

Preparation and characterization of nimesulide loaded poly (methyl methacrylate)/poly (ethylene oxide) blend microspheres: *In vitro* release studies

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Poly (methyl methacrylate)/poly (ethylene oxide) (PMMA/PEO) blend microspheres were prepared by solvent evaporation technique using poly (vinyl alcohol) (PVA) as a stabilizer. Nimesulide, an arthritis drug was successfully loaded into these microspheres. The effect of experimental variables such as ratio of poly (methyl methacrylate) to poly (ethylene oxide) on nimesulide encapsulation efficiency, release rate, size, and morphology of the microspheres has been investigated. Nimesulide loaded microspheres were analyzed using Fourier transform infrared (FTIR), differential scanning calorimetry (DSC), X-ray diffraction (X-RD), and scanning electron micrograph (SEM). FTIR spectroscopy was used to explain the blending of polymers. DSC and X-RD techniques were used to investigate the crystalline nature of the drug after encapsulation. DSC and X-RD results indicated a nonuniform dispersion of nimesulide in the PMMA/PEO blend matrix. SEMs indicated the formation of spherical microspheres with distinct size. Nimesulide was successfully encapsulated up to 85% in the polymeric matrices. *In vitro* dissolution experiments performed in pH 7.4 buffer medium indicated a controlled release of nimesulide from blend microspheres up to 12 h.

Key words: *In vitro* release, microspheres, nimesulide, poly (ethylene oxide) and poly (methyl methacrylate)

INTRODUCTION

To develop oral drug delivery systems, it is necessary to optimize both the residence time of the system within the gastrointestinal tract and release rate of drug from the system. The polymeric microparticulate drug delivery systems are being continuously under investigation for the controlled release (CR) of drugs from oral route when compared to single unit dosage forms. Advantages of microspheres for the oral delivery of drugs over the conventional dosage form approaches have been reported by Abu-izza *et al.*^[1] A uniform distribution of multiunit dosage form along the gastrointestinal tract (GIT) could result in more reproducible drug absorption and reduced risk of local irritations than the use of single-unit dosage forms.^[2] These particles protect the liable compound (e.g., proteins and peptides) from degradation in the GIT.^[3] Several methods have been described in the

literature on the preparation of microspheres and these includes solvent evaporation,^[4] phase separation,^[5] spray-dying,^[6] and *in situ* polymerization.^[7] Of these, solvent evaporation method has been the most widely used technique due to its good reproducibility and versatility to render desired properties to the microspheres. This method involves emulsification followed by the removal of solvent via extraction and evaporation. Therefore, it is necessary to monitor and understand independent process parameters that influence the end product.

Poly (methyl methacrylate) (PMMA) has wide spread biomedical applications, due to its biocompatibility. Various nondegradable polymers, for example, PMMA have been utilized for antibiotic delivery purposes. Antibiotic loaded poly (methyl methacrylate) (PMMA),

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is extremely used as a nondegradable antibiotic delivery system for the treatment of osteomyelitis.^[8-11] The antibiotic loaded bone cement based on PMMA has been used to prevent bone infection in total or joint arthroplasty.^[12-15] The nondegradability of PMMA has the inherent limitation that the polymer material remains intact inside the body even after its proposed application without any side effects. Poly (methyl methacrylate) has been widely used for drug delivery applications.^[16-20]

Polyethylene oxide (PEO) is a nontoxic and water soluble polymer, widely used in chemical, cosmetic, and pharmaceutical industries. PEO gels produced in water can be dehydrated and the material produced is extremely hydrophilic and possesses a good bioadhesive property.^[21] Due to its properties, PEO is used in various drug delivery systems. Christine *et al.*, have reported PEO blend copolymer micelles as a delivery vehicle for dihydrotestosterone.^[22] Zeng *et al.*, have also reported PEO blend nanoparticles with crosslinked cores as drug carrier.^[23] PEO is a good drug delivery vehicle in pharmaceutical industries.^[24,25]

The polymer blending technique can offer versatile and useful routes for improving polymeric material properties; it has been employed and applied for many polymeric systems.^[26] A broad range of studies on miscibility,^[27,28] crystallization,^[29,30] structure,^[31] and dynamics^[32] for PEO/PMMA system have been investigated. PEO/PMMA blends have been reported as marginally miscible^[33] with a weak enthalpic interaction,^[34] implying that it can often be immiscible in certain temperature and composition ranges.^[27] The miscibility of this blend is strongly dependent on the toxicity of PMMA.^[35] According to Rao *et al.*,^[36] such compatibility can be attributed to the physical interaction (e.g., van der Waals type) rather than the chemical interaction (e.g., hydrogen bonding).

