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Poly (2-hydroxyethyl methacrylate) (PHEMA) based nanoparticles for drug delivery applications: A review

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ABSTRACT

The nanomaterials exist in nature ever since the earth came into existence. Nature has created these materials in vivid environmental conditions. During the past two decades, extensive research has been carried out on the biomedical applications of nanostructured materials. Nanotechnology-based delivery systems can also protect drugs from degradation or prematured metabolism, and have longer plasma circulation times. If the release mechanism is stimuli-responsive, a therapeutic level of the drug can be sustained over days or even months. biodegradable polymers from which the drug will be released in a sustained manner.

The performance of a polymeric material relies greatly upon the properties of the boundaries in many applications because interactions between the material and its environment occur chiefly at its surfaces. For blood contacting implant devices, it is very important that surface show minimal protein adsorption and it can be achieved by increasing the hydrophilicity of the surface because it reduces protein fouling and improve biocompatibility. Poly (2-hydroxyethyl methacrylate) (PHEMA) is particularly attractive for biomedical engineering applications because of their high water content, non-toxicity and favorable tissue compatibility and its physical properties can be easily manipulated through formulation chemistry and it has been extensively used in medical applications. This review includes the preparation techniques, characterization and drug delivery applications of PHEMA based nanoparticles.

KEYWORDS

Poly (2-hydroxyethyl methacrylate);
PHEMA;
Drug delivery;
ATRP;
RAFT.

INTRODUCTION

The nanomaterials exist in nature ever since the earth came into existence. Nature has created these materials in vivid environmental conditions. Nature made nanophase materials such as clays, oxides and/or hydroxides of Fe, Al, Si, etc. and magnetite in magnetotactic bacteria, etc., long before man attempted to produce them, in some cases imitating the natural processes. Similarly, the organic molecules in the nanometer scale are the foundations of the life formation. However, from 1990s the scientists are popularly using

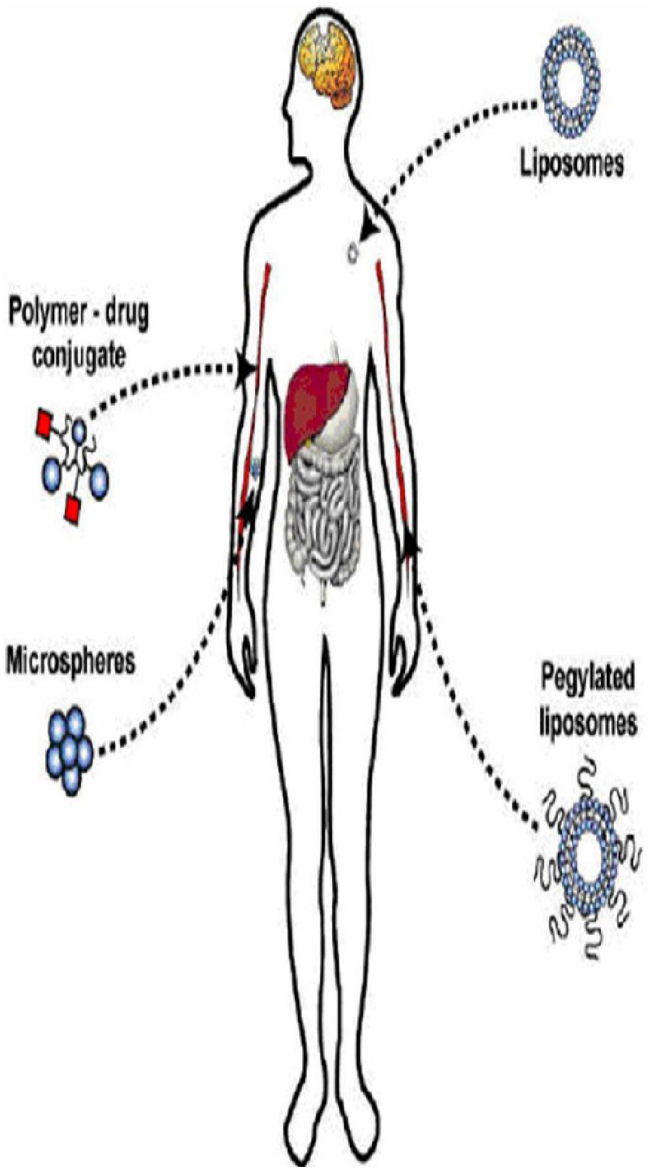

Figure 1 : Examples of different drug delivery approaches

the term nanotechnology to refer designing, characterization, production and application of structures, devices and systems that exist in between those of atoms and bulk materials with at least one dimension in the nanometer range (1 nm=one thousand millionth of a meter, 10•9 m)[1].

