# RESEARCH ARTICLE

## Novel Poly(Vinyl caprolactam-co-Sodium acrylate) Microspheres for Controlled Release of 5-Fluorouracil

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## ABSTRACT

Novel poly(vinyl caprolactam-co-sodium acrylate) copolymeric microspheres crosslinked with N, N′-methylene bisacrylamide have been prepared by free radical emulsion polymerization using varying amounts of Sodium acrylate (SA), vinyl caprolactam (VC) and N, N′-methylene bisacrylamide (NNMBA). 5-Fluorouracil was loaded into these microspheres during in situ polymerization. The microspheres have been characterized by differential scanning calorimetry (DSC) and x-ray diffractometry (x-RD) to understand the drug dispersion in the microspheres. Scanning electron microscopy (SEM) was used to assess the surface morphology of particles prepared. In vitro release of 5-fluorouracil was studied by varying of copolymer composition, amount of crosslinking agent and amount of 5-fluorouracil in the microspheres. Microspheres with different copolymer compositions have been prepared in yields of 80-85 %. DSC indicated the uniform distribution of 5-fluorouracil particles in the microspheres, whereas SEM suggested their spherical structure with slightly rough surfaces. The in vitro drug release indicated that particle size and release kinetics depend upon copolymer composition, amount of crosslinking agent used and amount of 5-fluorouracil present in the microspheres.

## KEYWORDS

## INTRODUCTION

Controlled delivery of drugs by means of biodegradable polymers began in the 1970s and continued to expand rapidly with numerous novel products[1,2]. The controlled release technology has lead to the development of newer methods of drug administration as well as the design and application of different types of CR formulations for effective targeting of certain drugs to the site of action. In particular, biodegradable polymeric systems have led to the development of CR dosage formulations to achieve the desired therapeutic results to obtain maximum dose regimen with minimum side effects[3]. The release of drug from a polymer matrix occurs due to the transport of drug to the surrounding medium system by the molecular diffusion mechanism. The CR systems offer many advantages over the conventional dosage forms, including improved efficacy, reduced toxicity as well as improved patient compliance and convenience[4-6]. Among the various types of polymers employed, hydrophilic biopolymers are quite suitable for oral applications[7] due to their several inherent advantages over the synthetic polymers.

Drug targeting to a specific tissue or organ has been the subject of creative and innovative research in medicinal and pharmaceutical

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chemistry since the beginning of the twentieth century. In many diseases (e.g. cancer, AIDS, rheumatoid arthritis, etc.) a considerable therapeutic advantage could be gained if drugs were delivered more selectively and in a controlled manner to their target sites. More particularly, it is conventionally accepted that efficient, compliant and reliable therapy requires that the drug reside as long as its therapeutic action is needed at a specific site, where it acts (by systemic absorption, binding, inhibition, etc.) as intact molecules. This concept has led to the development of a variety of physically based controlled release dosage forms such as drug dispersible matrices, coated tablets or particles, microcapsules. The development of an appropriate delivery system will first require a proper consideration of three related factors; the properties of the drug; the disease and the destination in the body.

Over the past few years, stimuli-responsive (sensitive) polymers have become the object of intensive study due to their ability to change drastically their physical state under minute changes in external environment such as temperature, pH, ionic strength, light illumination, etc. Recently, chromatographic[8,9] drug delivery[10,11] membrane technology[12,13] and kinetic inhibition[14] applications were reported. Poly(*N*-isopropylacrylamide)[15-17] (PNIPA) and poly(*N*-vinyl caprolactam)[18,19] (PVCL) were intensively investigated due to their thermo-sensitive properties since these are water soluble at low temperature. However, they exhibit lower critical solution temperature (LCST) in water and undergo a coil-to-globule transition and aggregation at higher temperatures. For PNIPA the coil-to-globule transition occurs at around 32°C. PVCL is a homolog of poly(*N*-vinylpyrrolidone) (PVP), which is a biocompatible polymer widely used in medicine and pharmaceutics[20]. PVCL combines the useful and important properties of PVP and PNIPAm. It is a biocompatible polymer with a phase transition in the region of physiological temperature (30-37 °C). Such properties make it a prospective material in designing CR systems. Further, the incorporation of ionic hydrophilic moieties into the PolyVCL hydrogel networks would enhance the LCST and the gels become sensitive towards PH, whereas hydrophobic moieties decrease the LCST. Liu et al.[21] found that salts of acrylic acid monomers are strong electrolytes, which are completely ionized in water, and their copolymeric units increased the swelling characteristics to a greater extent.

