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Development of 5-fluorouracil loaded poly(acrylamide-*co*-methylmethacrylate) novel core-shell microspheres: *In vitro* release studies☆

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Abstract

Novel poly(acrylamide-methylmethacrylate) copolymeric core-shell microspheres crosslinked with *N*,*N*′-methylene bisacrylamide have been prepared by free radical emulsion polymerization using varying amounts of acrylamide (AAm), methylmethacrylate (MMA) and *N*,*N*′-methylene bisacrylamide (NNMBA). 5-Fluorouracil was loaded into these microspheres during *in situ* polymerization (method-I) as well as by the absorption and adsorption technique (method-II). The core-shell microspheres have been characterized by differential scanning calorimetry (DSC) and X-ray diffractometry (X-RD) to understand about the drug dispersion in microspheres. Scanning electron microscopy (SEM) was used to assess the surface morphology of particles prepared. *In vitro* release of 5-fluorouracil has been studied in terms of core-shell composition, amount of crosslinking agent and amount of 5-fluorouracil in the microspheres. Core-shell microspheres with different copolymer compositions have been prepared in yields ranging 80–85%. DSC and X-RD techniques indicated a uniform distribution of 5-fluorouracil particles in core-shell microspheres, whereas SEM suggested the formation of well-defined core-shell structures. 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. Prolonged and controlled release of 5-fluorouracil was achieved when drug was loaded by method-I instead of method-II.

Keywords: Core shell; Microspheres; 5-Fluorouracil; Drug delivery

1. Introduction

Evolution of pharmaceutical technology has lead to the development of newer methods of drug administration as well as the design and application of controlled release (CR) formulations for the effective targeting of certain drugs to the site of action. In particular, the use of polymeric systems provides a clear optimization to develop the CR dosage formulations to achieve desired therapeutic results to the target site as well as optimization of CR of the drug to obtain maximum dose regimen with minimum side effects (Garcia et al., 2000). The release of a drug from a polymeric matrix occurs due to transport of solute molecules (drug) to the medium that surrounds the system by molecular diffusion through the polymeric walls of the microspheres. This makes the solubility of the solute in the polymer matrix an important factor in controlling the delivery. Drug diffusion from monolithic systems have been analyzed by Fick's second law of diffusion (Peppas et al., 1980), based on the principle of permeability of polymeric matrix after when it swells in the hydration media. Swelling kinetics and release rates depend strongly upon the degree of matrix swelling. However, the majority of polymeric drug-loaded formulations used in CR studies are often prepared from hydrophilic polymers that are crosslinked with acrylic monomers (Lorenzo et al., 2005) that are biocompatible. Alternatively, copolymers of hydrophilic and hydrophobic monomers with appropriate compositions have also been employed in CR studies of bioactive molecules (Kim et al., 2000).

One important step in the development of CR drug delivery systems is the loading of the drug into the polymeric matrix.

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In the previous literature, two methods have been mainly used (Kim et al., 1992). One is the polymerization in the presence of a drug (Hennick et al., 1996; Franssen et al., 1997; Ward and Peppas, 2001) or by imbibitions (Bromberg et al., 2002; Lorenzo and Concheiro, 2002). In the former case, drug is added to the polymerization media together with monomers, crosslinker and initiator. In the latter case, particles are soaked in the drug solution. The second method could offer some advantages over the first method, since polymerization may affect drug release characteristics because of the secondary reactions taking place between the drug and the active monomers. On the other hand, the first method presents some inconveniences such as those including the use of organic solvents that could be hazardous to the biological environment. In any case, drug loading within the polymer matrix depends upon the release, which involves factors such as rate and swelling degree of the microparticles (Kim et al., 2003), drug/polymer interactions (Lee et al., 1991; Fu et al., 2004), drug solubility and its concentration (Siepmann et al., 2002) in the swelling medium as well as diffusion of the drug throughout the swollen polymeric matrix. Langer et al. (1996) and Kim et al. (1992) reviewed the compositional/structural effects of polymers on drug loading and their CR characteristics. Lee and Kim (1991) investigated the effect of drug loading on drug release characteristics from the microparticles. They concluded that drug loading has a definite effect on drug release mechanism from such matrices.

