Poly(methylmethacrylate)-Poly(vinyl pyrrolidone) Microspheres as Drug Delivery Systems: Indomethacin/ Cefadroxil Loading and *In Vitro* Release Study

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ABSTRACT: Poly(methylmethacrylate)-poly(vinyl pyrrolidone) (PMMA-PVP) microspheres loaded with cefadroxil (water-soluble) and indomethacin (water-insoluble) drugs have been prepared by the dispersion polymerization technique using PVP as a steric stabilizer. Microspheres have been characterized by differential scanning calorimetry (DSC), scanning electron microscopy (SEM) and X-ray diffraction (X-RD) studies. DSC studies indicated coating of PVP onto PMMA microspheres. SEM suggested the formation of microspheres in the size of around 5 μm. X-RD confirmed that drug has been highly dispersed in polymer particles. Higher encapsulation efficiency of up to 84% was achieved for hydrophobic drug, indomethacin than for hydrophilic cefadroxil. *In vitro* release studies performed in pH 7.4 phosphate buffer saline indicated that release of indomethacin was controlled up to 12 h, whereas cefadroxil was released in a controlled manner up to 10 h. During *in vitro* release, properties of both the drugs remained unaltered. J Appl Polym Sci 104: 1860–1865, 2007

Key words: polymer microspheres; poly(vinyl pyrrolidone); dispersion polymerization; controlled release

INTRODUCTION

Micro- and nano-particulate drug delivery systems are the attractive devices in place of conventional delivery modes in biomedical and pharmaceutical areas for controlled release (CR) of drugs, since release profiles from such systems can be monitored accurately. Diffusive release of drugs can be controlled not only by the design or type of polymeric matrix, but also by the size of microspheres. One of the methods to prepare micrometer-sized particles is through dispersion polymerization of monomers; this technique has received a great deal of attention in the earlier literature.[1–4] Spherical micrometer-sized monodisperse particles can be obtained by dispersion polymerization, wherein the monomer is completely miscible with the reaction medium and the resulting polymer is insoluble under the same conditions. In contrast to ordinary precipitation polymerization, macroscopic separation of the polymer from the reaction mixture is prevented by the presence of a steric stabilizer. Thus, the technique[1] is based on a very peculiar particle forming process, which involves the polymerization of a monomer dissolved in an organic solvent, which is a poor solvent for the resulting polymer. Once polymerization reaction is initiated, the growth of macromolecular chains (initially oligomers) takes place in the presence of a polymeric stabilizer, which can be a graft copolymer or its precursor. When sufficient oligomeric chains are formed, nucleation takes place and the resulting particles continue to grow, since these are sterically stabilized by the graft copolymer. Therefore, dispersion polymerization is not limited to non-aqueous systems, and can also be performed in water. By appropriately choosing a stabilizer, it is possible to prepare a great variety of core-shell particles. In addition, monodisperse particles are often obtained, depending upon the experimental parameters of the reaction and concentration of the employed reagents. Examples of such dispersions include poly(methylmethacrylate) (PMMA) particles stabilized in hydrocarbon liquids by using block copolymers[5–7] and polystyrene particles stabilized in alcohols with partially hydrolyzed poly(vinyl alcohol)[8] or with poly(vinyl pyrrolidone) (PVP).[9,10] During particle formation, the stabilizer gets adsorbed or grafted onto the particle surface.

The most frequently used polymers for the production of particles used in the CR of drugs include acrylic acid derivatives, polyalkylcyanoacrylates and polyalkylmethacrylates. However, particles prepared from the above-mentioned monomers have low drug loading capacities particularly for hydrophilic drugs.[11] To increase the hydrophilicity of particle surface, attempts have been made to employ copolymerization of alkylmethacrylate with various acrylic acid

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derivatives[12,13] such as acrylamide and acrylic acid. However, poly(methylmethacrylate) based micro- and nano-particles have been prepared using Eudragit E 100, dextran, and so forth, as stabilizers for CR applications.[14,15] In a previous report,[16] it was shown that PVP, a widely used polymer in pharmaceutical formulations, forms covalent adducts with drugs containing nucleophilic functional groups. Realizing these findings and as a part of our continuing efforts, we report here the preparation of PMMA microspheres using PVP as a steric stabilizer for CR applications. Cefadroxil (water soluble) and indomethacin (water insoluble) are used as the model drugs to demonstrate the CR characteristics from the prepared PMMA-PVP microspheres. Encapsulation efficiency was studied by loading the drug during polymerization of PMMA. *In vitro* drug release studies have been carried out in 7.4 pH buffer medium.

