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Synthesis, characterization and use of Poly (N-isopropylacrylamide-co-N-vinylcaprolactam) crosslinked thermoresponsive microspheres for control release of Ciproflaxin hydrochloride drug

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ABSTRACT

Poly (N-isopropylacrylamide-co-N-vinyl caprolactam) copolymer was synthesized as an interesting thermoresponsive material possessing a phase transition temperature around 32°C in phosphate buffer, pH 7.4 (PB). Thermoresponsive Poly(N-isopropylacrylamide-co-N-vinylcaprolactam) designated as PNIPA-NVC microspheres crosslinked with N,N'-methylene bisacrylamide (NNMBA) have been prepared by dispersion polymerization using varying amounts of NIPA, NVC and NNMBA. ciproflaxin hydrochloride (CFH) an anti-bacterial drug, was loaded into the microspheres during *in situ* polymerization and *in vitro* release of CFH has been studied. The microspheres were characterized by Fourier Transform Infrared Spectroscopy (FTIR) Differential Scanning Calorimetry (DSC), X-Ray Diffractometry (XRD) and Scanning Electron Microscopy (SEM). The *in-vitro* release of CFH drug from the microspheres was studied in pH 7.4 medium, at the temperatures 25°C & 37°C. The microspheres consisting of NIPA and NVC provide thermo responsive nature to the microspheres. The system developed in this study showed a thermoresponsive for the controlled release of CFH. FTIR spectroscopy explained the formation of copolymer. The DSC and XRD techniques indicated the uniform distribution of drug in the microspheres. SEM studies indicated surface morphology of the microspheres. Prolonged and controlled release of CFH was achieved in a controlled manner upto 12 h.

Key words: Microspheres, NIPA, NVC, Ciproflaxin hydrochloride (CFH), Drug delivery.

INTRODUCTION

Thermally responsive drug delivery systems have attracted ever-increasing attention because they can control the release of drug in response to changes in the body temperature and therefore act as self-regulating systems (Qui and Park, 2001; Zhang et al., 2002; Huang and Lowe, 2005; Wu et al., 2005). Poly (N-isopropyl acryl amide) (PNIPA) is the most popular polymer among the thermoresponsive polymers since it exhibits a sharp phase transition close to 32°C (Li and D'Emanuele, 2003; Schild, 1992). The temperature at which this transition occurs is called the lower critical solution temperature (LCST). Below the LCST the polymer chain is hydrated and adopts an extended coil conformation, while above it, the polymer is dehydrated and adopts a globular conformation. Correspondingly, the cross-linked hydrogels obtained from these polymers swell under the LCST and shrink above it. The biomedical and biological applications of such gels usually involve the chemical modification of poly (NIPA). These modifications are usually performed to introduce functional groups that can increase the LCST towards body temperature

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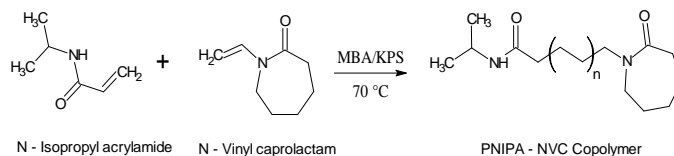
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(Feil et al., 1992; Park and Hoffman, 1992) to improve the mechanical properties (Dong and Hoffman, 1990) or to interact with certain drugs (Park, 1999). However, copolymerization of NIPA with acrylate-type co monomers usually lead to gels possessing relatively weak thermosensitivity (Yoshida et al., 1994). Therefore, the co monomer needs to be chosen carefully to preserve the thermosensitivity of the gel structure. Most of the studies concerning the applications of thermoresponsive hydrogels have focused on the use of devices in the form of discs or slabs (Gutowska et al., 1992; Zhuo and Li, 2003; Zhang et al., 2004); few papers have been dealt with the preparation and characterization of thermoresponsive microspheres. The majority of microspheres are prepared from monomers by suspension polymerization (D'Emanuele and Dinarvand, 1995; Oktar et al., 2005). Thermoresponsive microspheres from preformed polymers are prepared by dropping a polymer solution into a liquid at a temperature above the LCST (Serres et al., 1996; Ramkissoon-Ganorkar et al., 1999; Kim et al., 2001). These microspheres are not stable or easy to handle, and have a reduced number of biomedical applications. The most studied drug used as a model for pulsatile on-off drug release from thermoresponsive hydrogels is the hydrophobic indomethacin (Gutowska et al., 1997; Shin et al., 2001).