In continuation of the above mentioned studies and as a part of our on going program of research on the development of novel CR systems (Agnihotri and Aminabhavi, 2004; Agnihotri et al., 2005), we now present new experimental data on the development of novel core-shell microspheres involving monomers, viz., methylmethacrylate (MMA) and acrylamide (AAm) for the slow delivery of 5-fluorouracil (5-FU), an anticancer drug, used widely in pharmaceutical research. MMA has wide-spread biomedical applications, due to its biocompatibility and it can be easily copolymerized with other monomers like sulfopropylmethacrylate (Saraydin et al., 1994) and alkylmethacrylate with various acrylic acid derivatives including acrylamide, acrylic acid, butyl ester as well as with styrene (Rolland et al., 1986; Kreuter et al., 1988) to increase the hydrophilicity of the nanoparticles formed. However, poly(acrylamide) has limited applicability because of its poor mechanical properties due to its high degree of hydration. The copolymers of acrylamide as hydrogels are important in biomedical applications (Karadag et al., 1996; Sommadossi et al., 1982). 5-Fluorouracil is an antimetabolic drug, used extensively in cancer chemotherapy (Einmahl et al., 1999; Fournier et al., 2004) and is an antimetabolite, which is used to prevent the subsequent scarring following trabeculectomy and to improve the prognosis for long-term retinal reattachment. 5-Fluorouracil is an acidic, water soluble (Ermis and Yuksel, 1999), hydrophilic drug and is an antineoplastic agent of extensive use in clinical chemotherapy for the treatment of solid tumours. It has been widely used in drug administration due to its large number of secondary effects that accompany its conventional administration.

Traditionally, the core-shell particles can be lightly crosslinked by using difunctional monomers. In order to the prepare core-shell particles, it is important to maintain the precise spatial arrangement of the functional groups in the binding site and to preserve the overall shape of the template, all of which requisites for efficient imprinting. Core-shell microparticles usually refer to spheres formed by making the core units through a normal preparative method, followed by the addition of an outer layer by a dipping, mixing emulsifying or *in situ* polymerization (Jones and Lyon, 2000; Lee et al., 2002; Sparnacci et al., 2002; Zhou et al., 2002; Gref et al., 1994). Employment of a shell usually helps to enhance and possibly reduce the effect of the initial burst effect. Microparticles and nanoparticles based on core-shell structures or polymeric micelles are advantageous in terms of their long circulation in the body in addition to drug solubility, stability and high level of drug encapsulation (Kwon et al., 1995). Moreover, the main advantage of core-shell type microspheres is that both hydrophilic and hydrophobic drugs can be incorporated. In this research, novel 5-fluorouracil-loaded poly(acrylamide-*co*-methylmethacrylate) core-shell microspheres have been prepared. The particles formed have been characterized by particle size analyzer, differential scanning calorimetry, X-ray diffractometer and scanning electron microscopy. The *in vitro* release studies have been performed in 7.4 pH buffer solution at 37 °C.

2. Materials and methods

2.1. Materials

Acrylamide (AAm), methylmethacrylate (MMA), *N*,*N*′-methylene bisacrylamide (NNMBA), sodium laurylsulfate, sodium hydrogen phosphate, potassium persulfate and calcium chloride were all purchased from s.d. fine chemicals, Mumbai, India. 5-Fluorouracil was purchased from MP Biochemicals, Eschwege, Germany.

2.2. Synthesis of poly(acrylamide-co-methylmethacrylate)

Sodium laurylsulfate (1 g) and sodium hydrogen phosphate (100 mg) were 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 immersed in an oil bath with a thermostatic control to maintain the desired temperature accurate to ±1 °C. The solution was stirred at 800 rpm speed until it became clear and 100 mg of potassium persulfate was added. Required amount of AAm, MMA, the 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 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 and denoted AAM00 and 5-fluorouracil as 5-FU.