5-Fluorouracil is an acidic, water-soluble[22,23], hydrophilic, is an antineoplastic drug used extensively in clinical chemotherapy for the treatment of solid tumors. It has been widely used in drug administration due to its large number of secondary effects that accompany its conventional administration. We present here the development of 5-fluorouracil-loaded poly(vinyl caprolactam-co-Sodium acrylate) microspheres for investigating its slow release characteristics. The plasma lifetime of 5-Fu is 1-1.2 hand it needs to extend for its effective therapy. The microspheres prepared were characterized by particle size analyzer, differential scanning calorimetry (DSC) and scanning electron microscopy (SEM). The *in vitro* release studies have been performed in 7.4 pH buffer solution at 25 $^0$C and 37$^0$C to extend to the release rates of the drug.

## MATERIALS AND METHOD

### Materials

Vinyl caprolactam (VC) was purchased from Aldrich Chemicals, Milwaukee, WI USA. Sodium acrylate (SA), *N, N′*-methylene bisacrylamide (NNMBA), sodium lauryl sulfate, potassium persulfate, and calcium chloride were all purchased from s.d. fine chemicals, Mumbai, India. 5-Fluorouracil was purchased from MP Biochemicals, Eschwege, Germany.

### Synthesis of poly(vinyl caprolactam-co-sodium acrylate) microspheres

Sodium lauryl sulfate (1g) was dissolved in 80 ml 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

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immersed in an oil bath with a thermostatic control to maintain the desired temperature accurate to $\pm$ 1ºC. The solution was stirred at 800 rpm speed until it became clear and 100 mg of potassium persulfate was added. The required amount of SA, VC, crosslinking agent, NNMBA and 5-Fluorouracil were dissolved separately in 20 ml 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 70ºC 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[24]. Particles were then isolated by centrifuging the product at the rotor speed of 12,000 rpm, washed with water and dried under vacuum at 40ºC for 24 h.

**Conversion of Copolymer**

The yield of 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 water and methanol solvents to remove the remaining monomer and initiator and then dried in a vacuum oven at 50ºC until attainment of constant weight. The % conversion of monomers was calculated as:

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

Where $W$ is the weight of the dry copolymer obtained from the latex sample and $M$ is the weight of the monomers taken. The yield of copolymeric microspheres varied between 80 and 85 % for various formulations prepared in this study.

**pH and Temperature Sensitive Nature of Copolymer Microspheres**

pH and temperature sensitivity of copolymer microspheres were studied through swelling experiments. First, the microspheres were immersed in a buffer solution with various pH values (pH buffer solutions were prepared using $NaH_2PO_4$, $Na_2HPO_4$, $NaCl$ and $NaOH$ solution and pH values were measured using ELICO pH

meter, India) at 30ºC for 12 h. The swollen MGs were taken out for every 30 min and removed surface adhered buffer solution using tissue paper. The MGs were further immersed in various buffer solutions to reach equilibrium swelling. Swelling experiments were carried out in water by mass measurements at various temperatures to study temperature responsive behavior of microspheres. The percentages of swelling ratio (% SR) were calculated using the following equations.

$$\% \, SR = \left[ \frac{W_s - W_d}{W_d} \right] \times 100$$

Where, $W_s$ is the weight of swollen gel at time t, and $W_d$ is the dry weight of the hydrogel. Mass measurements were made on a digital ADAMS microbalance (Model AF 210L, U.K) with a sensitivity of 0.01 mg. Each value was averaged over three parallel measurements. Statistical analysis was performed using one-way ANOVA way in ORIGIN 8.0. All quantitative data are presented as means $\pm$ standard deviation.

**Differential Scanning Calorimetry (DSC) Studies**

Differential scanning calorimetric (DSC) curves were recorded on a Rheometric scientific differential scanning calorimeter (Model-DSC SP, UK). The instrument was calibrated using indium as the standard. Samples were heated in sealed aluminum pans between 30º and 400ºC at the heating rate of 10ºC/min under inert nitrogen purge gas at the rate of 20 ml/min.

