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Research Article

SYNTHESIS AND CHARACTERIZATION OF POLY (NIPAM-co-CAPROLACTAM) THERMORESPONSIVE MICRO-SPHERES FOR CONTROLLED RELEASE OF ACEBUTOLOL HYDROCHLORIDE

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ABSTRACT

Thermoresponsive poly (N-isopropylacrylamide-co-caprolactam) designated as P(NIPAAm-co-CL) copolymeric microspheres crosslinked with N,N–methylene *bis*-acrylamide (NNMBA) have been prepared by dispersion polymerization using varying amounts of NIPAAm, CL and NNMBA. Acebutolol hydrochloride (ABH), an anti-hypertensive drug, was loaded into the microspheres during *in situ* polymerization and *in vitro* release of ABH has been studied. The microspheres were characterized by Differential Scanning Calorimetry (DSC), X-Ray Diffractometry (X- RD) and Scanning Electron Microscopy (SEM). The release of ABH, drug from these microspheres was studied in pH 7.4 media, at the temperatures 25^{0}C and 37^{0}C. The microspheres consisting of NIPAAm and CL provide thermo responsive nature to the microspheres. The system developed in this study showed a thermoresponsive for the controlled release of ABH. The DSC and XRD techniques indicated that the uniform distribution of drug in the microspheres and the drug was released in a controlled manner upto 10 h.

Keywords: Caprolactam, N-isopropylacrylamide, Drug delivery, Acebutolol hydrochloride, Controlled release.

INTRODUCTION

In the past decade, temperature-induced hydrogels have gained increasing attention for many investigators for scientific interest and for practical biomedical or pharmaceutical applications since the administration is convenient[1]. Among the temperature-responsive hydrogels reported to date, Poly(N-isopropylacrylamide) (PNIPAAm) homopolymer and its copolymers have been most intensively investigated.[2–5] Controlled delivery systems via targeted drug delivery of a predetermined dose over a sustained period[6-13] have been used to overcome the short comings of conventional dosage forms. This is because the controlled drug delivery system can provide sustained therapeutic level of drug concentration without toxicity. Drug delivery technology also provides convenience for patients. It would be more beneficial and ideal if the drug could be delivered by a device that would respond to physiopathological signals from an underling disease. The correct amount of drug would be released upon the stimulation of such a physiopathological signal.

There have been many reports on the thermally sensitive P(NIPAAm) hydrogel in the past 30 years[14-16] because of its particular property, its volume or weight changes drastically and almost all the inside water is lost when the temperature is raised from room temperature to above the lower critical solution temperature (LCST).[17] This useful property has been used in many biomedical and pharmaceutical applications, such as drug-delivery systems, enzyme immobilization, tissue culture substrates, and gene carriers.[18] However, for some applications, the conventional P(NIPAAm) hydrogel has some serious limitations, such as weak mechanical strength in the highly swollen state and a slow response rate when the temperature is greater than the LCST.

Recently, there has been increased interest in responsive hydrogels for utilisation as the smart drug delivery system (smart-DDS) in the field of controlled drug release, to meet the need for prolonged and better control of drug administration.[19-22] As we know, in conventional drug delivery, the drug concentration in the blood increases to a toxic level as the drug is taken, and then the drug concentration decreases to an ineffective level and the patients have to take the drug frequently. In order to eliminate or reduce the above disadvantages, drug delivery system (DDS) for control release was designed to maintain the drug release with the predetermined dose and prolong the curing-time in the targeted body compartment. Compared to the conventional DDS, the advantages of the smart-DDS are self-evident because the drug amount can be auto-controlled by external changes, such as temperature, electric fields, pH and photo fields etc.

Thermo-responsive hydrogel is a most extensively studied, responsive and polymeric material, including various polymers, such as the *N*-substituted polyacrylamide, polymethylacrylamide and poly (ethylene oxide) etc. Poly(*N*-isopropylacrylamide) (PNIPAAm) hydrogel is a typically thermosensitive material[23], which exhibits a phase transition temperature (T_{tr}) or lower critical solution temperature (LCST) at ≈ 33 °C.[24,25] As the external temperature cycles around this phase transition temperature, the polymer chains undergo a coil globule transition.[36, 37] Correspondingly, the three-dimensional PNIPA hydrogel returns to a shrunken state and displays phase separation, i.e. abrupt collapse in volume as the temperature is increased above LCST. The abrupt shrinking in the volume of the PNIPAAm hydrogel to the increased temperature has produced extensive research interest directed at applications to the controlled release of drugs.