2.3. Loading of 5-fluorouracil

5-Fluorouracil was loaded into core-shell 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 core-shell 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.

2.4. 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 30 and 400 °C at the heating rate of 10 °C/min under inert nitrogen purge gas at the rate of 20 mL/min.

2.5. X-ray diffraction (X-RD) studies

X-ray diffraction (X-RD) patterns of the plain 5-fluorouracil, placebo AAm-*co*-MMA core-shell microspheres and 5-fluorouracil-loaded core-shell microspheres were recorded using Rigaku Geigerflex diffractometer equipped with Ni-filtered Cu Kά radiation (λ = 1.5418 Å). Dried core-shell microspheres of uniform size were mounted on a sample holder and the patterns were recorded in the angle range of 2–65° at the speed of 5°/min.

2.6. Scanning electron microscopic (SEM) studies

Core-shell 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.

2.7. 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.

Table 1
Results of % encapsulation efficiency and mean diameter of core-shell microparticles with different amounts of crosslinking agent, monomer concentration and 5-fluorouracil (method-I)

Sample code	AAm:MMA (wt./wt.)	% NNMBA	% 5-FU	% Encapsulation efficiency	Mean particle diameter (μm)
AAm-1	1:1	1	5	69.6	30.4
AAm-2	1:1	1	10	75.2	31.8
AAm-3	1:1	1	15	79.2	32.6
AAm-4	1:1	2	5	71.5	29.6
AAm-5	1:1	2	10	72.8	30.4
AAm-6	1:1	2	15	76.9	31.6
AAm-7	1:1	3	5	72.5	24.1
AAm-8	1:1	3	10	73.4	26.8
AAm-9	1:1	3	15	75.6	28.4

5-Fu = 5-fluorouracil; AAm = acrylamide; MMA = methylmethacrylate; NNMBA = *N*,*N* methylene bisacrylamide.

2.8. 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 Anthelie, Secomam, Dumont, France) at the fixed λ_{max} value of 270 nm. The results of % drug loading and encapsulation efficiency were calculated, respectively using Eqs. (1) and (2). These data are compiled in Tables 1 and 2, respectively:

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

$$\%\ \text{encapsulation efficiency} = \left(\frac{\text{actual loading}}{\text{theoretical loading}}\right) \times 100 \quad (2)$$

2.9. 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 water and methanol solvents to remove the remaining monomer and initiator, and then dried in a vacuum oven at 50 °C till attainment of constant weight. The conversion of monomers was

Table 2
Results of % encapsulation efficiency and mean size of core-shell microparticles with different amounts of crosslinking agent, monomer concentration and 5-fluorouracil (method-II)

Sample code	Weight ratio of AAm:MMA	% NNMBA	% 5-FU	% Encapsulation efficiency	Mean particle diameter (μm)
AAm-FU1	1:1	1	5	79	30.12
AAm-FU2	1:1	1	10	81	34.01
AAm-FU3	1:1	1	15	82	36.45

calculated as:

$$\text{conversion} = \left(\frac{W}{M}\right) \times 100 \quad (3)$$

where W is 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.

2.10. In vitro release study

Dissolution was carried out using Tablet dissolution tester (LabIndia, Mumbai, India) equipped with eight baskets. Dissolution rates were measured at 37 °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.

3. Results and discussion

3.1. Differential scanning calorimetry (DSC)

DSC tracings of pure 5-fluorouracil, drug-loaded core-shell microspheres and plain microspheres are displayed in Fig. 1. The onset-melting peak of 5-FU was observed at 285.16 °C. However, no characteristic peak of 5-FU was observed in DSC curves of the drug-loaded microspheres, suggesting that drug is molecularly dispersed in the polymer matrix. Fig. 1c shows a small sharp peak at 286 °C in which drug was loaded by solvent evaporation technique (method-II), confirming that drug was absorbed into surface as well as adsorbed onto the surface of the microspheres.