**Scanning Electron Microscopic (SEM) Studies**

Morphology of the microspheres was confirmed by scanning electron microscopy (SEM). Micrographs of the dry microspheres in powder form, dispersed in acetone, were all recorded using Leica 400, Cambridge, UK instrument.

**Particle Size Analysis**

Size distribution of the microspheres was determined using the particle size analyzer

(Mastersizer 2000, Malvern Instruments, UK) equipped with the dry accessory system.

## Estimation of Drug Loading and Encapsulation Efficiency

Loading efficiency of 5-FU in the microspheres was determined spectrophotometrically. About 10 mg of the drug-loaded core-shell microspheres were placed in 10 ml of buffer solution and stirred vigorously for 48 h to extract the drug from the microspheres. The solution was filtered and assayed by UV spectrophotometer (model Anthelme, Secomam, Dumont, France) at the fixed $\lambda_{max}$ value of 270 nm. The results of % drug loading and encapsulation efficiency were calculated, respectively using Equations. (1) and (2). These data are compiled in Tables 1 and 2, respectively.

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

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

## In-vitro Release Study

Dissolution was carried out using Tablet dissolution tester (Lab India, Mumbai, India) equipped with eight baskets. Dissolution rates were measured at $37^0$C under 100 rpm speed. Drug release from the microspheres was studied in 7.4 pH phosphate buffer solution. Aliquot samples were withdrawn at regular time intervals and analyzed by UV spectrophotometer as explained before.

Table 1: Results of % encapsulation efficiency and mean diameter of poly(VC-co-SA) microspheres with different amounts of crosslinking agent, monomer concentration and 5-fluorouracil

| Sample code | % Vinyl Caprolactum (VC) | % SA | % NNMBA | % 5-FU | % Encapsulation efficiency ± SD | Mean particle diameter (μm) ± SD |
|---|---|---|---|---|---|---|
| VCSA-1 | 20 | 80 | 1 | 5 | 70 ± 1 | 29 ± 6 |
| VCSA-2 | 20 | 80 | 1 | 10 | 74 ± 2 | 31 ± 8 |
| VCSA-3 | 20 | 80 | 1 | 15 | 78 ± 2 | 34 ± 6 |
| VCSA-4 | 20 | 80 | 2 | 10 | 75 ± 9 | 28 ± 4 |
| VCSA-5 | 20 | 80 | 3 | 10 | 71 ± 8 | 16 ± 2 |
| VCSA-6 | 10 | 90 | 1 | 10 | 68 ± 6 | 30 ± 4 |
| VCSA-7 | 30 | 70 | 1 | 10 | 71 ± 5 | 24 ± 1 |
| VCSA-8 | 00 | 100 | 1 | 10 | 72 ± 1 | 22 ± 8 |

Table 2: Release kinetics parameters of microspheres with different amounts of crosslinking agent, monomer concentration and 5-fluorouracil at $37^0$C

| Formulation codes | $K \times 10^2$ | $n$ | Correlation coefficient '$r$' |
|---|---|---|---|
| VCSA-1 | 0.008 | 0.74 | 0.972 |
| VCSA-2 | 0.023 | 0.57 | 0.999 |
| VCSA-3 | 0.026 | 0.55 | 0.999 |
| VCSA-4 | 0.021 | 0.57 | 0.996 |
| VCSA-5 | 0.011 | 0.66 | 0.971 |
| VCSA-6 | 0.014 | 0.64 | 0.979 |
| VCSA-7 | 0.011 | 0.71 | 0.978 |
| VCSA-8 | 0.027 | 0.59 | 0.990 |

## RESULTS AND DISCUSSION

### pH and Temperature Responsive Behavior of Microspheres

Figure 1 (a) shows the swelling ratio of microspheres at various pH solutions. As we can clearly see that the swelling ratio of microspheres slowly increases when pH increases up to 5.0 after that it increases rapidly up to pH 8. Because at low pH i.e., < 5.0 carboxyl groups present in Sodium acrylate are converted in to –COOH and hydrogen bonding developed. Beyond pH 5, the carboxyl groups are ionic nature and repelling effect increases so, the swelling also increases dramatically. The sharp increase in swelling ratio observed up to pH 8.0, and then further increases slowly with further increase in pH up to 12.0. These changes indicate that the prepared microspheres exhibit pH-sensitive behavior.