Normally, the selected drug is physically loaded in the swollen thermo-responsive hydrogel and the drug release is controlled by the external temperature changes due to the thermo-reversible properties of the PNIPAAm hydrogel. Generally regarded, the drug exhibits a Fickian release, which depends on the swelling ratio of the hydrogel. As the temperature is increased above the LCST, PNIPAAm hydrogel may shrink and quickly form a dense, thick skin layer, which leads to the burst release initially and then the release of the drug in the network matrix is stopped.

A typical release pattern was reported by Kim's research group and an on–off release pattern of the model drug, indomethacin, was achieved by regulating the temperature between 20 and 30°C. A series of investigations based on the thermo-responsive hydrogels was carried out and much useful data were obtained.[7, 21, 31-33] In these cases, the thermo-responsive hydrogels provide a negative temperature-responsibility to the drug release, i.e. slow drug release at increased temperature and rapid drug release at decreased temperature. In some cases, a positive controlled release pattern, i.e. rapid drug release at increased temperature and slow drug release at decreased temperature, is urgently needed when the DDS is

specially designed to respond to an increase in the body temperature resulting from diseases, such as inflammation or cancers etc.

In our research, the author prepared a novel thermo-responsive DDS to give a positive controlled release pattern. Acebutolol hydrochloride is an anti hypertensive drug, used in the treatment of curing the hypertension, which is easily soluble in water. Here, the author has chosen as model drug which was loaded into the PNIPAAm and Caprolactam microspheres. Then the drug incorporated microspheres was carefully enveloped in the dialysis bag to form a novel DDS with double controlled release layers (the polymer network and the dialysis membrane). At different predetermined temperatures (25°C and 37°C), the concentration of released ABH was monitored at 240 nm on an UV spectrophotometer. It was found that ABH was released more rapidly at 37 °C (>25 °C) than at 25 °C. This novel, thermoresponsive P(NIPAAm-co-CL) polymeric matrix may be more useful in cases where controlled drug delivery system is needed.

EXPERIMENTAL

Materials and methods

N-isopropylacrylamide (NIPAAm), caprolactam were purchased from Aldrich, Milawaukee, WI, USA. *N*,*N*-methylene *bis*-acrylamide (NNMBA), potassium persullate (KPS), sodium lauryl sulphate (SLS) were all of analytical grade purchased from s.d.fine chemicals, Mumbai, India and used without further purification. The model drug acebutolol hydrochloride was obtained as a gift sample from waksman salesman pharmaceuticals, Anantapur, A.P. India.

Synthesis of thermo responsive poly (NIPAAm-*co*-CL) microspheres

Sodium lauryl sulfate (1g) was dissolved in 75mL of water taken in a three necked round bottom flask equipped with a mechanical stirrer, a condenser and a gas inlet to maintain the inert nitrogen atmosphere. The flask was immersed in an oil bath with a thermostatic control to maintain the desired temperature accurate to ±0.1°C.

The solution was stirred at 800 rpm speed until it became clear and 100 mg of potassium per sulfate was added. Required amount of NIPAAm, Caprolactam, the crosslinking agent NNMBA and acebutolol hydrochloride were dissolved separately in 25mL of water. This mixture was added to the reaction mixture drop wise using a dropping funnel and the reaction was continued for 8 h at 70°C to obtain the maximum yield. The reaction mixture was taken out after 8 h and added to 1% calcium chloride solution drop wise to break the emulsion. Particles were then isolated by centrifuging the product at the rotor speed of 12,000 rpm, washed with water and dried under vacuum at 40°C for 24 h. The blank microspheres without drug incorporation were by prepared by above method. The microspheres were prepared by three different amounts of drug [ABH-1, ABH-2, ABH-3], three different amounts of crosslinker [NNMBA-1, NNMBA-2, NNMBA-3] and three different ratios of monomers [NIPAAm-1, NIPAAm-2, NIPAAm-3].