3.2. X-ray diffraction (X-RD) studies

X-RD analyses provide a clue about crystallinity of the drug in the crosslinked microspheres. X-RD patterns recorded for the placebo core-shell microparticles, drug-loaded microspheres and plain 5-FU are compared in Fig. 2. The 5-FU peaks are observed at 2θ of 16°, 19°, 21° and 29°, suggesting its crystalline nature. But, these peaks are not found in 5-FU loaded core-shell microspheres, indicating that drug is dispersed at a molecular level in the polymer matrix.

3.3. Scanning electron microscopic (SEM) studies

Scanning electron microscopy and transmission electron microscopy have been used to confirm the formation of core-shell structures (Shivakumar and Panduranaga Rao, 2002; Kong

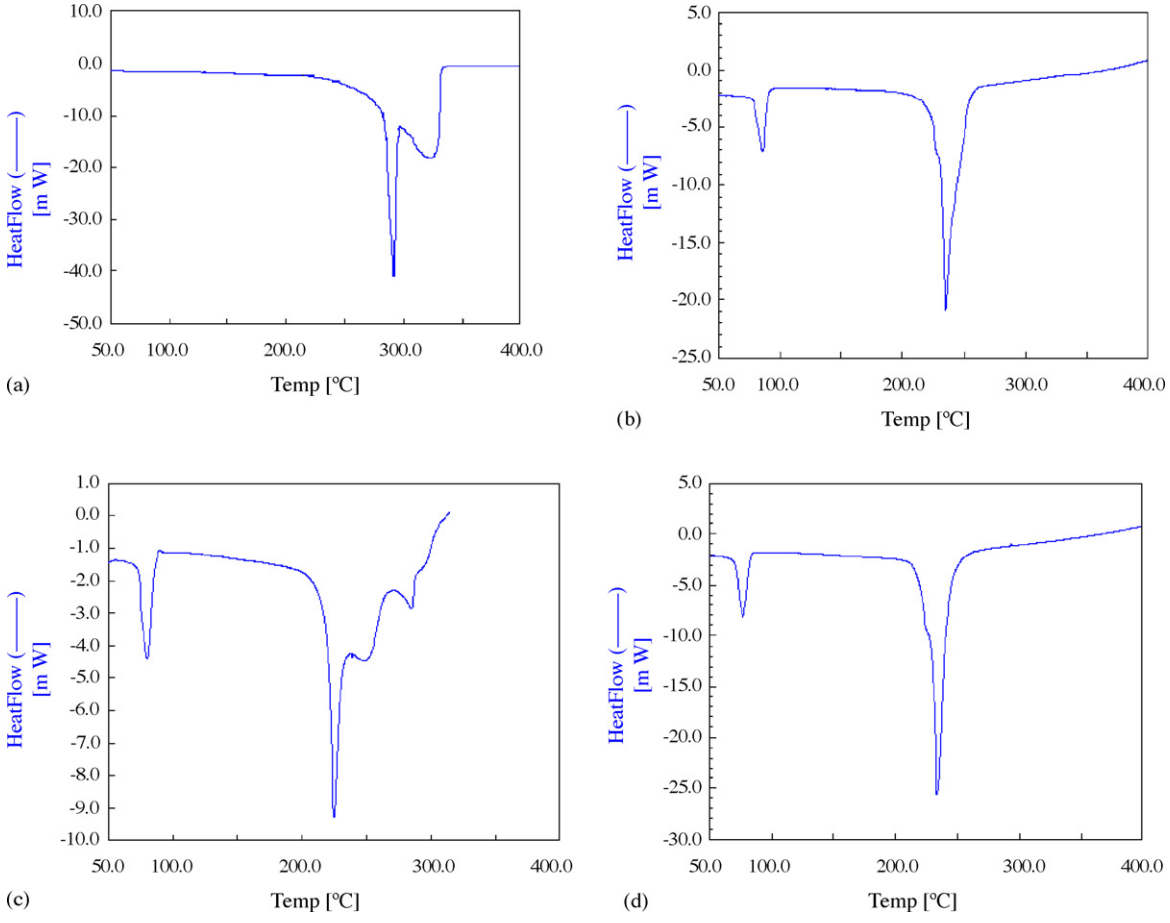

Fig. 1. DSC thermograms of (a) 5-FU, (b) AAM-1, (c) AAM-FU1 and (d) AAm00 core-shell microspheres.