Nimesulide is a potential nonsteroidal anti-inflammatory drug known to provide better activity profile, greater safety, and higher therapeutic index.^[37] Nimesulide belongs to the class-II biopharmaceutical classification and a low solubility high permeability drug.^[38,39] Nimesulide is a weak inhibitor of prostaglandin synthesis *in vitro* and it appears to show its effects by a variety of mechanisms like free-radical scavenging, involving in neutrophil myeloperoxidase pathway, phosphodiesterase type IV inhibition, histamine release, tumor necrosis factor- α release, cartilage degradation, bradykinin activity, metalloprotease synthesis, platelet aggregation, and synthesis of platelet activity factor.^[40-42] Dutet *et al.*, and Ravikumar *et al.*, used the nimesulide in control drug delivery.^[43,44] Nimesulide produces gastric irritation in some cases and shows loss of its inhibitory cyclooxygenase-2 (COX-2) selectivity.^[45,46] Nimesulide is sparingly soluble in water (0.01 mg/mL). This poor aqueous solubility would create difficulties in pharmaceutical formulations for oral and parenteral

delivery that in turn may lead to variable bioavailability.^[39] To overcome some of these drawbacks, we have planned to utilize PMMA and PEO to encapsulate nimesulide and synthesize microparticles for drug release in a controlled manner.

Though there are several reports present on PMMA/PEO blends for different applications; none have used these blends for drug delivery application. In continuation of our ongoing research work on drug delivery studies,^[20] we aimed to prepare biodegradable blend microspheres consisting of PMMA and PEO, by taking different amounts of PMMA as well as PEO in the matrix. Nimesulide was loaded into the PMMA/PEO blend microspheres using poly (vinyl alcohol) (PVA) as a stabilizer cum emulsifier to produce drug loaded microspheres of uniform size. The microspheres were characterized by Fourier transform infrared (FTIR) spectroscopy, scanning electron microscope (SEM), X-Ray diffraction (X-RD), and differential scanning calorimetry (DSC). The dissolution experiments were performed to study the drug release characteristics of the microspheres.

MATERIALS AND METHODS

PEO and PMMA was purchased from Aldrich, Milwaukee, WI, USA. PVA was purchased from S. D. Fine Chemicals, Mumbai, India. A model drug nimesulide was obtained as a gift sample from Dr. Reddy's Laboratory, Hyderabad. Dichloromethane was purchased from S.D. Fine Chemicals, Mumbai.

Preparation of poly (methyl methacrylate)/poly (ethylene oxide) blend microspheres

0.25 g of PMMA and 0.25 g of PEO were dissolved in 10 mL of dichloromethane. After dissolving both the polymers, 50 mg nimesulide drug solution was added. The solution was stirred until homogeneous solution was formed. The resulting blend solution was slowly added into the 100 mL of 1% PVA solution through a glass syringe. The emulsion was stirred at the stirring speed of 400 rpm using Euro Star (IKA Labortechnik, Germany) high speed stirrer for 3 h. The solvent was evaporated using rota evaporator. The resulting product was washed twice with 10 mL of distilled water and the separated microspheres were dried overnight at 40°C. Similarly different ratios of microsphere formulations were prepared and are listed in Table 1. The microspheres were kept in desiccator for further analysis.

Characterization techniques

Fourier transform infrared spectroscopy

FTIR spectral measurements were performed using Perkin Elmer spectrophotometer to confirm the blending of the two polymer matrix. The interpenetrating polymer networks (IPN) particles were finely grinded with the KBr to prepare pellets under a hydraulic pressure of 700 dynes/m² and spectra were scanned between 4,000 and 400 cm⁻¹.