Loading of Acebutolol hydrochloride

Acebutolol hydrochloride was loaded into polymeric microspheres by two methods. In the first method (method-I), drug was added during *in situ* polymerization, i.e., drug was mixed with monomer, crosslinking agent, initiator, and the mixture was added to the polymerization medium. In the second method (method-II), drug was loaded into polymeric microspheres by keeping the weighed amount of microspheres in methanolic drug solution of known concentration and evaporating methanol under vacuum. During this process, drug in the solvent will absorb into the surface as well as adsorbed onto the microspheres.

Estimation of drug loading and encapsulation efficiency

Loading efficiency of acebutolol hydrochloride in the microspheres was determined spectrophotometrically. About 10 mg of the drug-loaded microspheres were placed in 10 mL of buffer solution and stirred vigorously for 24 h to extract the drug from the microspheres.

The solution was filtered and assayed by UV-spectrophotometer (model Labindia-3000+, Mumbai, India) at the fixed λ_{max} value of 240 nm. The results of % drug loading and encapsulation efficiency were calculated, respectively using Eqs. (1) and (2).

$$\%\ \text{Drug loading} = \left(\frac{\text{Amount of drug in microspheres}}{\text{Amount of microspheres}}\right) x100 \quad \textbf{(1)}$$

$$\%\ \text{Encapsulation efficiency} = \left(\frac{\text{Actual loading}}{\text{Theoretical loading}}\right) x100 \quad \textbf{(2)}$$

Conversion of copolymer

The yield of the copolymeric microspheres was determined gravimetrically. After copolymerization, the latex solution was added to 1% calcium chloride solution and centrifuged to isolate the particles from the mixture. The copolymeric microspheres were washed several times successively with distilled water and methanol solvents to remove the remaining monomer and initiator, and then dried in a vacuum oven at 50°C till constant weight is attained. The conversion of monomers was calculated as:

$$\text{Conversion} = (W/M)x100 \quad \textbf{(3)}$$

In-vitro release studies

In-vitro release studies have been carried out by performing the dissolution experiments using a tablet dissolution tester (LabIndia, Mumbai, India) equipped with eight baskets. Dissolution rates were measured at other temperatures 25°C and 37°C under 100 rpm speed. Drug releases from the microspheres were studied in intestinal (7.4 pH phosphate buffer media) fluids like atmosphere. At regular intervals of time, sample aliquots were withdrawn and analyzed using UV spectrophotometer (Model LabIndia-3000 +, UK) at the fixed λ_{max} value of 240 nm.

RESULTS AND DISCUSSION

Differential scanning calorimetry (DSC)

DSC tracings of plain microspheres (curve-a), pure Acebutolol hydrochloride (curve-b) and drug-loaded microspheres (curve-c) are displayed in Fig. 1. The onset-melting peak of acebutolol hydrochloride was observed at 152.8°C. However, no characteristic peak of acebutolol hydrochloride was observed in DSC curves of the drug-loaded microspheres, suggesting that drug is molecularly dispersed in the polymer matrix.

X-ray diffraction (X-RD) studies

Dried microspheres of uniform size were mounted on a sample holder and X-RD patterns were recorded in the range 0- 60° at the speed of 5°/min. X-RD analysis provide a clue about crystallinity of the drug in the crosslinked microspheres. X-RD patterns recorded for the plain ABH drug (A) placebo polymeric microparticles (B) and drug-loaded microspheres (C) are shown in Fig.2. The acebutolol hydrochloride peaks are observed at 2θ of 7°, 17°, 20°, 21° and 25° suggesting its crystalline nature. But, these peaks are not found in acebutolol hydrochloride loaded microspheres, indicating that the drug is dispersed at a molecular level in the polymer matrix.

Scanning electron microscopic (SEM) studies

Scanning electron microscopy has been used to confirm the formation of spherical structures of the microspheres. SEM micrographs of Poly(NIPAAm-*co*-CL) microspheres are displayed in Fig.3. The microspheres were coated with gold colour and subjected to SEM, which revealed that the formation nearly spherical structure of the microspheres with porous nature.