The present study is a continuation of our efforts, which demonstrates the development and applicability of PMMA-PVP microspheres for the release of hydrophilic (cefadroxil) and hydrophobic (indomethacin) drugs. Indomethacin is a nonsteroidal anti-inflammatory drug (NSAID) used widely as an analgesic in the treatment of local and systemic inflammatory pathologies. It is effective in the management of rheumatoid arthritis, ankylosing spondylitis, osteoarthritis and acute gout. Cefadroxil, an antibiotic drug has a biological half-life of 1.2–2 h for a dose containing 0.5 and 1.5 g. Cefadroxil is produced by chemical coupling of the side chain (D)-*p*-hydroxy phenyl glycine to β-lactam nucleus. It may be noted that cephalosporin antibiotics used in the treatment of bacterial infections are available in the market for more than two decades; these contain β-lactam nucleus and a D-amino acid side chain. Hence, developing slow release formulations of both these drugs are essential in pharmaceutical applications. The present study addresses these issues.

EXPERIMENTAL

Materials and methods

Poly(vinyl pyrrolidone) (PVP; MW: 360,000), ethylene glycol dimethacrylate (EGDMA), methylmethacrylate (MMA) and azobisisobutyronitrile (AIBN) were purchased from Aldrich, WI. Indomethacin and cefadroxil (USP grade) were received as gift samples from Bio-ethicals, Hubli, India. Methanol (AR grade) was purchased from s.d. fine chemicals, Mumbai, India.

Preparation of drug-loaded microspheres

PVP, cefadroxil and azobisisobutyronitrile (AIBN) were dissolved in 50 mL of water-methanol (1 : 1) mixture taken in a 250-mL round bottom flask equipped with a reflux condenser and a nitrogen inlet. Nitrogen gas was bubbled through the system for 20 min. The monomer MMA (2 g) and crosslinker EGDMA (0.5 wt % based on MMA) mixture was added to the above reaction mixture, stirred well at 100 rpm and heated to 70°C. Turbidity was observed within the first 30 min, but the reaction was continued for 8 h. At the end of the reaction time, drug-loaded microspheres were isolated by centrifugation at the rotor speed of 18,000 rpm. Particles were washed with methanol to remove the unreacted monomer and isolated particles were dried at 40°C. In preparing the indomethacin-loaded microparticles, indomethacin was first dissolved in MMA-EGDMA mixture and the mixture was added to methanol-water medium. However, the plain particles were prepared under the same condition as in the absence of drug.

Differential scanning calorimetric studies

DSC thermograms of plain drug, plain microspheres, and drug-loaded microspheres were recorded using a Rheometric Scientific, Model DSC-SP, UK. Thermograms were recorded from 20 to 400°C at the heating rate of 10°C/min under an inert nitrogen atmosphere.

X-ray diffraction studies

X-ray diffractograms of the plain and drug-loaded microspheres were recorded on a Rigaku Geigerflex diffractometer equipped with a Ni-filtered CuKα radiation ($\lambda = 1.5418$ Å). The particles were mounted on a sample holder and spectra were recorded in the angle range of 10°–50° at a speed of 5°/min to estimate the crystallinity of the samples.

Scanning electron microscopic studies

SEM images of the drug-loaded microspheres were recorded using a JSM 6400 scanning electron microscope (Japan) at the required magnification. A working distance of 39 mm was maintained and acceleration voltage used was 20 kV with the secondary electron image (SEI) as a detector.