The effect of temperature on the equilibrium swelling ratios for microspheres is shown in Figure 1(b) The swelling ratio of microspheres is higher at low temperature (< LCST) and lower at a higher temperature (> LCST). This is because below LCST VCL contains a hydrophilic group (-CONH-) and hydrophobic isopropyl group present in the linear polymer chain. So, the hydrophilic group in the polymer structure will form an intermolecular hydrogen bond with surrounding water at low temperature (below the gel transition temperature); above LCST the hydrogen bonds are broken and the water molecules are expelled from the polymer. These two results make the water molecule inside the gel change from a bound state to a free State and release from the gel. This phenomenon makes the swelling ratios of the microspheres decrease rapidly at the gel transition temperature.

### Differential scanning calorimetry (DSC)

DSC tracings of pure 5-fluorouracil, drug-loaded microspheres, and plain microspheres are displayed in Figure 2. The pure 5-FU exhibits a sharp peak at 285$^{\circ}$C (curve c) is due to polymorphism and melting. However, this peak has not appeared in the case of drug-loaded microspheres (curve b) which confirms that the drug is molecularly dispersed in the polymeric microspheres.
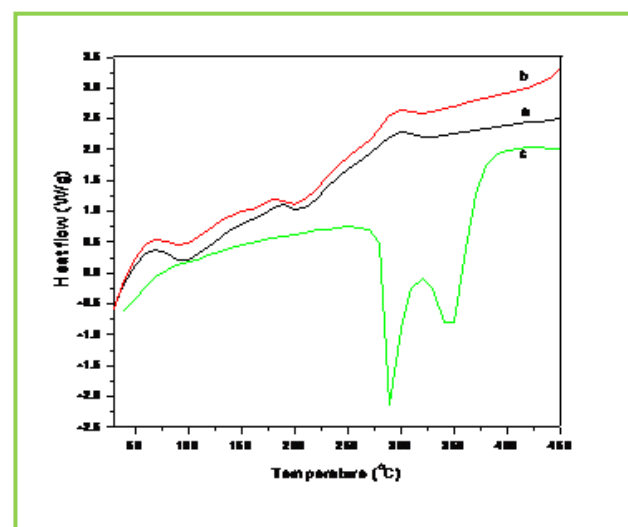


Figure 1.(a)



Figure 1.(b)

Figure 1. Swelling studies of MGs (a) various pH conditions, and (b) different temperatures



Figure 2: DSC thermograms of (a) plain Poly(VC-co-SA) microspheres (c) 5-FU loaded Poly(VC-co-SA) microspheres and (c) 5-FU

**Scanning Electron Microscopic (SEM) Studies**

Figure 3. shows the morphology of microspheres. The formed copolymer particles are spherical with the diameters of around 10 $\mu$m.
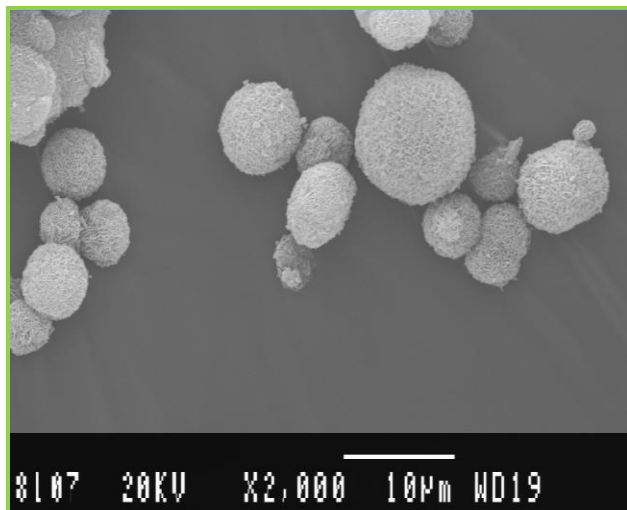