Differential scanning calorimetry studies

DSC curves of the placebo PMMA/PEO microspheres, plain drug, and drug loaded microspheres were recorded using Rheometric scientific DSC (Model-DSC SP, UK). The analysis was performed by heating the sample from 30 to 350°C at the rate of 10°C/min under inert atmosphere.

X-Ray diffraction 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 0-50° at a scanning rate of 5°/min to determine the crystallinity.

Scanning electron microscopic studies

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

Estimation of drug loading and encapsulation efficiency

Specific amount of drug loaded dry microspheres were vigorously stirred in a beaker containing 10 mL of 7.4 pH buffer solution to extract the drug from microspheres. The solution was then filtered and analyzed by ultraviolet (UV) spectrophotometer at the λ_{max} of 398 nm. These results of % nimesulide loading and encapsulation efficiency were calculated using Equations (1) and (2). These results are compiled in Tables 1 and 2, respectively.

% Drug loading

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

% Encapsulation efficiency

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

In vitro release

In vitro release studies have been carried out by dissolution experiments using the tablet dissolution tester (LabIndia, DS 8000, Mumbai, India) equipped with eight baskets peddle without peak vessel. Dissolution rates were measured at 37°C under 100 rpm rotation speed in 600 mL dissolution medium. Drug release from the microspheres was studied in intestinal (7.4 pH phosphate buffer) fluids. At regular intervals of time, aliquot samples were withdrawn, and analyzed using UV spectrophotometer at fixed λ_{max} value of 398 nm.

RESULTS AND DISCUSSIONS

Fourier transform infrared spectroscopy

Figure 1a shows the FTIR spectrum of pure PEO. The peak at

Table 1: Results percentage of encapsulation efficiency of different formulations

| Formulation code | % PMMA (w/w) | % PEO (w/w) | Nimesulide (w/w) | Encapsulation efficiency (%) |
|------------------|--------------|-------------|------------------|------------------------------|
| PMMA/PEO-1 | 50 | 50 | 10 | 72.3 \pm 0.5 |
| PMMA/PEO-2 | 50 | 50 | 20 | 75.2 \pm 1.2 |
| PMMA/PEO-3 | 50 | 50 | 30 | 79.5 \pm 0.9 |
| PMMA/PEO-4 | 60 | 40 | 10 | 64.8 \pm 0.8 |
| PMMA/PEO-5 | 60 | 40 | 20 | 70.4 \pm 1.0 |
| PMMA/PEO-6 | 60 | 40 | 30 | 76.2 \pm 1.2 |
| PMMA/PEO-7 | 70 | 30 | 10 | 62.3 \pm 0.9 |
| PMMA/PEO-8 | 70 | 30 | 20 | 65.7 \pm 1.1 |
| PMMA/PEO-9 | 70 | 30 | 30 | 68.8 \pm 0.6 |

PMMA/PEO: Poly (methyl methacrylate)/poly (ethylene oxide)

Table 2: Results of *k*, *n*, and correlation coefficient (*r*) values

| Formulation codes | <i>k</i> | <i>n</i> | Correlation coefficient, <i>r</i> |
|-------------------|----------|----------|-----------------------------------|
| PMMA/PEO-1 | 0.1538 | 0.7759 | 0.9407 |
| PMMA/PEO-2 | 0.6668 | 0.4469 | 0.9768 |
| PMMA/PEO-3 | 0.2472 | 0.7481 | 0.9853 |
| PMMA/PEO-4 | 0.1618 | 0.7180 | 0.9592 |
| PMMA/PEO-5 | 0.3866 | 0.8824 | 0.9304 |
| PMMA/PEO-6 | 0.5601 | 0.4856 | 0.9297 |
| PMMA/PEO-7 | 0.6959 | 0.4524 | 0.8912 |
| PMMA/PEO-8 | 0.0675 | 0.6793 | 0.9701 |
| PMMA/PEO-9 | 0.1068 | 0.7014 | 0.9851 |

PMMA/PEO: Poly (methyl methacrylate)/poly (ethylene oxide)