Estimation of drug loading and encapsulation efficiency

Encapsulation efficiency of cefedroxil and indomethacin loaded microparticles was determined by UV spectrophotometer at λ_{max} of 240 and 320 nm, respectively. A 10 mg of cefadroxil-loaded microspheres were placed in 10 mL of buffer solution and stirred vigorously for 48 h to extract the drug from polymeric microspheres. Indomethacin-loaded drug microspheres were placed in dichloromethane and 10 mL of phosphate buffer solution was added to it and stirred

TABLE I
Encapsulation Efficiency (%) and Mean Size of PMMA Microspheres for Different Formulations Containing Indomethacin

Formulation code	MMA (g)	PVP (%)	Indomethacin (%)	Encapsulation efficiency (%)
MMIN-5	1	2	5	76
MMIN-10	1	2	10	79
MMIN-15	1	2	15	84

vigorously to extract the drug. Dichloromethane was evaporated by gentle heating and the aqueous solution was analyzed at λ_{max} of 320 nm using the UV spectrophotometer (model Anthelie, Secomam, Dumont, France). The results of percentage encapsulation efficiency were calculated using eq. (1). These results are listed in Tables I and II, respectively.

$$\% \text{ Encapsulation efficiency} = \left(\frac{\text{Actual loading}}{\text{Theoretical loading}}\right) 100 \quad (1)$$

In vitro release study

Dissolution was carried out using the tablet dissolution tester (LabIndia, Mumbai, India) equipped with eight glass baskets. Dissolution rates were measured at 37°C below 100 rpm speed. Drug release from the microspheres was studied in intestinal (7.4 pH phosphate buffer) fluids. Aliquot samples were withdrawn at regular time intervals and analyzed by UV spectrophotometer as discussed before.

RESULTS AND DISCUSSION

Differential scanning calorimetry

The presence of PVP on PMMA particles was confirmed by DSC (DSC thermograms of PMMA particles are shown in Fig. 1 (A)). DSC curve of PVP showed an endotherm around 185°C, indicating its glass transition temperature (T_g). DSC thermograms of PMMA-PVP microparticles have an endotherm around 185°C representing the T_g of PVP. This indicates that PVP used as a stabilizer is coated on the surface of PMMA particles. The stabilizer used in polymerization was coated onto PMMA particles, thus preventing the macroscopic precipitation of polymeric debris.

DSC curves of cefadroxil, cefadroxil-loaded microspheres and plain microspheres are displayed in Figure 1(B). Exothermic transition of cefadroxil was observed at 207.4°C. However, no characteristic peak of cefadroxil was observed in the DSC curves of drug-loaded microspheres, suggesting that drug is highly dispersed in the polymer matrix. DSC tracings of indomethacin, indomethacin-loaded microspheres and plain microspheres are displayed in Figure 1(C). The onset melting peak of indomethacin was observed at 160°C. However, no characteristic peak of indomethacin was observed in the DSC curves of the drug-loaded microspheres, suggesting that drug is highly dispersed in the polymer matrix.

X-ray diffraction studies

X-RD diffractograms of cefadroxil, plain PMMA-PVP and cefadroxil-loaded microspheres are displayed in Figure 2. These curves reveal the crystalline nature of the drug after encapsulation by microspheres. Cefadroxil has shown characteristic intense peaks between 2θ of 10° and 25° due to its crystalline nature. However, the peaks observed for plain drug were masked in the drug-loaded microspheres. The X-RD diffractograms recorded for plain microspheres and cefadroxil-loaded microspheres did not show any characteristic peak of the drug, indicating that encapsulated drug is in the amorphous state.

Scanning electron microscopy

SEM micrographs of PMMA microparticles shown in Figure 3 indicate the formation of spherical particles with a size of around 5 μm as obtained from the dispersion polymerization. Dispersion polymerization has thus an advantage of preparing spherical microparticles in the presence of a steric stabilizer such as PVP. In the earlier literature, dispersion polymerization was employed to prepare microparticles for drug delivery applications as well as to prepare nano-sized conducting polymeric particles.[14–17] Even though the spherical shape was maintained, a close look at the SEM image of a single particle indicates the formation of a rough surface, possibly due to the formation of the mixture of linear and crosslinked polymer chains in the microparticles.[18]

In vitro release study

Effect of drug concentration

Figure 4 displays the *in vitro* drug release characteristics of formulations containing different amounts of indomethacin in PMMA microspheres prepared with 2% of PVP as stabilizer. Each data point was obtained