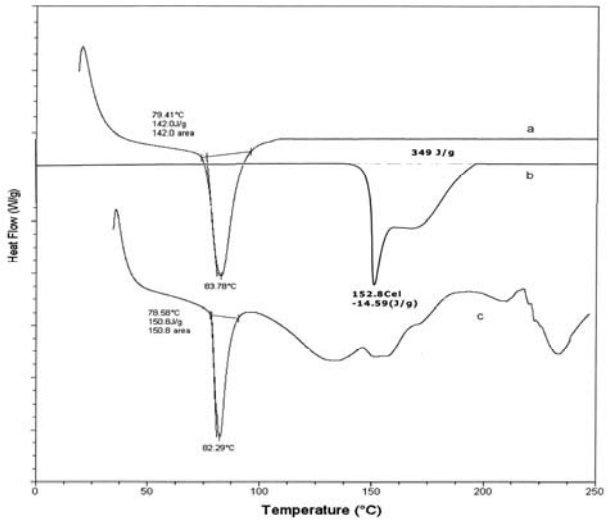

Fig. 1: DSC Thermographs of (a) Plain poly (NIPAAm-*co*-CL) microspheres (b) pure ABH drug and (c) drug loaded poly (NIPAAm-*co*-CL) microspheres

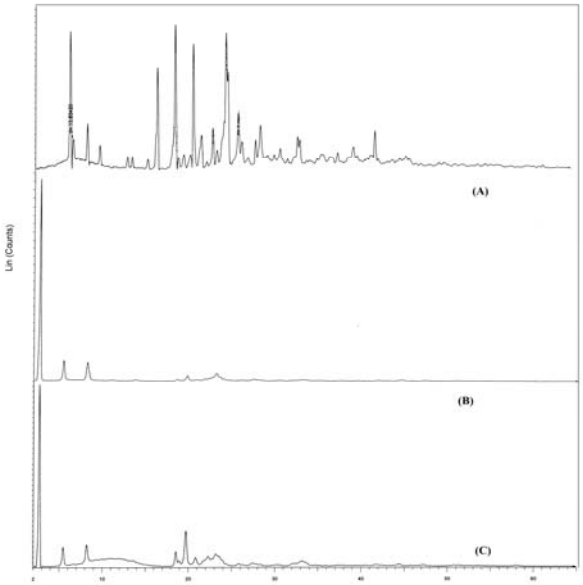

Fig. 2: X-RD studies of (A) pure ABH drug, (B) plain poly (NIPAAm-*co*-CL) microspheres and (C) drug loaded poly (NIPAAm-*co*-CL) microspheres

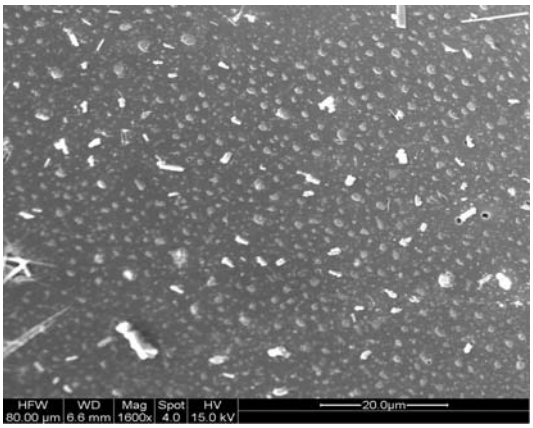

Fig. 3: SEM Photograph of poly (NIPAAm-*co*-CL) microspheres

Encapsulation efficiency

Three different concentrations of drug (5, 10 and 15 wt %) were loaded in the Poly(NIPAAm-*co*-CL) microspheres during crosslinking. The % encapsulation efficiency was included in Table.1. From the Table.1, it is noticed that the encapsulation efficiency values increased with increasing drug loading in the polymeric microspheres. In the case of ABH-1, ABH-2 and ABH-3 microspheres, the % encapsulation efficiency increased from 50.3 % to 60.9 % as the drug content increased from 5 to 15 wt %. The % encapsulation efficiency increased with an increasing amount of NIPAAm in the microspheres. For example, to study the effect of NIPAAm in the microspheres [e.g., formulations containing different ratios of NIPAAm and Caprolactam with 10 % of ABH (NIPAAm-1, NIPAAm-2, NIPAAm-3)], encapsulation efficiencies were found to be 68.3 %, 57.6 % and 53.2 %, respectively. The effect of crosslinking on size and entrapment efficiency of the microspheres using percentage of crosslinker 10, 20 and 30 % containing Poly (NIPAAm-*co*-CL) microspheres are also represented in Table.1. With an increase in degree of crosslinking, the % encapsulation efficiency was decreased, e.g., formulations crosslinked with 10, 20, 30 wt% of NNMBA (NNMBA-1, NNMBA-2 and NNMBA-3), entrapment efficiencies were 57.6 %, 51.2 % and 48.6 %, respectively. This may be due to the increasing degree of crosslinking, which leads to microspheres becoming more rigid and thus, reducing the free volume space within the polymeric network to yield a reduction in the percentage of encapsulation efficiency.

