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Preparation and Characterization of Poly (2-hydroxyethyl methacrylate) (PHEMA) Nanoparticles with Possible Applications in Controlled Drug Delivery

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Abstract
The present work describes preparation, structural and morphological characterization of PHEMA nanoparticles. It is found that the nanoparticles are having size up to 100 nm and are almost identical in shape. The small size of nanoparticles makes them a suitable candidate for biomedical and pharmaceutical applications especially to controlled drug delivery field.
Key words : Nanoparticals, PHEM, TEM, SEM

Introduction

The number of reported cases of cancer is steadily increasing in both industrialized and developing countries. The latest world cancer statistics indicate that the number of new cancer cases will increase to more than 15 million in 2020 whereas another report issued by the World Health organization says that there are over 10 million new cases of cancer each year and over 6 million deaths annually are caused by the disease [1]. In spite of the fact that significant progress has been achieved in tumor biology, molecular genetics and in the prevention, detection and treatment of cancer over the last few years, adequate therapy remains elusive due to late diagnosis, inadequate strategies for addressing aggressive metastasis, and the lack of clinical procedures overcoming multi drug resistant (MDR) cancer [2]. The integration of nanotechnology and medicine has the potential to uncover the structure and function of biosystems at the nanoscale level. Nanobiotechnology may provide a reliable and effective tool to treat diseases at a molecular scale. Nanobiotechnology offers an unprecedented opportunity to rationalize delivery of drugs and genes to solid tumors following systemic administration [3]. Examples of nanotechnologies applied in pharmaceutical product development include polymer-based nanoparticles, lipid-based nanoparticles (liposomes, nanoemulsions, and solid-lipid nanoparticles), self-assembling nanostructures such as micelles and dendrimers-based nanostructures among others. In recent years, much research has gone into the characterization of nanoparticles and their biological effects and potential applications. These include bottom-up and molecular self-assembly, biological effects of naked nanoparticles and nano-safety, drug encapsulation and nanotherapeutics, and novel nanoparticles for use in microscopy, imaging and diagnostics [4].

To be successful a cancer treatment approach needs to overcome physiological barriers such as vascular endothelial pores, heterogeneous blood supply, heterogeneous architecture to name just a few and it strongly depends on the method of delivery. In the past, many anticancer drugs had only limited success and had major adverse side effects. Nanoparticles have attracted considerable attention worldwide because of their unique functional characters such as small particle size, high stability, lower toxicity, tunable hydrophilic-hydrophobic balance and the ability to bear surface features for target specific localization, etc. Thus, polymeric nanoparticles constitute a versatile drug delivery system , which can potentially overcome physiological barriers, and carry the drug to specific cells or intracellular compartments by passive or ligand-mediated targeting approaches. The use of some polymers also allows, at least in principle, to achieve controlled release and the sustained drug levels for longer periods of time. Numerous biodegradable polymeric nanoparticles made of natural polymers such as proteins or polysaccharides have been tried for drug delivery and controlled drug release. More recently the focus of such studies moved onto synthetic polymers, and much progress have been achieved in this area. Recent examples include, for example polycationic nanoparticles for encapsulation and controlled release of amphotericin B by *Vieria* and *Carmona-Ribeiro* ; or encapsulation of cur cumin for human cancer therapy by *Maitra et al*.

Ideally, a successful nanoparticulate system should have a high drug loading capacity thereby reducing the quantity of matrix material for administration. The drug may be bound to the nanoparticles either (i) by polymerization in the presence of drug in most cases in the form of solution (incorporation method) or (ii) by absorbing/adsorbing the drug after the formation of nanoparticles by incubating them in the drug solution. In the present work we set to further

investigate the latter method by studying swelling and controlled release of antitumor drug doxorubicin from synthetic PHEMA nanoparticles. PHEMA attracted significant attention and is well documented in the literature. Many useful properties which make PHEMA attractive for a wide range of biomedical applications include high water content, low toxicity and tissue compatibility. PHEMA has been used in applications such as soft contact lenses, drug delivery systems, kidney dialysis membranes, artificial liver support systems and nerve guidance channels. The presence of polar groups of hydroxyl and carboxyl on each repeat unit makes this polymer compatible with water and the hydrophobic α-methyl groups of the backbone convey hydrolytic stability to the polymer and enhance mechanical strength of the polymer matrix. The drug chosen for this study was doxorubicin hydrochloride, which belongs to the family of anti-tumor drugs(Fig.1).. Doxorubicin is a cytotoxic anthracycline antibiotic, it is widely used in the treatment of non-Hodkin's lymphoma, acute lymphoblastic leukemia, breast carcinomas and several other types of cancer. We aimed to design a better PHEMA nanoparticulate delivery system for clinical administration of doxorubicin to achieve higher therapeutic efficacy and reduce side effects, with the overall aim to develop effective oral chemotherapy system.

Materials

2-Hydroxyethyl methacrylate (HEMA) and ethylene glycol dimethacrylate (EGDMA) were purchased from Sigma Aldrich Co. USA. Benzoyl peroxide (BPO) (MERCK) and polyvinyl alcohol (PVA) (Mol. Wt. 14000) (MERCK) were used as the initiator and the stabilizer, respectively. Toluene (MERCK) was used as the diluent. All chemicals were of analytical grade.