Recently, there has been a growing interest in another temperature sensitive polymer namely poly (N-vinyl caprolactam, PNVC) (Eisele et al., 2003; Makhaeva et al., 2003; Gao et al., 1999; Lau and Wu, 1999). Both PNIPA and PNVC have the LCST near the body temperature and consequently they may find several biomedical applications (Galaev and Mattiasson, 1999). PNVC is especially interesting due to the fact that it is very stable against hydrolysis. Owing to its stability, PNVC is expected to be a biocompatible polymer. If the amide bond in the side group is hydrolysed in strongly acidic conditions a polymeric carboxylic acid builds up (Lau and Wu, 1999). Applications of PNVC in biomedical materials, in the stabilization proteases, and in control drug delivery and drug release have been published, by Peng and Wu (Peng and Wu, 2000), Markvicheva and coworkers (Markvicheva et al., 1996), and Vihola and coworkers (Vihola et al., 2002). PNVC collapses when the temperature exceeds 32°C (Kirsh, 1998) and therefore, the thermo- sensitive PNVC has presumably, similar characteristics to PNIPA.

The main objectives of this paper were the preparation of stable thermoresponsive microspheres from preformed polymers and the study of the influence of physico – chemical characteristics of drug on their release profile. Here the PNIPA-NVC microspheres were prepared as a thermoresponsive polymer with its LCST tailored towards the body temperature. This copolymer was transformed into thermoresponsive stable microspheres by an original approach that assumes the crosslinking of two monomers with methylene bis acrylamide (MBA). In this thermoresponsive copolymer an anti bacterial drug, Ciprofloxacin hydrochloride drug was incorporated. The drug is used to treat bacterial infections. Then the *in-vitro* study was carried out at two different predetermined temperatures (25°C & 37°C), the concentration of

CFH drug release was monitored at 271 nm on an UV spectrophotometer. It was found that CFH was released more rapidly at 25°C than at 37°C. This thermoresponsive PNIPA-NVC polymeric matrix may be more useful in the cases where controlled drug delivery system is needed.



Schematic diagram of formation of PNIPA - NVC Copolymer

EXPERIMENTAL

Materials and methods

N-isopropylacrylamide (NIPA), *N*-vinyl caprolactam (NVC) were purchased from Aldrich, Milwaukee, WI, USA. *N*, *N*-methylene bis-acrylamide (NNMBA), potassium persulfate (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 Ciprofloxacin hydrochloride was obtained as a gift sample from waksman salesman pharmaceuticals, Anantapur, A.P. India.

Synthesis of thermo- responsive PNIPA-NVC 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 $\pm 0.1^\circ\text{C}$. The solution was stirred at 800 rpm speed until it became clear and 100 mg of potassium per sulfate was added. Required amount of NIPA, NVC, the crosslinking agent MBA and Ciprofloxacin hydrochloride (CFH) 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 prepared by above method.

Loading of Ciprofloxacin Hydrochloride

Ciprofloxacin 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 this mixture was added into 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, microspheres will absorb the drug into the surface as well as adsorbed onto the surface from the solution.

CHARACTERIZATION TECHNIQUES

Fourier Transform Infrared (FTIR) Studies

Fourier transform infrared spectroscopy (FTIR) measurements were performed using Perkin Elmer (model Impact 410, Wisconsin, MI, USA) spectrophotometer to confirm the formation of copolymer PNIPA-NVC. The copolymer particles are finely grounded with KBr to prepare the pellets under a hydraulic pressure of 600 dynes/m² and spectra were scanned between 4000 to 400 cm⁻¹.

Differential Scanning Calorimetric (DSC) Studies

Differential Scanning Calorimetry (DSC) curves of the placebo copolymer, plain CFH drug and drug loaded copolymer microspheres were recorded using a Rheometric Scientific differential scanning calorimeter (Model-DSC SP, UK). The analysis was performed by heating the samples at the rate of 10°C/min under inert atmosphere.