Effect of drug concentration

Fig.4.a. and 4.b displayed the release profiles of Poly (NIPAAm-*co*-Caprolactam) microspheres that are loaded with different amounts of ABH at 25^{0}C and 37^{0}C, respectively. From the figures 4.a & 4.b it is noticed that initially, during the first hour the release is quite fast in all formulations, but later it is slowed down. Release data suggest that those formulations containing the highest amount of drug (i.e., 15 wt %) displayed the higher release rates than those containing smaller amounts of ABH (i.e., 10 and 5 wt %). A prolonged and slow release was observed for formulation containing a lower amount of ABH (i.e., 5 wt %) at 37^{o}C. This may be attributed to the factor that free volume spaces are available in the matrix through which, a lesser number of ABH molecules would transport showing. Generally, drug release through microspheres depend upon the particle size, polymer crystallinity, surface character, molecular weight, polymer

composition, swelling ratio, degradation rate, drug binding affinity, rate of hydration, etc. In the present study among the factors responsible for this Invitro release of the drug through this system, the binding affinity might be predominant. It is further noticed from the Figures 4.a and 4.b that for all the ABH loaded formulations, the complete release of ABH was not observed even after 600 min, since the % cumulative release data tend to increase continuously.

Effect of crosslinking agent

The % cumulative release data *versus* time plots for the microspheres prepared with varying amounts of NNMBA, i.e., 1, 2 and 3% at the fixed amount of the drug (5 wt %) at 25°C and 37°C are displayed in Fig.5.a and Fig 5.b, respectively. The % cumulative release is quite fast and large at the lower amount, i.e., 1% of NNMBA, whereas the release is quite slower at higher amount, i.e., 3% NNMBA. The cumulative release is also higher at the lower amount of NNMBA, because at higher concentration of NNMBA, the polymeric chains will become rigid due to contraction of microvoids thereby, giving a decrease in % cumulative release of the drug. The crosslinking agent could help to form a bridge between the copolymeric chains. Therefore, as expected, the drug release becomes slower at higher amount of NNMBA, but it will be faster when a lower amount of NNMBA is present in the polymer matrix at both 25° and 37°C.

Effect of poly (NIPAAm) content

Drug release profiles from the microspheres containing different amounts of NIPAAm at 25°C and 37°C are displayed in Fig.6.a and 6.b respectively. A systemic increase in % cumulative release is observed with increasing amount of PNIPAAm of microspheres, but the time, required in releasing ABH remained almost the same for all the compositions of NIPAAm. The reason for this effect could be that, during the process of dissolution, a general trend is observed in all formulations i.e., microspheres have shown a systemic increase in swelling with increasing amount of NIPAAm, due to the loosely crosslinked hydrophilic chains of PNIPAAm. Microscopically speaking, there is a relaxation response of the polymer chains due to stresses that are induced during the drug dissolution stage through the microspheres, resulting in an increased dimension of the polymer coil and subsequently, in a significant increase of molecular volume of the overall hydrated polymer matrix due to an increased swelling of PNIPAAm component of the copolymer. This will further reduce the free volume of the matrices. Notice that the nature of release profiles remained almost identical for all the matrices containing different amounts of PNIPAAm, indicating that the swelling of PNIPAAm has a linear relationship with their release profiles.