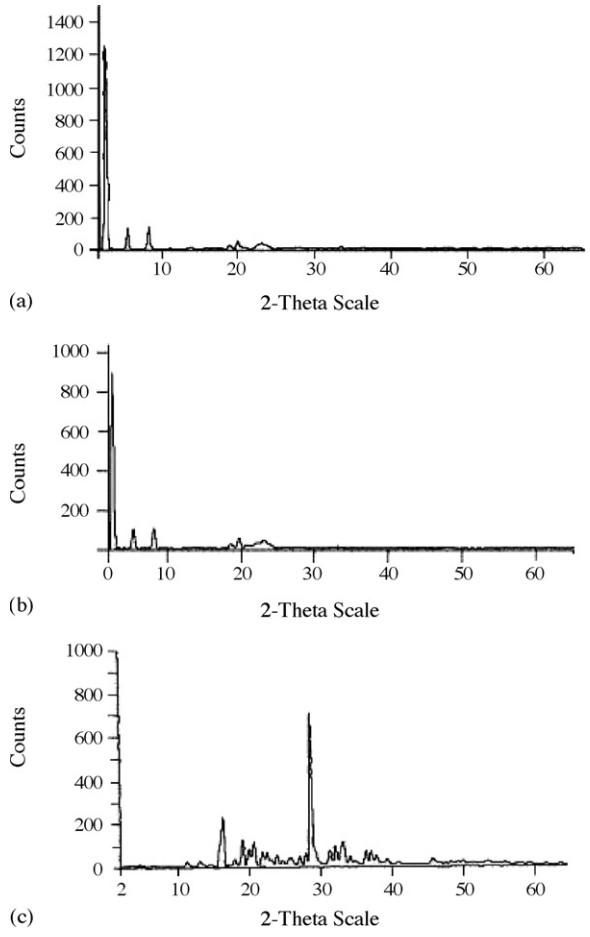

Fig. 2. X-RD tracings of (a) AAm00, (b) AAM-1 microspheres and (c) plain 5-FU.

and Ruckenstein, 1999). SEM micrographs of AAm-*co*-MMA core-shell microspheres are displayed in Fig. 3. The microspheres were dispersed in acetone solvent and subjected to SEM, which observed the formation core-shell structure of the microspheres with hydrophobic core and hydrophilic shell. In this, the core formed is by the hydrophobic methylmethacrylate, but the shell is formed by the hydrophilic acrylamide.

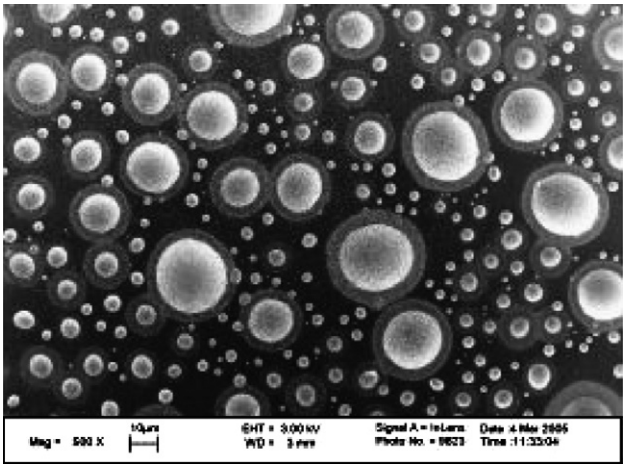

Fig. 3. Scanning electron micrographs of AAm00 core-shell microspheres.