TABLE II
Encapsulation Efficiency (%) and Mean Size of PMMA Microspheres with Different Formulations Containing Cefadroxil

Formulation code	MMA (g)	PVP (%)	Cefadroxil (%)	Encapsulation efficiency (%)
MMACF-20	1	2	20	58
MMACF-40	1	2	40	62
MMACF-60	1	2	60	65
MMAPVP-1	1	1	20	54
MMAPVP-2	1	4	20	66

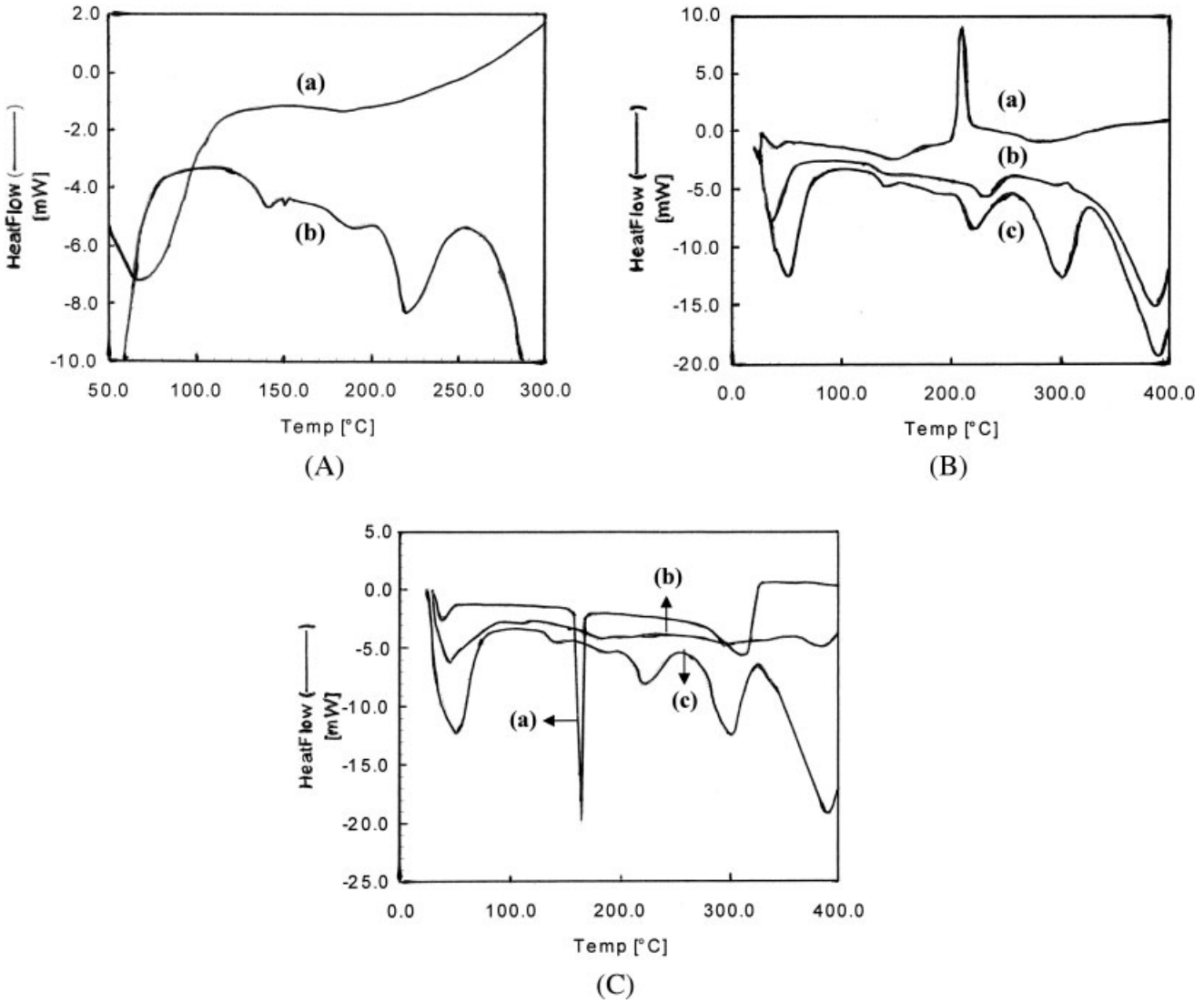

Figure 1 (A) DSC thermograms of (a) PVP and (b) PMMA-PVP microspheres; (B) DSC thermograms of (a) cefadroxil, (b) cefadroxil loaded microspheres, and (c) PMMA-PVP plain microspheres; (C) DSC thermograms of (a) indomethacin, (b) indomethacin loaded microspheres, and (c) PMMA-PVP plain microspheres.