Methods

Purification of HEMA

HEMA monomer was purified by using a previously reported method [5]. The purity of distilled HEMA was determined by high-pressure liquid chromatography (HPLC), [Backmen System (Gold 127)] equipped with a ultraviolet detector and a 25 cm × 46 mm id separation columns ODS (C_{18}) of 5 µm particle size. The UV detector was set at 217 nm. The mobile phase was methanol-water (60:40 v/v) and the flow-rate was kept at 1 mL/min. All samples were diluted with pure methanol to 1/1600. 10 µL samples were injected for each analysis. Samples of known concentrations of MAA and EGDMA were injected into the HPLC and the resultant chromatogram was used to construct a standard curve of known concentrations vs. area under the curve. The chromatogram showed two distinct peaks. The first peak, at 3.614 min was identified as MAA. The next peak at 5.503 min was the major peak due to HEMA monomer. The amounts of impurities of MAA and EGDMA in the monomer samples were found to be less than 0.01 mol% MAA and 0.001 mol% EGDMA.

Preparation of PHEMA Nanoparticles

Preparative methods for making nanoparticles for pharmaceutical use are broadly divided into two categories, those based on physiochemical properties such as phase separation and solvent evaporation, and chemical reactions such as polymerization, and polycondensation. In the present study cross-linked PHEMA nanoparticles of defined composition were prepared by using a modified suspension polymerization technique.. In particular, the polymerization was carried out in an aqueous phase containing PVA, which was used as the stabilizing agent. The mixture containing the 12.37 mM HEMA (the monomer), 1.06 mM EGDMA (the cross-linker) and 0.248 mM Bz_2O_2 (the initiator) dispersed in toluene was added into 500 mL conical flask containing the suspension medium (200 mL aqueous PVA solution (0.5% W/V)). The reaction mixture was flushed by bubbling nitrogen and then sealed. The reaction mixture was then placed on magnetic stirrer and heated by vigorous stirring (600-700 rpm) at 80°C for 2 h and then at 90°C for 1 h. The cross-linking reaction was completed within three hours. After cooling, the polymeric particles were separated from the polymerization medium by washing thrice with toluene and twice with acetone. The collected nanoparticles were dried at room temperature to obtain the fine white powder and thereafter stored in airtight polyethylene bags. Doubly distilled water was used throughout the experiments.

Characterization

1.IR Studies

The IR spectra of cross-linked PHEMA nanoparticles were recorded on a FTIR spectrophotometer (Perkin-Elmer,

1000 Paragon) (Shimadzu). While recording FTIR spectra KBr disc method was used for preparation of samples.

2.SEM and Particle Size Analysis

Morphological studies of cross-linked PHEMA nanoparticles were performed on scanning electron micrographs (SEM). SEM observations were carried out with a Philips, 515, fine coater. Drops of the polymeric nanoparticles suspension were placed on a graphite surface and freeze dried. The sample was then coated with gold by ion sputter. The coating was performed at 20 mA for 4 min, and observation was made at 10 KV. Nanoparticles were further characterized by particle size analysis for size and size distribution. The particle size analysis of prepared nanoparticles was performed on a particle size analyzer (Malvern Mastersizer 2000).

Zeta potential studies were performed with a digital potentiometer (Model No. 118, EI Product, Mumbai, India). In a typical experiment 0.1 g nanoparticles were dispersed in 20 mL of respective pH solution and emf was recorded using a compound electrode system. A similar experiment was also repeated for drug-loaded nanoparticles.

Results and Discussion

The FTIR spectra of the pure drug (doxorubicin) and loaded nanoparticles are shown in Fig. 2(a) and 2(b), respectively. The IR spectra (b) of loaded nanoparticles clearly indicate the presence of HEMA as evident from the observed bands at 1728 cm^{-1} (C=O stretching), 1172 cm^{-1} (O-C-C stretching), 3556 cm^{-1} (O-H stretching), 2951 cm^{-1} (asymmetric stretching of methylene group) and 1454 cm^{-1} (O-H bending) respectively. The spectra (b) also mark the presence of drug (doxorubicin) as evident from the observed bands at 1000-1260 cm^{-1} (C-O stretching of alcohol) and 675-900 cm^{-1} (out of plane O-H bending). The resemblance of spectra shown in Fig. 2(a) (the pure drug) and in Fig. 2(b) (loaded nanoparticles) confirms the presence of drug in the loaded nanoparticles.