X-Ray Diffraction (X-RD) Studies

The X-Ray diffraction (X-RD) patterns of plain drug, plain microspheres and drug-loaded microspheres were recorded using a Rigaku Geigerflex diffractometer (Tokyo, Japan) equipped with Ni-filtered CuK α radiation ($\lambda=1.5418\text{\AA}$). The dried microspheres of uniform size were mounted on a sample holder and the patterns were recorded in the range 0 to 50° at the speed of 5°C/min to know the crystallinity.

Scanning Electron Microscopic (SEM) studies

SEM micrographs of microspheres were obtained under high resolution (Mag.300X 5kV) using JOEL MODEL JSM 840A, scanning electron microscope (SEM), equipped with phoenix energy dispersive analysis of X-rays (EDAX) and Leica 400, Cambridge, UK instrument.

Estimation of drug loading and encapsulation efficiency

Loading efficiency of Ciproflaxin hydrochloride in the microspheres was determined spectrophotometrically. About 10 mg of the drug-loaded microspheres were placed in 10 mL 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 271 nm. The results of % drug loading and encapsulation efficiency were calculated using Eqs. (1) and (2) respectively.

$$\% \text{ Drug loading} = \left(\frac{\text{Amount of drug in microspheres}}{\text{Amount of microspheres}} \right) \times 100 \quad (1)$$

$$\% \text{ Encapsulation efficiency} = \left(\frac{\text{Actual loading}}{\text{Theoretical loading}} \right) \times 100 \quad (2)$$

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:

$$\text{Conversion} = (W/M) \times 100 \quad (3)$$

In-vitro release studies

Dissolution was carried out using the Tablet dissolution (LabIndia, Mumbai, India) equipped with eight baskets. Dissolution rates were measured at two temperatures i.e 25°C and 37°C under 100 rpm speed. Drug release from the microspheres was studied in intestinal (7.4 pH phosphate buffer media) fluids. At regular intervals of time, aliquot sample were withdrawn and analyzed by using UV spectrophotometer (Model LabIndia-3000⁺, Mumbai, India) at the fixed λ_{max} value of 271 nm.

RESULTS AND DISCUSSIONS

Fourier transform infrared spectroscopy

The FTIR spectrum of PNIPA-NVC copolymer as shown in the above Fig.1. The Pure NVC shows adsorption peak at 1626 cm⁻¹ is assigned as –C=C- stretching vibration and 1671 cm⁻¹ is an –C=O stretching vibration and the peak at 971 cm⁻¹ indicates –CH=CH-H swing plane bending vibration peak. But in Fig 1(b) the peak 3436 cm⁻¹ assigned as –NH stretching vibration and the peak at 1640 cm⁻¹ indicates –C=O stretching vibration of amide peak. In Fig 1(b) there is no double bond peak observed in the FTIR Spectrum of PNIPA-NVC copolymer that indicated the formation of copolymer.

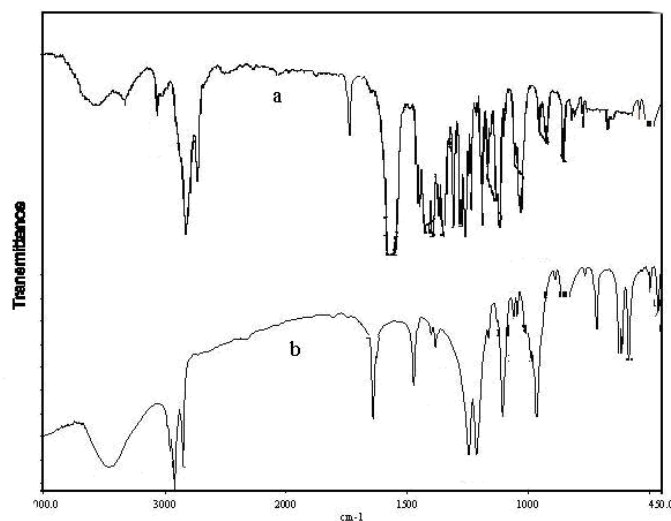


Fig. 1 FTIR Spectra of (a) Pure NVC (b) Poly (NIPA-NVC) Copolymer.