as the average of at least three replications with standard deviation being 3%. Release rates were faster for formulations containing higher percentage of indomethacin than those microparticles containing the lower amount of drug. However, release curves vary almost identically up to 600 min without showing any burst effect. The release became slow after about 500 min of dissolution runs. After about 600 min, nearly 100% release was achieved.

In case of cefadroxil-PMMA microspheres (see Fig. 5), release was much faster from the microspheres containing higher amount (i.e. 60%) of cefadroxil than those containing lower amount (i.e. 20%) of drug. Notice that drug release reached equilibrium much faster than indomethacin-loaded microparticles, probably due to hydrophilic nature of the drug. Comparatively, better encapsulation efficiency and prolonged drug release patterns were observed for hydrophobic indomethacin than hydrophilic cefadroxil. This could be due to the fact that indomethacin was mixed with MMA monomer and then added to polymerization medium; whereas, cefadroxil was dissolved in the polymerization medium along with monomer and initiator. Indomethacin, being a hydrophobic drug, will be solubilized in methylmethacrylate during the loading step and it will then be encapsulated into the hydrophobic PMMA. However, smaller level interactions between PMMA and cefadroxil might have led to smaller encapsulation efficiency. Most of the drug has adhered to the surface of the microspheres.

Effect of PVP content

Effect of PVP content on encapsulation efficiency and *in vitro* release of cefadroxil was investigated. *In vitro*

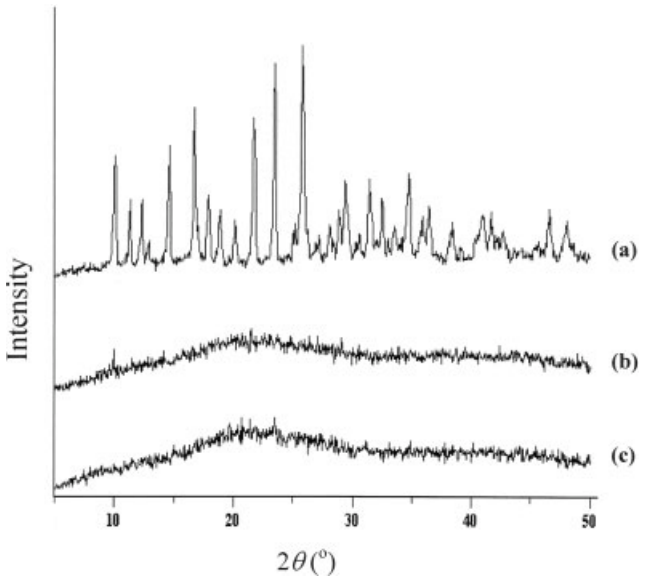

Figure 2 X-RD spectra (a) cefadoxil, (b) plain PMMA-PVP microspheres, and (c) cefadroxil-loaded microspheres.