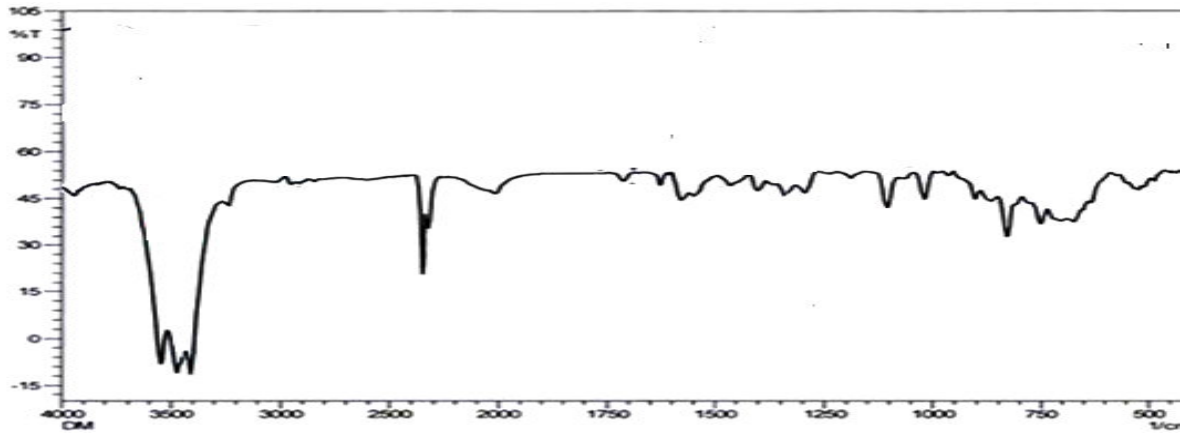

Figure 1 FTIR spectra of PHEMA nanoparticles

SEM Analysis and Particle Size Analysis

The SEM image of nanoparticles is shown in Fig. 2(a), which also reveals the morphology of PHEMA nanoparticles. The size of nanoparticles was estimated using SEM images. Under our experimental conditions it has been shown to vary between 100 and 300 nm. The particle size distribution curve of prepared nanoparticles is shown in Fig. 2(b). The small (defined) size of the nanocarriers' results in the increased surface to volume ratio [20], enhanced frictional forces as well as adsorption. These properties allow nanoparticles to be held in suspension and largely define their biological fate, toxicity and targeting ability, as well as drug loading potential, their stability and drug release properties. The interaction of nanoparticles with living systems depends on their characteristic dimensions. Previously published studies proved the ability of ultra small nanoparticles to translocate throughout the body (see ξ-Potential is the difference in the electrical charge developed between the dense layers of ions surrounding the particles and the charge of the bulk of the suspended fluid surrounding the particle; it gives information about the overall surface charge of the particles.

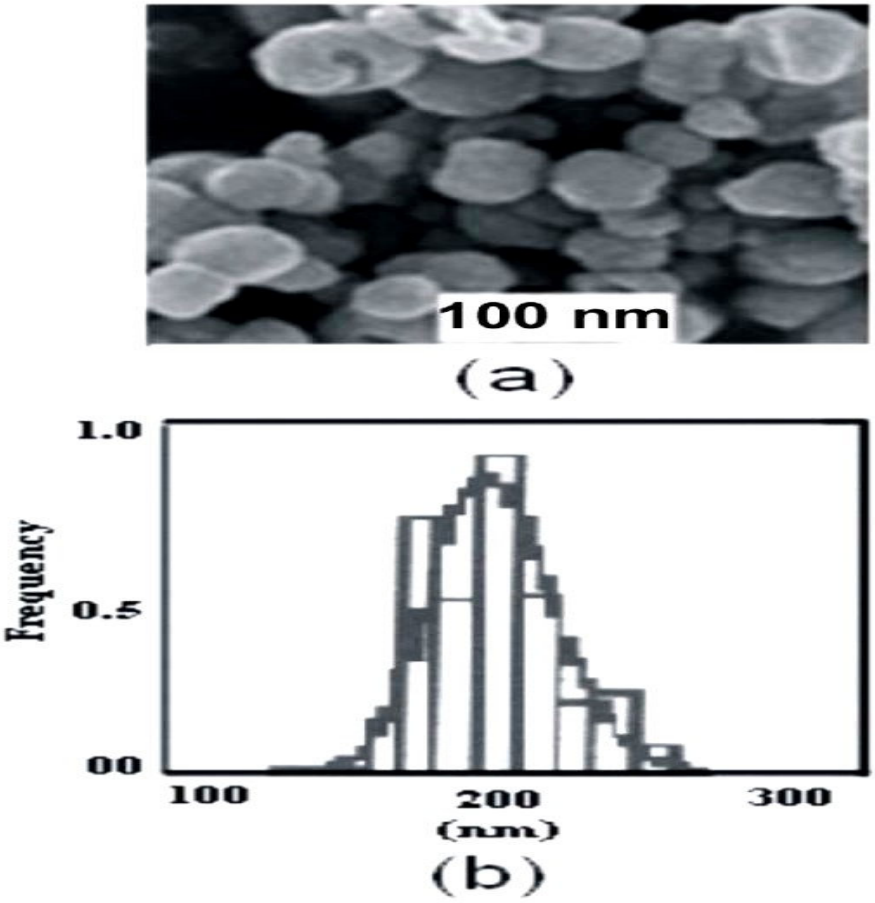

Figure 2 SEM image and particle size distribution curve of PHEMA nanoparticles

Conclusions

The prepared nanoparticles of PHEMA are will within 100 nm and may be employed as carrier for controlled delivery of anticancer and antitumor drugs.

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