2894 cm⁻¹ shows the -C-H asymmetric stretching frequency. The peak at 1132 cm⁻¹ shows the -C-O symmetric stretching frequency. In Figure 1b, the peaks at 2920 and 1735 cm⁻¹ shows asymmetric stretching of -C-H and the -C=O stretching frequency of ester group in PMMA; whereas in Figure 1c, the peak at 2997 cm⁻¹ shows asymmetric stretching frequency and 1742 cm⁻¹ peak shows the -C=O symmetric stretching frequency of ester in poly (methyl methacrylate), whereas the most intense peak at 1080 cm⁻¹ indicated the -C-O symmetric stretching frequency. In Figure 1c, the shifting of -C-H, -C=O, and more intense -C-O peaks indicated both the groups of PMMA/PEO are present in blended polymer microspheres, and it clearly explained the blending of two polymers. In Figure 1d the -C=O (1736 cm⁻¹) stretching frequency is decreased due to the formation of hydrogen bonding interaction between drug molecules and polymer chains (C=O group of ester and NH group of drug molecules).

Differential scanning calorimetry studies

Figure 2 shows DSC thermograms of plain nimesulide (a), plain PMMA/PEO microspheres (b), and nimesulide loaded PMMA/PEO microspheres (c) were recorded. DSC thermographs suggest that nimesulide shows an onset melting peak at 153.98°C [Figure 2a]. In the microspheres, drug fusion peak was shifted to lower temperature with

reduced intensity indicating a significant reduction of the drug crystallinity due to incorporation into polymeric matrix.

Scanning electron microscopic studies

Figure 3 shows SEMs of the nimesulide loaded PMMA/PEO microspheres. The microspheres are found to be distinct spherical in shape and surface of the particle is smooth.

X-Ray diffraction 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 blended microspheres. X-RD patterns recorded for plain nimesulide drug (a), placebo polymeric microparticles (b), and drug-loaded microspheres (c) are shown in Figure 4. The nimesulide peaks are observed at 2θ of 19°, 21°, and 23° suggesting its crystalline nature. But, these peaks are almost disappeared

in case of drug loaded microspheres confirming a significant reduction of its crystallinity as suggested by DSC analysis. On the basis of DSC and X-RD results, it could be concluded that incorporation of the drug into PMMA/PEO microspheres resulted in almost complete amorphization of the drug.

Encapsulation efficiency

The EE of all formulations depends on the amount of drug content and polymer composition. The results of % EE values are given in Table 1. These results indicated that % of EE increases with increasing drug loading. The EE of formulation containing 50:50 PMMA/PEO with varying drug content in the microspheres, that is, 10, 20, and 30 wt% have ranged from 72.3 to 79.5%. The EE of formulations (PMMA/PEO-1, PMMA/PEO-4, and PMMA/PEO-7) containing constant drug content (10%) with varying amount of PEO 30, 40, and 50 wt% have between 62.3 and 72.3. Thus, EE of the formulations increased with increasing amount of PEO in

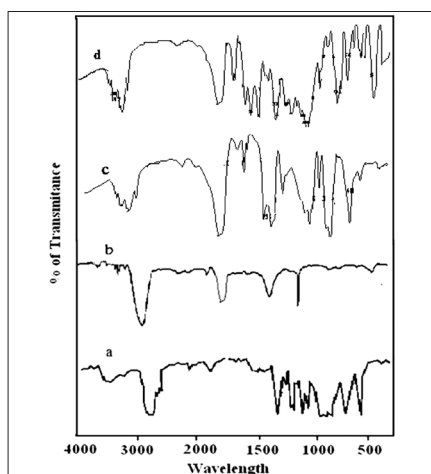


Figure 1: Fourier transform infrared spectra of (a) Pure poly (ethylene oxide) (b) Pure poly (methyl methacrylate), (c) Pure PMMA/PEO blend microspheres, and (d) Drug loaded PMMA/PEO blend microspheres