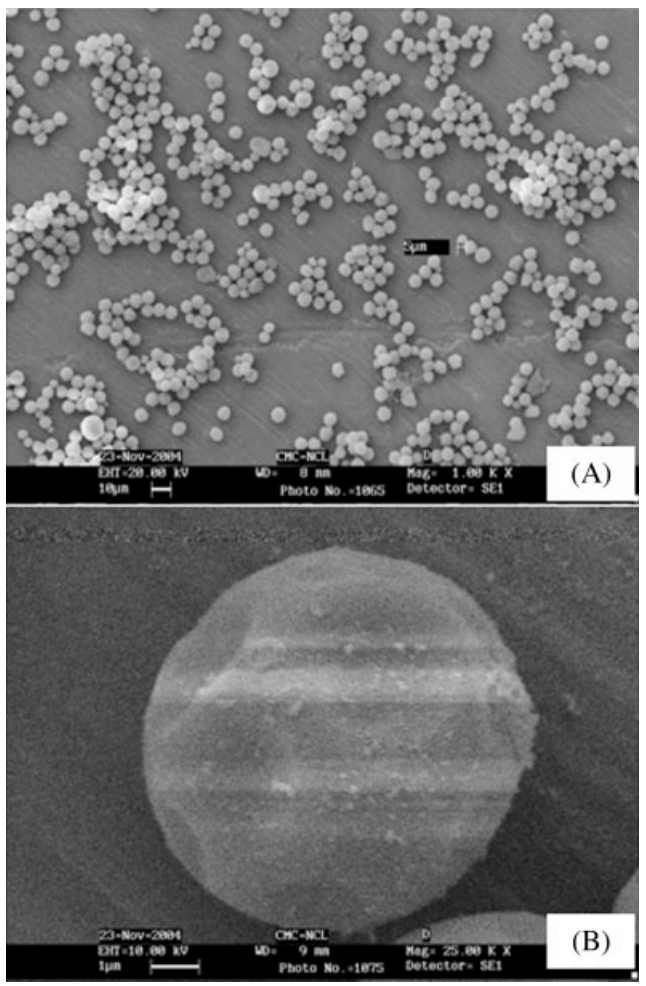

Figure 3 Scanning electron micrographs of plain PMMA-PVP microspheres: (A) group of microspheres and (B) single microsphere.

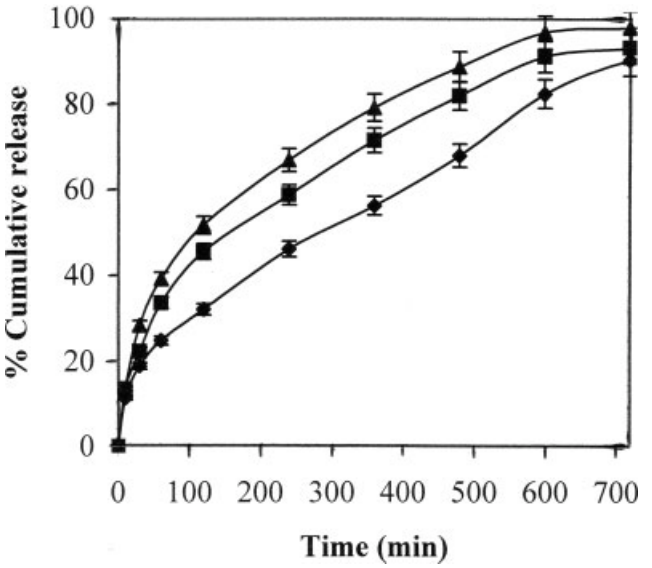

Figure 4 Percentage cumulative release of indomethacin through PMMA microspheres containing different amount of indomethacin: (◆) 5%, (■) 10%, and (▲) 15% and 2% PVP as stabilizer.

release profiles of cefadroxil from formulations prepared by taking different amounts of PVP and 20% of cefadroxil are shown in Figure 6. Faster release rates were observed from formulations prepared with higher amount of PVP (i.e. 4%) than those formulations prepared using a lower amount of PVP, that is, 1%. About 98% of the drug was released within the first 10 h from formulations prepared with higher amount of PVP, whereas only 77% of cefadroxil was released within 10 h from formulations prepared with a lower amount of PVP. Faster drug release observed from formulations prepared with higher amount of

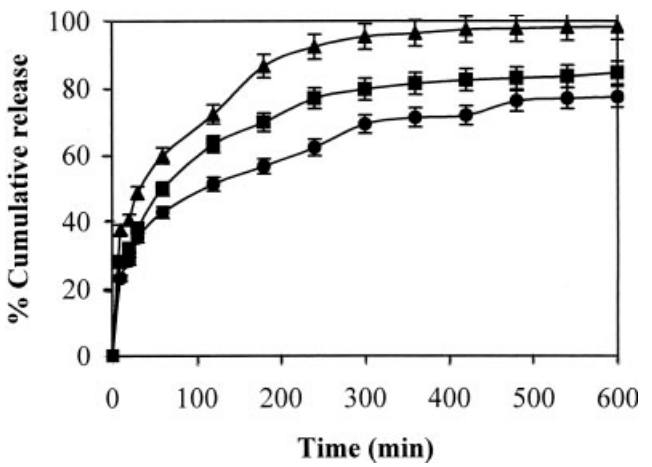

Figure 5 Percentage cumulative release of cefadroxil through PMMA microspheres containing different amount of cefadroxil content with 2% PVP content: (●) 20%, (■) 40%, and (▲) 60% of cefadroxil.

