamide using CAN as initiator. The graft copolymer subsequently mixed physically with chitosan in different amount ratios to encapsulate TH-based microspheres, by w/o emulsification method, which later hardened by crosslinked with different amount of glutralaldehyde. The study indicated that it is possible to load slight water soluble drug such as TH. The produced MPs exhibited encapsulation efficiencies up to 78%. The drug release depends on amount of crosslinking agent GA and % Dx-g-AAm into the blend MPs and pH conditions. The n values ranged between 0.531 and 0.472, indicating that the drug release from the MPs shifted from non-Fickian or anomalous to Fickian trends. In other words, the release mechanism shifted from relaxation controlled to diffusion controlled. The average size of the MPs ranged from 270 to 400 μm. SEM micrographs exhibited a spherical morphology of the prepared microspheres. However, the polymeric debris are seen around some of the particles are probably owing to preparation methods. FTIR spectroscopy confirmed the graft copolymer and formation of semi-IPN structure of Cs-(Dx-g-AAm)MPs. DSC technique confirmed the molecular distribution of the drug molecules in the polymer matrix.

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