Differential scanning calorimetry (DSC)

DSC thermograms of pure Ciproflaxin hydrochloride, placebo PNIPA-NVC microspheres and drug-loaded PNIPA-NVC microspheres are displayed in Fig. 2. The onset-melting peak of Ciproflaxin hydrochloride was observed at 160.5°C, but in case of drug loaded and placebo PNIPA-NVCL microspheres, that peak was not observed, suggesting that drug is molecularly dispersed in the polymer matrix.

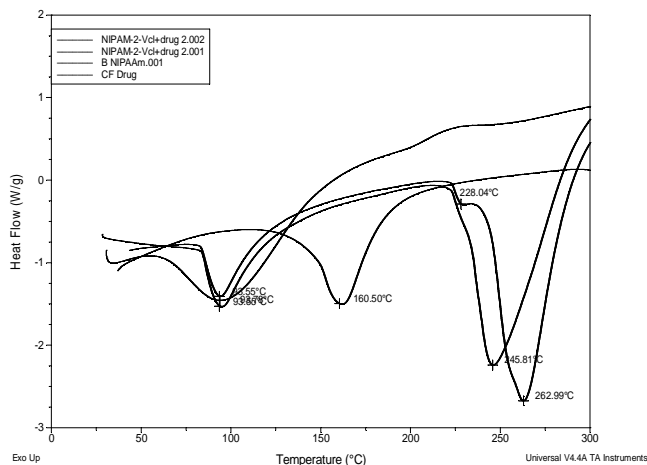


Fig.2 DSC thermograms of (a) Plain Ciproflaxin hydrochloride (b) Plain PNIPA-NVC microspheres (c) CFH-loaded PNIPA-NVC microspheres (d) Pure NIPA.

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- 50° 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 CFH drug (a) placebo PNIPA-NVC microspheres (b) and drug-loaded PNIPA-NVC microspheres (c) are shown in Fig.3. The Ciproflaxin hydrochloride peaks are observed at 2θ of 12, 20 and 27° suggesting its crystalline nature. But, these peaks are not found in Ciproflaxin hydrochloride loaded microspheres, indicating that the drug is dispersed at a molecular level in the polymer matrix.

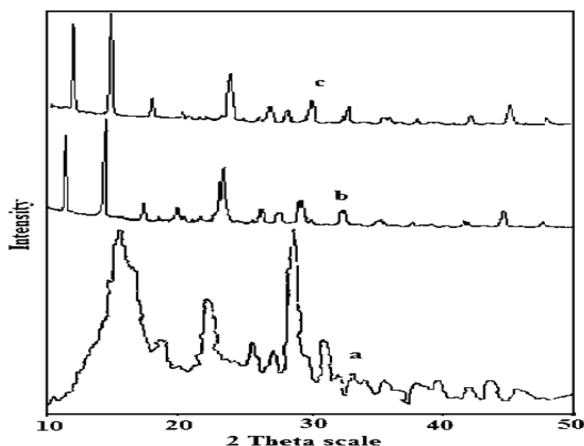


Fig.3. X-Ray diffraction spectra of (a) Ciproflaxin hydrochloride (b) Plain PNIPA-NVC microspheres and (c) CFH- loaded PNIPA-NVC microspheres.

Scanning electron microscopic (SEM) studies

Scanning electron microscopy has been used to confirm the formation of spherical structures of the microspheres. SEM micrographs of PNIPA-NVC microspheres are displayed in Fig.4. The microspheres were coated with gold color and subjected to SEM, which revealed that the formation of microspheres were nearly spherical in structure with porous nature.