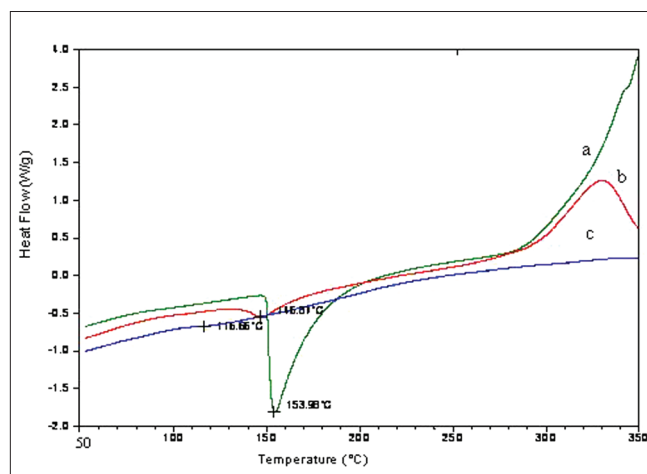


Figure 2: Differential scanning calorimetry thermograms of (a) Pure nimesulide drug, (b) Drug loaded PMMA/PEO blend microspheres, and (c) Pure PMMA/PEO blend microspheres

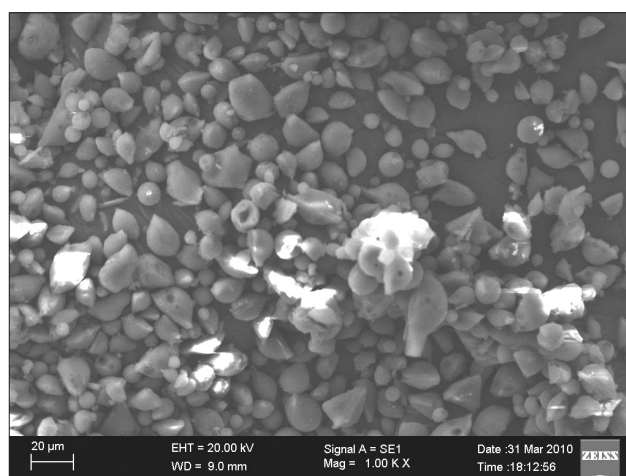


Figure 3: Scanning electron microscopy photographs of PMMA/PEO blend microspheres

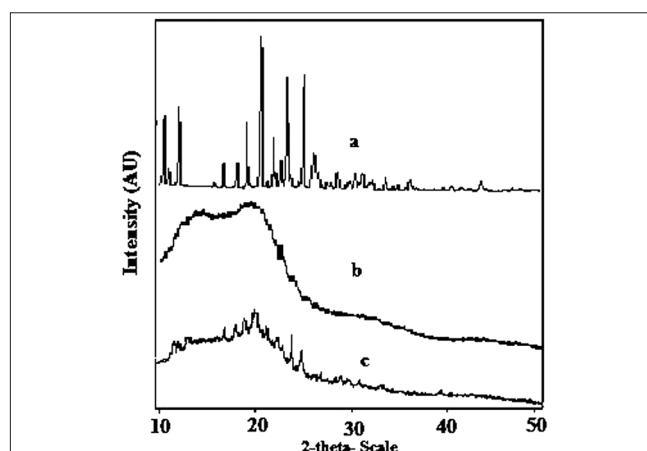


Figure 4: X-ray diffraction (X-RD) spectra of (a) Pure nimesulide drug, (b) Pure PMMA/PEO microspheres, and (c) Drug loaded PMMA/PEO microspheres

the microspheres.

Effect of PEO content

The effect of PEO content on encapsulation efficiency and *in vitro* release of nimesulide was investigated. *In vitro* release profiles of 10 wt% nimesulide in formulations prepared by taking different amounts of PEO are shown in Figure 5. Faster release rates were observed from formulations prepared with higher amount of PEO, that is, 50 wt% than those formulations prepared using lower amount of amount of PEO, that is, 30 wt%. About 80% of nimesulide was released within 12 h from formulations prepared with higher amount of PEO, whereas only 68% of nimesulide was released within 12 h from formulations containing lower amount of PEO. A faster drug release was observed from formulations with higher amount of PEO is due to higher swelling of the blend microspheres. PMMA is hydrophobic in nature, whereas PEO is hydrophilic. The hydrophilic nature

of the blend system increases as the amount of PEO in the blend system increases, thus resulting in an excess swelling of the microspheres, thereby leading to a faster release of nimesulide.