Figure 3: Scanning electron micrographs of Poly(VC-co-SA) microspheres

**Laser Particle Size Analyzer**

Results of the mean particle size with standard errors are presented in Table 1, while the size distribution curve for a typical formulation containing SA-5 is displayed in Figure 4.
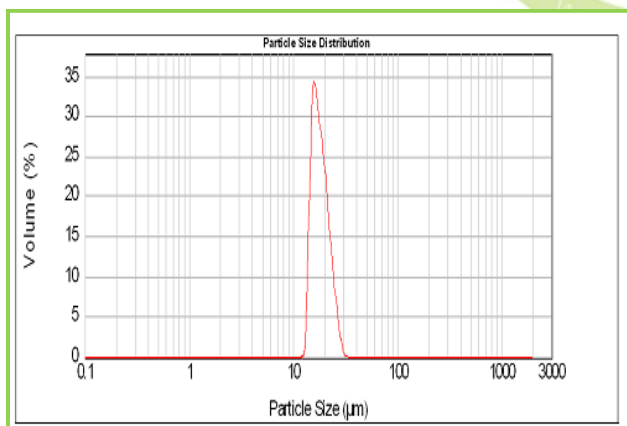


Figure 4: Particle size distribution curve of Poly(VC-co-SA) microspheres

It is found that size distribution is broad and volume means diameter of the particle is around 16 $\mu$m. The particle size of different formulations containing different amounts of drug, crosslinking agent and different ratios of VC-co-SA are given in Table 1. The particle size of formulations containing different amounts of crosslinking agent (NNMBA) i.e., 1, 2 and 3 % are 34, 28 and 16, respectively. The particle size decreased with increasing amount of crosslinking due to the formation of a rigid structure due to a reduction in chain length of the polymer formed.

**Encapsulation Efficiency**

Results of encapsulation efficiencies are given in Table 1. The % encapsulation efficiency varied depending upon the initial loading of the drug. In general, for formulations VCSA-1, VCSA-2 and VCSA-3, the % encapsulation efficiency increased systematically with increasing drug content of the matrices. At higher amount of crosslinking agent i.e., 2 % or 3 % of NNMBA in the matrix, the % encapsulation efficiency decreased. The highest % encapsulation efficiency of 79 was observed for VCSA-3 containing 15 % of 5-FU with a higher amount of SA in the copolymer matrix and its size was also highest i.e., 34 $\mu$m.

**Drug Release Kinetics**

While studying the drug release from the polymer matrices, it has been the usual practice to analyze the release data using the empirical relationship proposed by Ritger and Peppas[25]. In the present study, we have analyzed the cumulative release data using[26]:

$$\left(\frac{M_t}{M_\infty}\right) = kt^n$$

Here, the ratio, $M_t/M_\infty$ represents the fractional drug release at the 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 nine formulations at a 95% confidence limit; these data are given in Table 2 at $37^0$C. If the values of $n = 0.5$, then drug diffuses and releases out of the microsphere matrix following the Fickian diffusion. If $n > 0.5$, anomalous or non-Fickian transport occurs.

For $n = 1$, non-Fickian or more commonly called Case II release kinetics is operative. The values of $n$ ranging between 0.5 and 1 indicate the anomalous type transport[27].

The values of $k$ and $n$ have shown a dependence on the extent of crosslinking, % drug loading and SA content of the matrix. Values of $n$ for microspheres prepared by varying the amount of SA 90, 80 and 70 % in the microspheres of by keeping 5-FU (10 %) and 1 % NNMBA, ranged from 0.70 to 0.56 leading to a shift of transport from Fickian to anomalous type. The 5-FU-loaded particles have the $n$ values ranging from 0.55 to 0.73, indicating the shift from erosion type release to a swelling-controlled non-Fickian type of mechanism. This could be possibly due to a reduction in the regions of low microviscosity and closure of microcavities in the swollen state. Similar findings have been observed elsewhere, wherein the effect of different polymer ratios on dissolution kinetics was observed. On the other hand, the values of $k$ are quite smaller for drug-loaded microspheres, suggesting their lesser interactions compared to microspheres containing varying amount of SA.

### Effect of Sodium Acrylate Content

Figure 5 shows the *in vitro* release data of 5-fluorouracil from poly(VC-co-SA) particles performed with particles taking the different ratio of SA. These data show that higher amount of SA containing particles have more encapsulation efficiencies and also release studies have shown that higher amounts SA containing particles have shown prolonged release characteristics than the microspheres containing lower amounts of SA. Generally, the drug release pattern depends upon factors like particle size, crystallinity, surface character, molecular weight, polymer composition, swelling ratio, degradation rate, drug binding affinity, the rate of hydration of polymeric materials, etc.[27]. In the release behavior of poly(VC-co-SA) system, one can consider the binding affinity of drug and polymer swelling property of SA. A rapid release of more than 98% of the drug was observed within 12 h. from the microspheres containing a lower