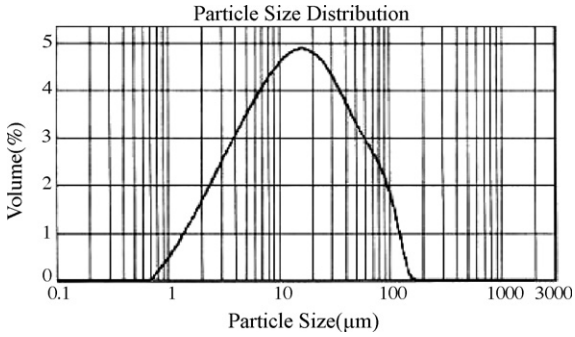

Fig. 4. Particle size distribution curve of AAm00 core-shell microspheres.

3.4. 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 1:1 of AAm:MMA with 10% of 5-FU and 3% NNMBA is displayed in Fig. 4. It is found that size distribution is broad and volume mean diameter of the particle is around 24 μm. Particle size of different formulations containing different amounts of drug, crosslinking agent and different ratios of AAM:MMA are given in Tables 1 and 2. The % encapsulation efficiency varied depending upon the initial loading of the drug. In general, for formulations AAm-1, AAm-2 and AAm-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 increased, which followed the same trends as those of AAm-1, AAm-2 and AAm-3 matrices. The highest % encapsulation efficiency of 81 was observed for AAm-FU containing 5% of 5-FU with a higher content of AAm in the copolymer matrix and its size was also highest, i.e., 36.45 μm.

3.5. In vitro drug release

3.5.1. Effect of 5-fluorouracil

5-Fluorouracil is a water-soluble drug and therefore, it is difficult to encapsulate it into hydrophobic polymers by solvent exchange process. In the present research, 5-FU formulations with loadings ranging up to 62–81% could be achieved at different copolymer compositions that are quite higher than those reported in the literature for 5-FU loading using the adsorption technique. The % encapsulation efficiency data are given in Table 1. Fig. 5a–c displays the drug release characteristics of the formulations containing different amounts of drug with different wt.% of crosslinking agent (viz. 1, 2 and 3). Notice that faster release rates have been observed for formulations containing higher amount of 5-FU than those microspheres containing lower amount of drug at 1% NNMBA in the matrix. Release data showed that formulations containing higher encapsulation efficiency displayed much faster and higher release rates than those formulations containing the lower encapsulation efficiency. However, a prolonged drug release was observed for formulation containing lower amount of 5-FU. Notice that the release rate becomes quite slower when a lower amount of