Effect of drug loading

Figures 6-8 shows the release profiles of nimesulide loaded microspheres of PMMA/PEO microspheres at different amounts of drug loading. These formulations exhibited EE in the range of 62.3-79.5%, which is due to lesser solubility of nimesulide in the polymer solution. Lesser encapsulation efficiency is observed due to the loss of nimesulide in the PVA solution. Release data showed that formulations containing highest amount of nimesulide (30 wt%) displayed higher release rates than those containing lower amount of nimesulide. Formulation containing highest amount of nimesulide released 79.5% of the total encapsulated drug. On the other hand, formulations containing lower amount

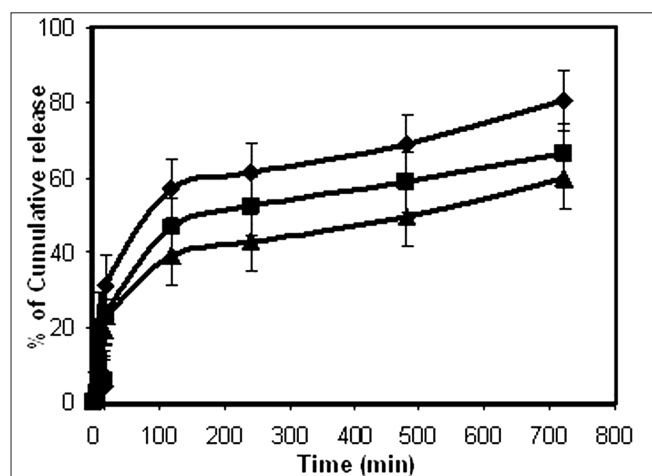


Figure 5: Percentage cumulative release of nimesulide through PMMA/PEO blend microspheres containing different amount PEO: (♦) 50% PMMA, (■) 40% PMMA, and (▲) 30% PMMA at pH 7.4

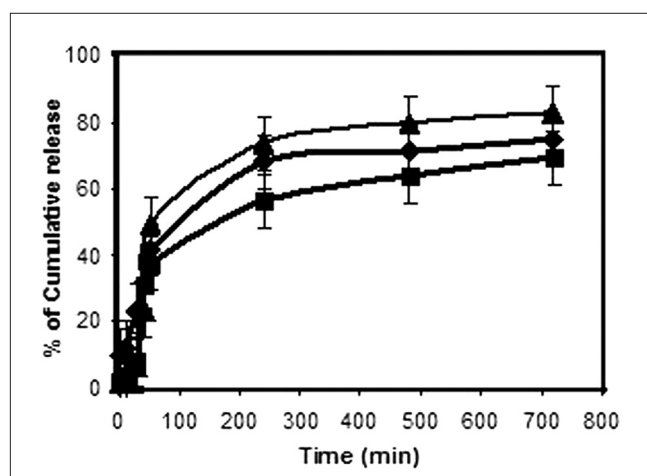


Figure 6: Percentage cumulative release of nimesulide through (50:50) PMMA/PEO blend microspheres containing different amounts of drug: (▲) 30% nimesulide (♦) 20% nimesulide (■) 10% nimesulide at pH 7.4

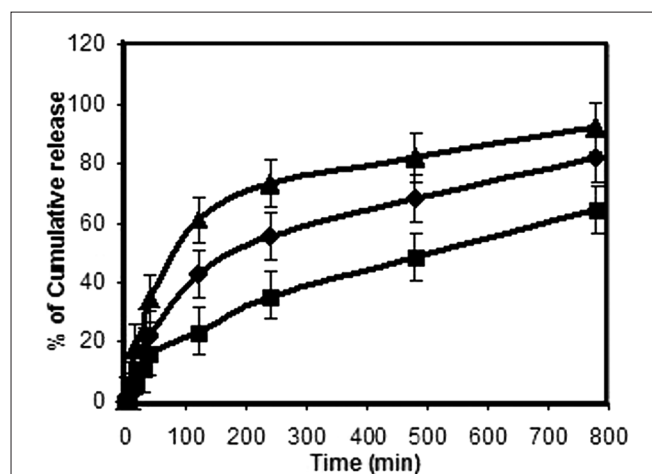


Figure 7: Percentage cumulative release of nimesulide through (60:40) PMMA/PEO blend microspheres containing different amounts of drug: (▲) 30% nimesulide, (♦) 20% nimesulide, and (■) 10% Nimesulide at pH 7.4