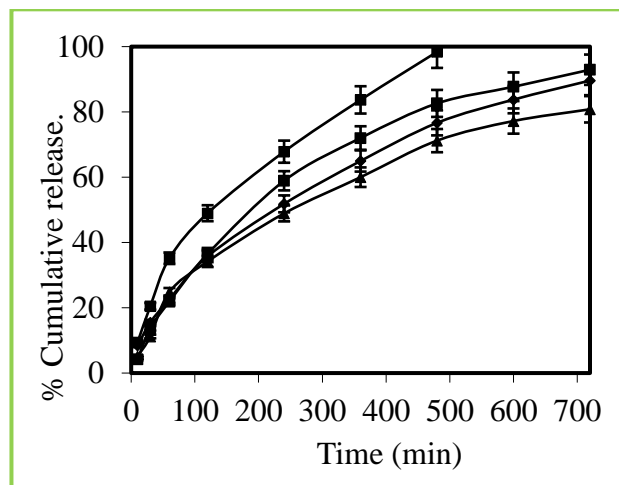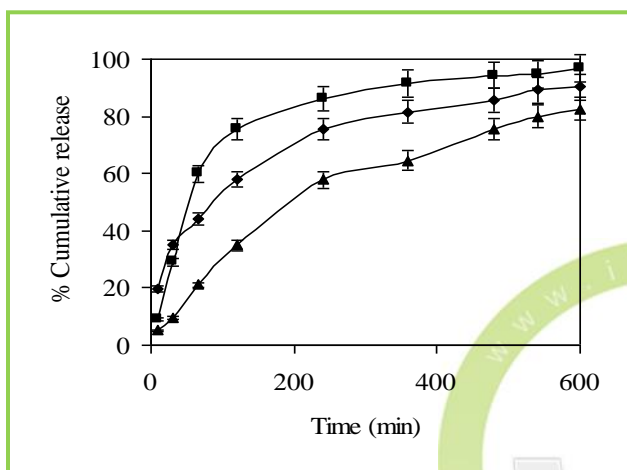amount of SA, indicating on the interaction between the two polymers.



Figure 5: % Cumulative release of 5-fluorouracil through Poly(VC-co-SA) microspheres containing different amount of acrylamide at 37 $^0$C, Symbols: (■)100 %, (■)30 %, (♦) 20 % and (▲) 10 %

### Effect of Temperature

The cumulative release data vs time curves for varying amounts of vinyl caprolactam are displayed in Figure 6 at 25$^0$C. Drug release profiles exhibited drastic changes by variations in temperature from 37$^0$ to 25$^0$C as shown in Figures 4 and 5, respectively. It may be noticed that drug was released slowly at 37$^0$C i.e., above the LCST of 32$^0$C, but the release was much faster at 25$^0$C i.e., below the LCST than at 37$^0$C. This is due to the fact that at a higher temperature, the surface of microspheres would shrink, causing the drug to migrate toward the surface of the microspheres as seen by the initial burst effect during the dissolution experiments (Figure 6 and 7). However, dense surfaces of the microspheres will prohibit the release of more amount of drug. At lower temperatures, the already shrunken surface layer starts to re-swell, which would allow the drug to be released after a certain period of time, depending upon the minimum time required for re-swelling of the surface. Thus, the time required for drug release was accelerated as a result of cooling below the LCST, which further slowed down upon reheating. Microspheres were thus found to be

sensitive to changes in temperature. At $25^0$C (in the swollen state), the release rate and the total amount of drug release 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 get 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 a decrease in drug diffusion rate.



Figure 6: % Cumulative release of 5-fluorouracil through Poly(VC-co-SA) microspheres containing different amount of Vinyl Caprolactum at 25 $^0$C, Symbols: (■)10 %, (♦) 20 % and (▲) 30 %.
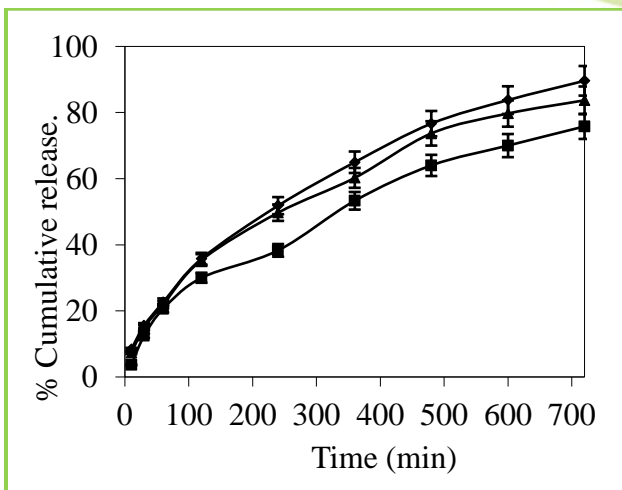