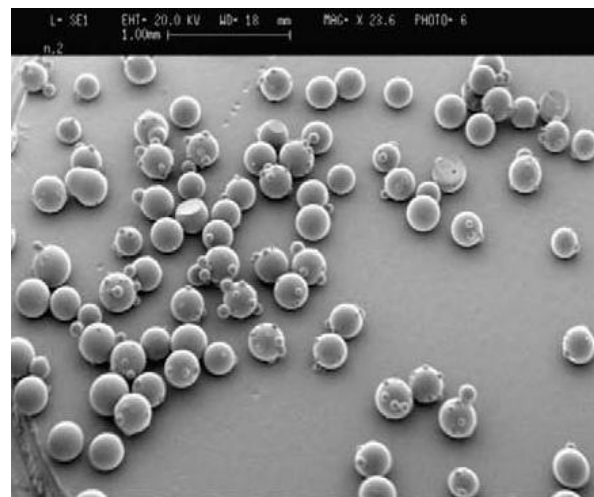


Fig. 4 SEM micrographs of PNIPA-NVC microspheres.

Encapsulation Efficiency

Three different concentrations of drug (5,10 and 15 wt %) were loaded in the PNIPA-NVC microspheres during crosslinking. The % of encapsulation efficiency was included in Table.1. From the Table.1. it is explained that the encapsulation efficiency values increased with increasing drug loading in the polymeric microspheres. In the case of NIPVC-1, NIPVC-2 and NIPVC-3 microspheres, the % of encapsulation efficiency increased from 64.4 % to 77.5 % as the drug content increased from 5 to 15 wt % . The % of encapsulation efficiency increased with increasing amount of NIPA in the microspheres. The formulation containing different amount ratios of NIPA and NVC with 5% of CFH drug (NIPVC-2, NIPVC-6 and NIPVC-7), the encapsulation efficiency values were found to be 69.3 %, 71.6 % and 74.3 % respectively. The effect of crosslinking on size and entrapment efficiency of the microspheres using percentage of Crosslinker 2,4 and 6 % containing PNIPA-NVC microspheres are also represented in Table . 1.

Table.1 Formulation details and % of encapsulation efficiency data for PNIPA-NVC microspheres.

Formulation codes	% NIPA	% NVC	% CFH	Amount of NNMBA added %	% of Encapsulation efficiency ± S.D.
NIPVC-1	20	80	5	2	64.4 ± 0.9
NIPVC-2	20	80	10	2	69.3 ± 1.2
NIPVC-3	20	80	15	2	77.5 ± 0.5
NIPVC-2	20	80	10	2	69.3 ± 1.2
NIPVC-4	20	80	10	4	65.7 ± 0.3
NIPVC-5	20	80	10	6	63.1 ± 1.4
NIPVC-2	20	80	10	2	69.3 ± 1.2
NIPVC-6	40	60	10	2	71.6 ± 0.6
NIPVC-7	60	40	10	2	74.3 ± 0.7

NVC microspheres.

With an increasing crosslinker percentage, the encapsulation efficiency decreased. The formulation containing different ratios of crosslinker (NIPVC-2, NIPVC-4, NIPVC-5) entrapment efficiencies were 69.3%, 65.7 % and 63.1% 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 Temperature

Release profiles of CFH from PNIPA-NVC microspheres prepared with different amounts of the crosslinking agent and drug loadings have been studied at two temperatures 25°C & 37°C in the chosen dissolution medium. Drug release profiles exhibited drastic variations due to changes in temperature. It may be noted that drug was released slowly at 37°C (i.e., above LCST), but release was much faster at 25°C (i.e., below LCST) than at 37°C. This is due to the fact that at higher temperature, the surface of microspheres will shrink, thereby causing the drug 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, 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°C (in the swollen state), release rate and total amount of the drug were considerably higher than those found at 37°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°C, the network structure is collapsed and exhibits a lesser tendency to uptake water or buffer solution, leading to decrease in drug diffusion rate.

Effect of Drug Concentration

Fig.5.a and 5.b displayed the release profiles of PNIPA-NVC microspheres that are loaded with different amounts of CFH at 25°C & 37°C, respectively. From the Fig. 5.a and Fig.5.b, it is explained initially that during the first hour the release is quiet 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 %) shows the higher release rates than those formulations containing smaller amounts of CFH (i.e., 10 and 5 wt %). A prolonged and slow release was observed for formulation containing a lower amount of CFH (i.e., 5 wt %) at 37°C. This may be due to the free volume spaces are available in the matrix through which, a lesser number of CFH molecules would transport and it is further explained from the Fig. 5.a and Fig. 5.b that for all the CFH loaded formulations, the complete release of CFH was not observed even after 720 min, since the % cumulative release data tend to increase continuously.