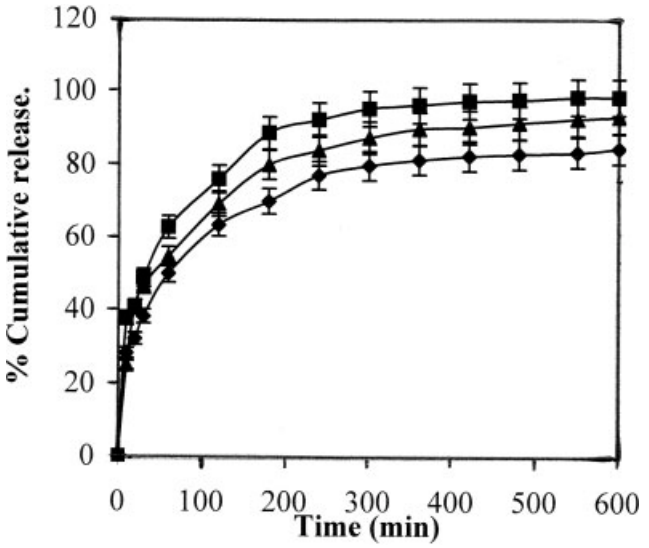

Figure 6 Percentage cumulative release of cefadroxil through PMMA microspheres containing different amounts of PVP with 20% cefadroxil: (◆) 1%, (■) 2%, and (▲) 3% of PVP.

PVP is due to the coating of higher amount of PVP onto PMMA particles.

Drug release kinetics

Drug release kinetics was analyzed by plotting the cumulative release data versus time and by fitting these data to an exponential equation of the type[19]:

$$\left(\frac{M_t}{M_\infty}\right) = kt^n \qquad (2)$$

Here, M_t/M_∞ represents the fractional drug release at time t; k is a constant characteristic of 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; these data are given in Table III. If $n = 0.5$, drug diffuses and releases from the polymer matrix following the Fickian diffusion. For $n > 0.5$, anomalous or non-Fickian type drug diffusion occurs. If $n = 1$, non-Fickian or Case II release kinetics is operative. The intermediary values ranging between 0.5 and 1.0 are attributed to an anomalous type of transport trend.[19] In the present study, the values of n range between 0.26 and 0.50, indicating a Fickian transport. The correlation coefficients, r, values are in the range of 0.972 to 0.996, suggesting a good fit of experimental release data.

TABLE III
Release Kinetics Parameters of Different Formulations

Formulation code	K	n	Correlation coefficients, r
MMAPVP-1	0.122	0.296	0.993
MMAPVP-2	0.204	0.260	0.972
MMACF-20	0.089	0.335	0.974
MMACF-40	0.082	0.287	0.976
MMACF-60	0.149	0.310	0.980
MMIN-5	0.035	0.479	0.992
MMIN-10	0.050	0.449	0.996
MMIN-15	0.048	0.455	0.981

CONCLUSIONS

In this investigation, two model drugs, namely, cefadroxil and indomethacin were chosen to encapsulate into PMMA-PVP microspheres during *in situ* dispersion polymerization. Spherically shaped monodisperse drug-loaded PMMA microspheres coated with PVP were successfully prepared. Higher encapsulation efficiency was obtained with hydrophobic indomethacin than for hydrophilic cefadroxil. *In vitro* drug release studies indicated that the release of cefadroxil was controlled up to 10 h, whereas indomethacin release was controlled up to 12 h. Release profile studies indicated that both the drugs could be loaded *in situ* dzuring the polymerization step into the matrices without altering their properties. The release kinetics data indicated the presence of Fickian transport.

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