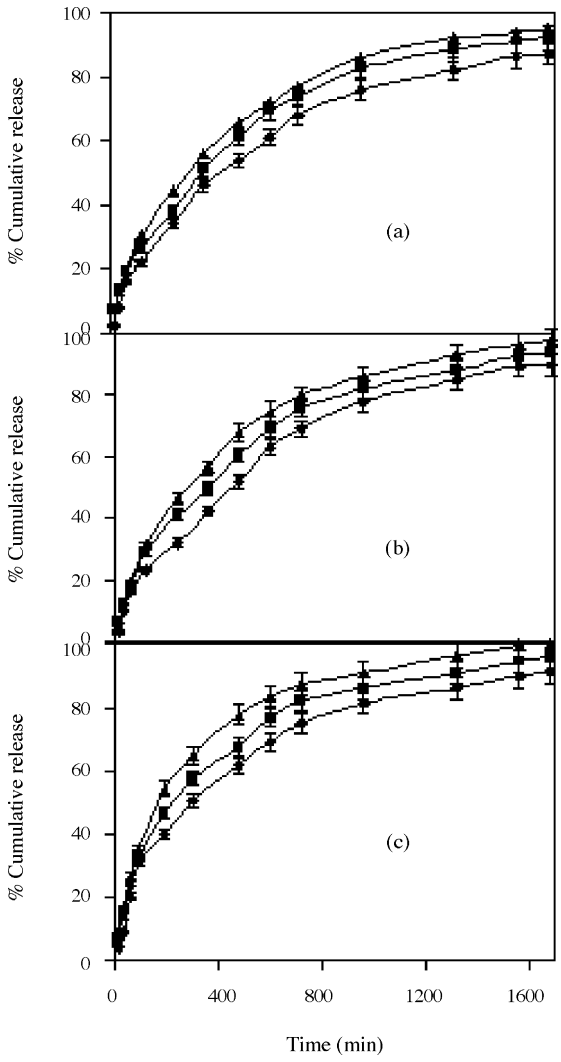

Fig. 5. % Cumulative release of 5-fluorouracil through AAm:MMA core-shell microspheres. Symbols: (a) (▲) AAm-1, (■) AAm-2 and (♦) AAm-3; (b) (▲) AAm-4, (■) AAm-5 and (♦) AAm-6; (c) (▲) AAm-7, (■) AAm-8 and (♦) AAm-9.

drug is present in the matrix, probably due to the availability of more free-void spaces through which, lesser number of drug molecules could possibly transport. 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. (Ratner et al., 1996). While *in vitro* release of the drug from the AAm–MMA core-shell system in addition to binding affinity of the drug seem to be dominant.

3.5.2. Effect of crosslinking agent

The % cumulative release data *versus* time plots for varying amounts of NNMBA, i.e., 1, 2 and 3% at the fixed amount of the drug (5%) are displayed in Fig. 6. 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.

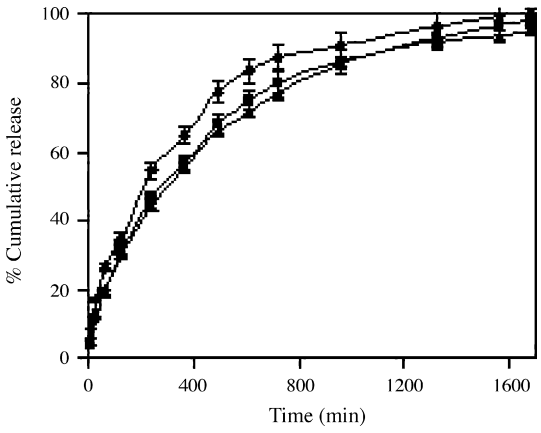

Fig. 6. % Cumulative release of 5-fluorouracil through AAm:MMA core-shell microspheres. Symbols: (▲) AAm-7, (■) AAm-4 and (♦) AAm-1.

3.5.3. Effect of drug loading by absorption and adsorption technique

Fig. 7 displays the *in vitro* release profiles of 5-FU from the core-shell microspheres loaded by method-II. The encapsulation efficiency is higher when drug loading was done by absorption and adsorption technique (method-II) as compared to method-I. This method is most suitable for developing slow release systems. 5-Fluorouracil was loaded into microspheres by dissolving the drug in the solvent medium and then, soaking the polymer particles into the solution. It can be seen that the amount of 5-fluorouracil loaded into microspheres increased with increasing amount of 5-FU. Drug loading can be efficient because of the interaction between hydrophilic 5-FU and the polymeric shell in which drug can be adsorbed onto the surface of the shell. The release data indicated that more than 95% of the drug was released within 14 h. However, the drug adsorbed on the surface of microparticles exhibit a lesser interaction and binding efficiency with the polymeric matrix with a higher affinity to buffer solution used. The results have shown that drug release

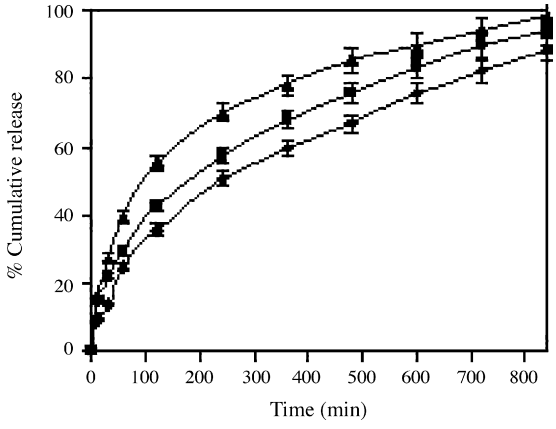

Fig. 7. % Cumulative release of 5-fluorouracil through AAm–MMA core-shell microspheres. Symbols: (♦) AAm-FU1, (■) AAm-FU2 and (▲) AAm-FU3.