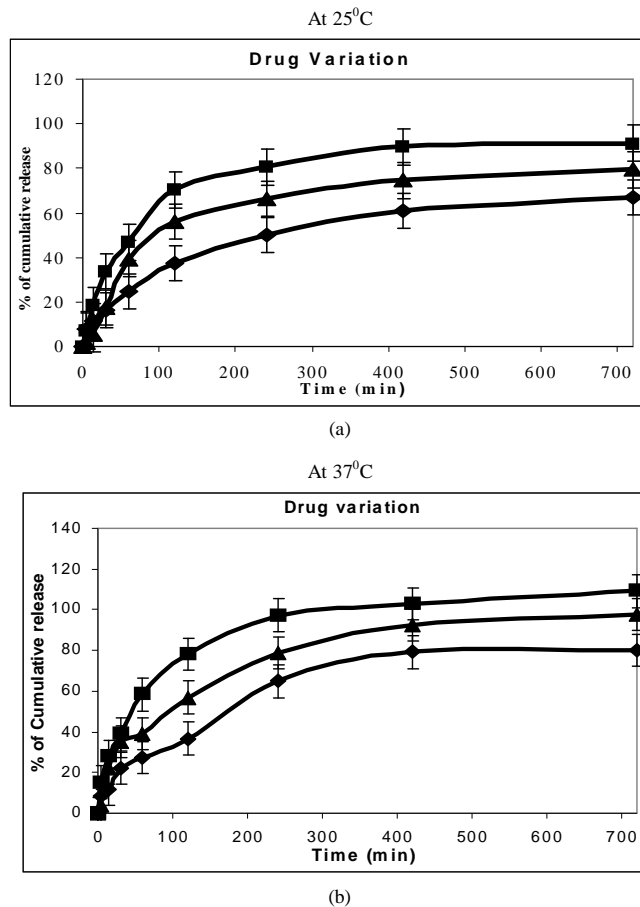


Fig.5 (a, b). % of cumulative release with drug variation at 25°C & 37°C.

Effect of cross-linking agent

The % cumulative release data *versus* time plots for the microspheres prepared with varying amounts of MBA, i.e., 2, 4 and 6wt% at the fixed amount of the drug (10 wt %) at 25°C & 37°C are displayed in Fig.6.a and Fig.6.b respectively.

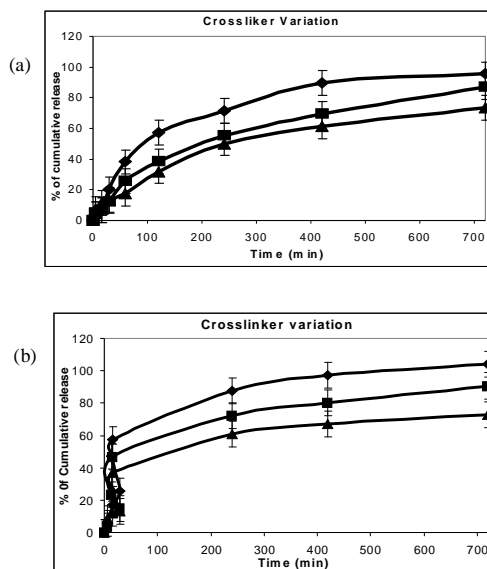


Fig.6 (a,b). % of cumulative release with Crosslinker variation at 25°C & 37°C.

The % cumulative release is quite fast and large at the lower amount of crosslinker, (i.e., 2wt% of MBA), whereas the release is quite slower at higher amount of crosslinker, (i.e., 6wt% MBA). The cumulative release is also higher at the lower amount of MBA, because at higher concentration of MBA, 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 MBA, but it will be faster when a lower amount of MBA present in the polymer matrix at both 25° & 37°C.

Effect of poly (NIPA)

Drug release profiles from the microspheres containing different amounts of NIPA at 25°C & 37°C are displayed in Fig.7.a and Fig .7.b respectively. A systematic increase in % cumulative release is observed with increasing amount of NIPA of microspheres, but the time required in releasing CFH remained almost the same for all the compositions of NIPA. 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 systematic increase in swelling with increasing amount of NIPA, due to the loosely cross-linked hydrophilic chains of NIPA. 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 NIPA 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 NIPA, indicating that the swelling of NIPA has a linear relationship with their release profiles.