Figure 7: % Cumulative release of 5-fluorouracil through Poly(VC-co-SA) microspheres containing different amount of crosslinking agent at 37 $^0$C, Symbols: (■) 3%, (▲) 2% and (♦) 1 %

## *Effect of Crosslinking Agent*

The % cumulative release vs time curves for varying amounts of NNMBA are displayed in Figure 7. The % cumulative release is quite fast and large at the lower amount of NNMBA, whereas release is quite slower at a higher amount of NNMBA. The cumulative release is somewhat smaller when a lower amount of NNMBA was used probably because, at higher concentration of NNMBA, polymeric chains would become rigid due to the contraction of microvoids, thus decreasing the % cumulative release of 5-FU through the polymeric matrices. As expected, the release becomes slower at a higher amount of NNMBA but becomes faster at a lower amount of NNMBA.

## *Effect of Drug Concentration*

Figure 8 displays the release profiles of poly(VC-*co*-SA) microspheres that are loaded with different amounts of 5-FU. Notice that initially, during the first hour, the release is quite fast in all the formulations, but later it slowed down. The similar findings were observed in earlier literature of 5-fluorouracil loaded microspheres of a different kind [22,23]. Release data suggest that those formulations containing the highest amount of drug (i.e., 15 wt. %) displayed higher release rates than those containing smaller amounts of 5-FU (i.e., 10 and 5 wt. %).
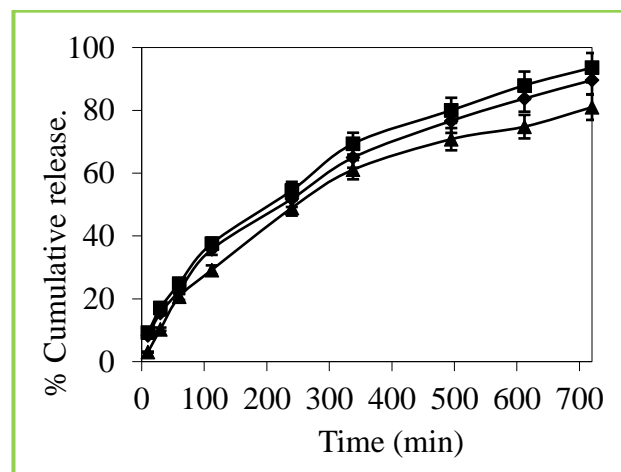


Figure 8 % Cumulative release of 5-fluorouracil through Poly(VC-co-SA) microspheres containing different amount of 5-FU at 37 $^0$C, Symbols: (■) 15 %, (♦) 10 % and (▲) 5 %

A prolonged and slow release was observed for the formulation containing a lower amount of 5-FU (i.e., 5 wt. %) at $37^0$C; this is due to the large free volume spaces available in the matrix through which, a lesser number of 5-FU molecules would transport. Notice that for all the 5-FU-loaded formulations, the almost complete release of 5-FU was achieved after 720 min.

## CONCLUSION

Poly(vinyl caprolactam-Sodium acrylate) copolymeric microspheres crosslinked with N, N′-methylene bisacrylamide were prepared by free radical emulsion polymerization. The microspheres have been characterized by differential scanning calorimetry (DSC) and x-ray diffractometry (x-RD) to understand the drug dispersion in microspheres. Microspheres with different copolymer compositions were prepared in yields of 80-85 %. DSC indicated a uniform distribution of 5-fluorouracil particles in microspheres, whereas SEM suggested a spherical structure of the microspheres with the slight rough surface. The *in vitro* drug release indicated that particle size and release kinetics depend upon copolymer composition, amount of crosslinking agent and amount of 5-fluorouracil present in the microspheres.

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