Table 1: Formulation details and % of encapsulation efficiency data for Poly (NIPAAm-*co*-CL) microspheres

Formulation codes	% NIPAAm	% *Caprolactam*	% ABH	Amount of NNMBA added (gm)	% Encapsulation efficiency ± S.D.
Drug Variation at constant monomer and crosslinker					
ABH-1	4	6	5	1	49.5 ± 0.8
ABH-2	4	6	10	1	56.2 ± 1.4
ABH-3	4	6	15	1	60.7 ± 0.2
Crosslinker Variation at constant monomer and drug					
NNMBA-1	4	6	10	1	56.2 ± 1.4
NNMBA-2	4	6	10	2	50.4 ± 0.8
NNMBA-3	4	6	10	3	47.6 ± 1.0
Monomer Variation at constant drug and crosslinker					
NIPAAm-1	4	6	10	1	56.2 ± 1.4
NIPAAm-2	6	4	10	1	67.7 ± 0.6
NIPAAm-3	2	8	10	1	52.8 ± 0.4

NIPAAm = N-isopropylacrylamide
ABH= Acebutolol hydrochloride
NNMBA = N,N-methylene *bis*-acrylamide
S.D = standard deviation calculated 95% accurately

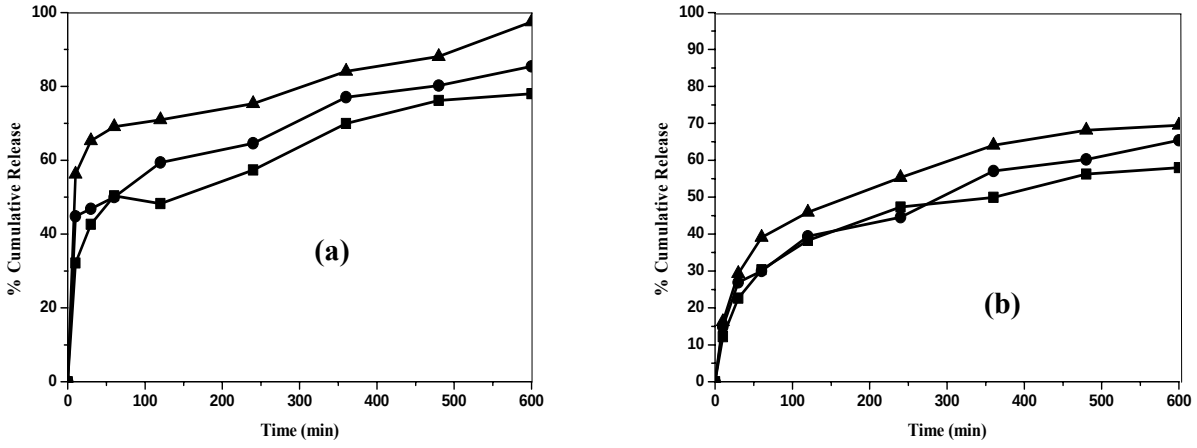

Fig. 4: % cumulative release of ABH at 25°C (a) and 37°C (b) through poly (NIPAAm-*co*-CL) microspheres crosslinked with 1% NNMBA and % NIPAAm containing (■) 5%, (●) 10% and (▲) 15% of ABH.