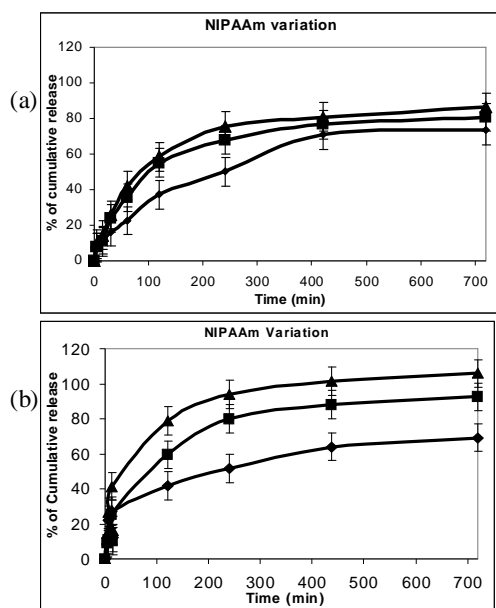


Fig.7 (a,b). % of cumulative release with NIPA variation at 25°C & 37°C.

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 (Ritger and Peppas, 1987).

$$M_t/M_\infty = kt^n \text{-----} (4)$$

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.

Table.2 Release kinetic parameters for different formulations at-25°C and 37°C.

Formulation codes	k	n	Correlation coefficient, r
NIPVC-1	0.6569	0.3841	0.9654
NIPVC-2	0.5581	0.3657	0.9115
NIPVC-3	0.3184	0.3429	0.9545
NIPVC-2	0.5581	0.3657	0.9115
NIPVC-4	0.6396	0.4593	0.9381
NIPVC-5	0.6883	0.4961	0.9361
NIPVC-2	0.5581	0.3657	0.9115
NIPVC-6	0.6312	0.3594	0.9918
NIPVC-7	0.7414	0.4961	0.8582
At 37°C			
NIPVC-1	0.6296	0.5124	0.9723
NIPVC-2	0.4955	0.5365	0.9255
NIPVC-3	0.3564	0.7337	0.9272
NIPVC-2	0.4955	0.5365	0.9255
NIPVC-4	0.5773	0.6754	0.9648
NIPVC-5	0.7305	0.5372	0.9457
NIPVC-2	0.4955	0.5365	0.9255
NIPVC-6	0.5828	0.5658	0.9213
NIPVC-7	0.6067	0.8354	0.9825

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 (Ritger and Peppas, 1987).

In the present investigation, the values of k and n have shown a dependence on the extent of crosslinking, % drug loading as well as NIPA content of the microspheres. The values of n for microspheres, prepared with varying amounts of NIPA (i.e., 20, 40 and 60 wt %) by keeping CFH (10 %) and MBA (2%) as constant, ranged from 0.3657 to 0.4961 and 0.5365 to 0.8354, respectively at 25°C & 37°C, suggesting a slight deviation from the Fickian mode of diffusion.

The CFH-loaded microspheres exhibited the n values ranging from 0.2594 to 0.4961 and 0.5124 to 0.8354, respectively at 25°C & 37°C (see 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 0.8582 to 0.9918 and 0.9213 to 0.9825 at 25°C & 37°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.

CONCLUSION

The thermo-responsive Ciproflaxin hydrochloride loaded PNIPA-NVC microspheres were prepared by dispersion polymerization using sodium laurylsulfate as a surfactant. Ciproflaxin hydrochloride, anti-bacterial drug, was chosen as model drug to investigate the percentage of cumulative release using the developed matrices. The developed thermoresponsive microspheres show a prolonged release of CFH over an extended period of 12h. The prepared microspheres have thus shown thermo-responsive trends during in vitro drug release studies of Ciproflaxin hydrochloride. The fast release rates were observed at 25°C whereas slow release rates were observed at 37°C when dissolution experiments were performed at 25°C & 37°C.

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