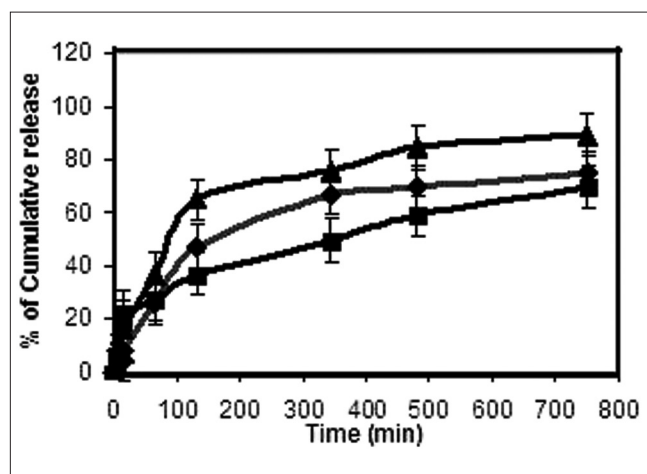


Figure 8: Percentage cumulative release of nimesulide through (70:30) PMMA/PEO blend microspheres containing different amounts of drug: (▲) 30% nimesulide, (♦) 20% nimesulide, and (■) 10% Nimesulide at pH 7.4

of nimesulide have released only 62.3% of nimesulide. Thus, sustained release was observed for the formulation containing lower amount of nimesulide. Thus, the release rates are slower for lower amount nimesulide in the matrix, probably due to the availability of more free void spaces through which a lesser number of drug molecule will transport. For all the nimesulide-loaded formulations, a prolonged release of nimesulide occurred for about 720 min.

Drug release kinetics

Drug release kinetics was analyzed by plotting the cumulative release data vs time by fitting to the empirical equation.^[47]

$$M_t/M_\infty = kt^n \quad (3)$$

Here; M_t/M_∞ represents the fractional drug release at time t , k is a constant characteristic of the drug-polymer system, and n is an empirical parameter characterizing the release mechanism. Using the least squares procedure, we have estimated the values of n and k for all the seven formulations and these values are given in Table 2. If $n = 0.5$, then drug diffuses and releases from the polymer matrix following a Fickian diffusion. For $n > 0.5$, anomalous or non-Fickian type drug diffusion occurs. If $n = 1$, a completely non-Fickian is operative. The intermediary values ranging between 0.5 and 1.0 are attributed to the anomalous type transport.^[45]

In the present research, values of k and n showed a dependence on the extent of PEO content as well as percentage of drug loading of PMMA-PEO blend microspheres. Values of n for microspheres prepared using varying amounts of PEO (30, 40, and 50 wt%) keeping nimesulide constant (20 wt%) have ranged from 0.4469 to 0.6793. The nimesulide loaded microspheres have shown n values ranging from 0.4469 to 0.8824 [see Table 2], indicating a shift from erosion type release to swelling controlled non-Fickian transport. Correlation coefficients, r obtained while fitting the release data are in the range of 0.8912-0.9853, but non-Fickian trends are due to a reduction in the regions of low microviscosity and closure of microcavities in the swollen state of the IPN matrix. Similar findings were reported elsewhere.^[48]

CONCLUSION

Blend microspheres of PMMA/PEO were prepared and nimesulide was loaded into the blend microspheres. DSC analysis of the drug loaded microspheres confirmed the molecular level dispersion of drug in the blend microspheres. SEM pictures have shown the formation of distinct spherical microspheres with smooth surfaces. Nimesulide was successfully loaded into the blend microspheres and encapsulation efficiency was found to vary between 62.3 and 79.5%, depending on the blend composition and amount of drug loading. Drug release studies indicated controlled release of nimesulide extended up to 12 h from the blend microspheres.

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