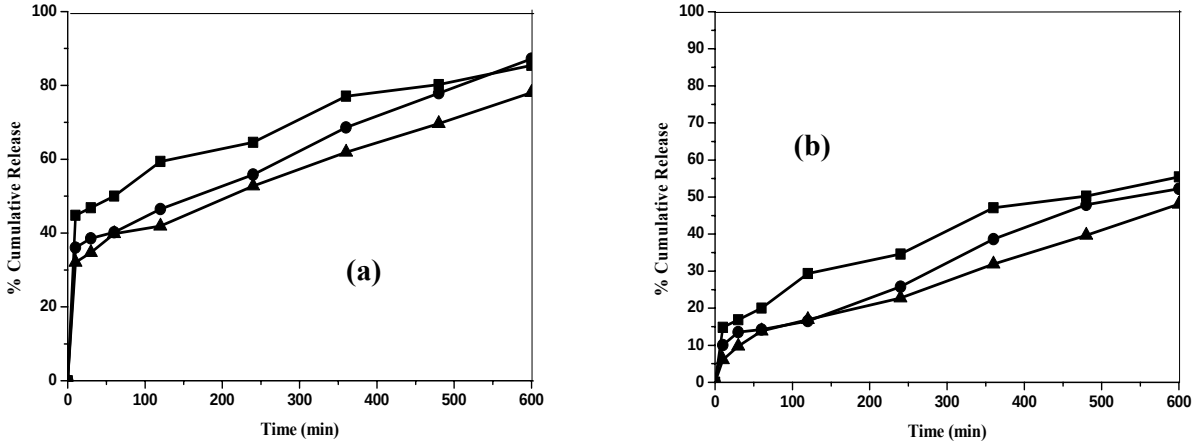

Fig. 5: % Cumulative release of ABH at 25^{0}C (a) and 37^{0}C (b) through Poly (NIPAAm-*co*-CL) microspheres loaded with 10 % ABH and 40% NIPAAm containing (■) 1 %, (●) 2 % and (▲) 3 % of NNMBA.

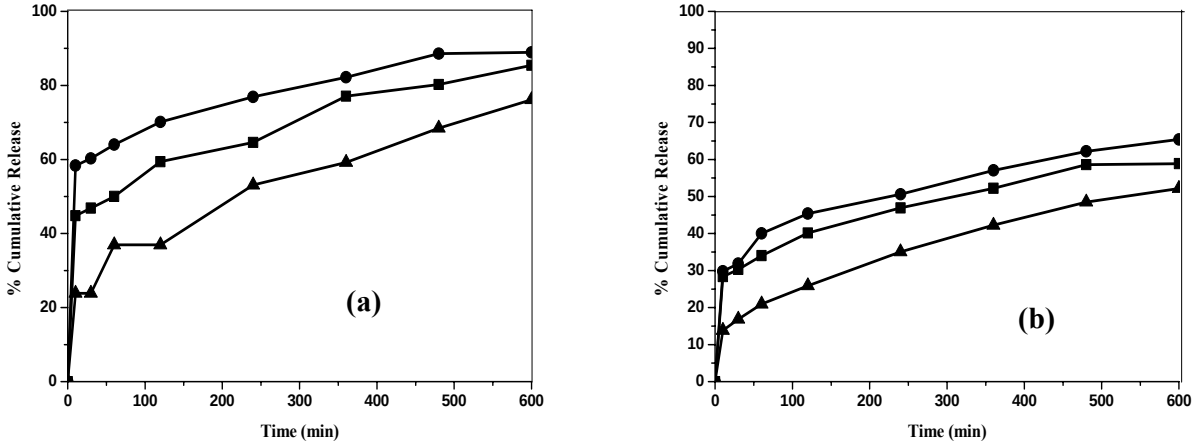

Fig. 6: % Cumulative release of ABH at 25^{0}C (a) and 37^{0}C (b) through Poly (NIPAAm-*co*-CL) microspheres loaded with 10 % ABH and rosslinked with 2% NNMBA containing (●) 60%, (■) 40% and (▲) 20% of NIPAAm.

Effect of temperature

Release profiles of ABH from poly (NIPAAm-co-Caprolactam) microspheres prepared with different amounts of the crosslinking agent and drug loadings have been studied at two temperatures in the chosen dissolution medium, alternatively from 25^{0}C to 37^{0}C and vice versa. Drug release profiles exhibited drastic variations due to changes in temperature from 25^{0}C to 37^{0}C. It may be noted that drug was released slowly at 37^{0}C i.e., above LCST, but release was much faster at 25^{0}C (i.e., below LCST) than at 37^{0}C. This is due to the fact that at higher temperature, the surface of microspheres will shrink, thereby causing the drug to migrate towards the surface of the microspheres as seen by the initial burst effect during the dissolution experiments. However, dense surfaces of the microspheres will prohibit the release of more amount of the drug. At lower temperatures, the already collapsed surface layer will start to re-swell, which will allow the drug to be released after a certain period of time, depending upon the minimum time required for reswelling of the surface. Thus, the time required for drug release was accelerated as a result of cooling below LCST, which further slowed down upon reheating. Microspheres of this study were proved to be sensitive to changes in temperature. At 25^{0}C (in the swollen state), release rate and total amount of the drug were considerably higher than those found at 37^{0}C (in a collapsed state). Drug molecules entrapped inside the polymer network will diffuse out of the microspheres, since they quickly got hydrated in the swollen state. In contrast, at 37^{0}C, the network structure is collapsed and exhibits a lesser tendency to uptake water or buffer solution, leading to decrease in drug diffusion rate.