Table 3
Release kinetics parameters of core-shell microparticles with different amounts of crosslinking agent, monomer concentration and 5-fluorouracil (method-I)

Formulation code	k	n
AAm-1	0.0257	0.624
AAm-2	0.0269	0.617
AAm-3	0.0298	0.597
AAm-4	0.0269	0.602
AAm-5	0.0284	0.612
AAm-6	0.0309	0.593
AAm-7	0.0346	0.568
AAm-8	0.0346	0.546
AAm-9	0.0347	0.493

rates are much faster when drug was loaded by method-II than by method-I.

3.5.4. 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):

$$\left(\frac{M_t}{M_\infty}\right) = kt^n \quad (4)$$

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 nine formulations and these values are given in Tables 3 and 4. If $n = 0.5$, then drug diffuses and releases from the polymer matrix following a Fickian diffusion. For $n > 0.5$, an anomalous or non-Fickian type drug diffusion occurs. If $n = 1$, a completely non-Fickian or Case II release kinetics is operative. The intermediary values ranging between 0.5 and 1.0 are attributed to the anomalous type transport (Ritger and Peppas, 1987).

The values of k increased with increasing % loading of 5-fluorouracil into the core-shell microspheres, but the n values decreased with decreased % loading of 5-FU. This indicates the interaction between the core-shell microspheres and drug as studied from the release kinetics Eq. (4) proposed by Ritger and Peppas (1987). The values of exponent n are found to range between 0.493 and 0.625 as calculated from the empirical equation, which indicated that drug release slightly deviated from the Fickian trend.

Table 4
Release kinetics parameters of core-shell microparticles with different amounts of crosslinking agent, monomer concentration and 5-fluorouracil (method-II)

Formulation code	k	n
AAm-FU1	0.0274	0.629
AAm-FU2	0.0525	0.582
AAm-FU3	0.0695	0.496

4. Conclusions

A common way to prepare new materials is to combine two or more polymers. Grafting, block polymerization or copolymerization are most often used for this purpose. Poly(acrylamide) and poly(methylmethacrylate) are among the most popular polymers; consequently, their combination is of great interest to develop the core-shell microspheres. In this research, core-shell microparticles have been prepared by copolymerizing hydrophilic and hydrophobic monomers by free radical emulsion polymerization. The core-shell microparticles have been employed to study the controlled release of 5-fluorouracil. Indeed, the matrices prepared in this study could offer a wide array of release patterns and rates. Depending upon the matrix loading dose and preparation method employed, the release was controlled by the penetration of external medium into the core-shell matrix or by drug diffusion into the matrix pores or by both. The matrix prepared with a 3:1 ratio of AAm to MMA, prepared by method-I was deemed to be the most appropriate one to offer a successful CR system. Differential scanning calorimetry and X-ray diffraction of 5-fluorouracil-loaded microspheres have shown a molecular level dispersion of the drug in the matrices. SEM micrographs confirmed the formation of well-defined core-shell microspheres with distinct spherical cores and shells. Higher drug loadings and faster release rates have been observed when drug was loaded into core-shell microspheres by the solvent evaporation technique. Sustained and prolonged drug release rates have been observed from the *in situ* drug-loaded microparticles of this study. The study further demonstrated that by exploiting the relationship between the outer shell–inner core combinations, the drug action would offer important new information to design improved core-shell microparticles for fine-tuning of drug release as well as for a deeper understanding of the drug action mechanisms through the core-shell structures.

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