Drug release kinetics

Drug release kinetics was analyzed by plotting the cumulative release data *versus* time and by fitting these data to the exponential equation of the type[34].

$$M_t/M_\infty = kt^n \qquad \textbf{(4)}$$

Here, M_t/M_∞ represents the fractional drug release at time *t*, *k* is a constant characteristic of the drug-polymer system and *n* is an empirical parameter characterizing the release mechanism. Using the least squares procedure, we have estimated the values of *n* and *k* for all the seven formulations and these values are given in Table.2. If *n* = 0.5, then drug diffuses and releases from the polymer matrix following a Fickian diffusion. For *n* > 0.5, anomalous or non-Fickian

type drug diffusion occurs. If *n*=1, a completely non-Fickian is operative. The intermediary values ranging between 0.5 and 1.0 are attributed to the anomalous type transport[34].

In the present investigation, the values of *k* and n have shown a dependence on the extent of crosslinking, % drug loading as well as NIPAAm content of the microspheres. The values of n for microspheres, prepared with varying amounts of NIPAAm (i.e., 20, 40 and 60 wt %) by keeping ABH (10 %) and NNMBA (10 %) as constant, ranged from 0.201 to 0.342 and 0.561 to 0.991, respectively at 25^{0}C and 37^{0}C, suggesting a slight deviation from the Fickian mode of diffusion. The ABH-loaded microspheres exhibited the n values ranging from 0.201 to 0.486 and 0.561 to 0.991, respectively at 25^{0}C and 37^{0}C (Table.2), indicating a shift from the erosion type release trend to a swelling-controlled non-Fickian trend. Values of the correlation coefficient, 'r' falls in the range of 0.902 to 0.981 and 0.902 to 0.972 for 25^{0}C and 37^{0}C, respectively, indicating a good fit of the experimental data. This is due to reduction in the regions of low microviscosity of the medium and closure of the microcavities in the swollen microspheres.

Table 2: Release kinetics parameters of *k, n* and correlation coefficients(*r*) for different formulations at different temperatures

At 25^{0}C			
Formulation codes	***k***	***n***	**Correlation coefficient, *r***
ABH-1	1.214	0.365	0.970
ABH-2	1.131	0.342	0.981
ABH-3	1.068	0.340	0.970
NNMBA-1	1.131	0.342	0.981
NNMBA-2	1.502	0.413	0.902
NNMBA-3	1.732	0.486	0.980
NIPAM-1	1.131	0.342	0.981
NIPAM-2	0.757	0.201	0.974
NIPAM-3	1.251	0.339	0.976
At 37^{0}C			
ABH-1	0.217	0.711	0.939
ABH-2	0.168	0.561	0.929
ABH-3	0.171	0.574	0.902
NNMBA-1	0.168	0.561	0.929
NNMBA-2	0.294	0.918	0.972
NNMBA-3	0.197	0.562	0.906
NIPAM-1	0.168	0.561	0.929
NIPAM-2	0.215	0.685	0.964
NIPAM-3	0.301	0.991	0.936

CONCLUSION

Novel types of thermo-responsive Acebutolol hydrochloride poly (N-isopropylacrylamide-*co*-caprolactam) microspheres were prepared by dispersion polymerization using sodium dodecylsulfate as a surfactant. Acebutolol hydrochloride, a hypertensive drug, was chosen as model drug to investigate the percentage of cumulative release using the developed matrices. The microspheres prepared were characterized by differential scanning calorimetry. X-ray diffractometry and scanning electron microscopy. DSC indicated that ABH is molecularly distributed in the microspheres, which exhibited a prolonged release of ABH over an extended period of time. In the dry state, the size of microspheres exhibited and differentiates the % of cumulative drug release by varying the temperature from 25^{0}C to 37^{0}C. The prepared microspheres have thus shown thermo-responsive trends during in vitro drug release studies of acebutolol hydrochloride when dissolution experiments were performed at 25^{0}C and 37^{0}C.

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