The field of nanotechnology has given rise to a plethora of new terms prefixed by 'nano-' and indeed by 'nanobio-' (orbionano-') (Greek word nano, meaning dwarf) without being too rigorous or prescriptive, it is important to keep some perspective here and we believe that science at the nanoscale is best served by a combination of good discipline accompanied by pragmatism[2].

Nanoparticles are submicron moieties may be nanocrystalline materials (a material that is comprised of many crystals) and nanocomposite (multi-phase material in which the majority of the dispersed phase components have one or more dimensions) between 1 nm and 100 nm according to the usual definition, although there are examples of NPs several hundreds of nanometers in size made of inorganic or organic (e.g. polymeric) materials, which may or may not be biodegradable[3,4].

During the past two decades, extensive research has been carried out on the biomedical applications of nanostructured materials. The world market in these materials was estimated to be about $120 billion in 2002, and it is growing at an annual rate of 15% to reach $370 billion by 2010. NSF has predicted that by 2015 the nanotechnology will become a trillion dollar industry worldwide[1,5].

In general, Nanoparticles including dendrimers, micelles, emulsions, nanoparticulated drugs, and liposomes offer much improved performances than those of bulk materials of the same composition, which is mainly due to their larger surface-to-volume ratios, unusual chemical synergistic effects, hydrophilicity/hydrophobicity, surface functionalization, biodegradability, physical response properties (temperature, pH, electric charge, light, sound), magnetic and electronic properties, and the role played by surface phenomena as the size is reduced therefore constitute a bridge between single molecules and bulk material systems[6,7] Nanotechnology-based delivery systems can also protect drugs from degradation or prematured metabolism, and have longer plasma circulation times. If the release mechanism is stimuli-responsive, a therapeutic level of the drug can be sustained over days or even months. These properties can help reduce the number of doses required, make treatment a better experience and reduce treatment expenses[8,9]. Figure 1 shows examples of different drug delivery approaches by nanomaterials.

Polymeric nanoparticles constitute a versatile drug delivery system, which can potentially overcome physiological barriers, and guide the drug to specific cells or intracellular compartments by passive or ligand-mediated targeting approaches because of their submicron size which makes extravasations possible and occlu-

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sion of terminal blood vessel unlikely[10,11]. It also allows controlling the release pattern and sustaining drug levels for a longer time by appropriately selecting the polymeric carriers. Although numerous biodegradable polymeric nanoparticles of natural polymers such as proteins or polysaccharides are largely used as a drug delivery carrier in controlled drug delivery technology, but now-a-days synthetic polymers have received significantly more attention in this area because from polymeric nanoparticles both controlled drug release and disease-specific localization can be achieved by tailoring their polymer characteristics and surface chemistry[12].

Drug delivery technology that can be defined as technique that is used to get the therapeutic agents inside human body represents one of the broader areas of science, which involves multidisciplinary scientific approach, contributing to human health care. The design of a drug delivery system is usually based on the drug's physicochemical and pharmacokinetic properties[13]. It is possible to modify the pharmacokinetics and biodistribution of the drugs, improving the efficacy and security of the therapy by including the drug in technologically optimized drug delivery systems or conjugating the drugs with different polymers[14].

Conventional delivery systems do not provide ideal pharmacokinetic profiles especially for drugs, which display high toxicity and/or narrow therapeutic windows because conventional oral and intravenous routes of drug administration follow first order kinetics[15]. In case of controlled drug delivery systems ideal pharmacokinetic profile will be observed wherein the drug concentration reached therapeutic levels without exceeding the maximum tolerable dose and maintains these concentrations for extended periods of time till the desired therapeutic effect is reached due to zero order[16]. The main problems currently associated with systemic drug administration are; even distribution of pharmaceuticals throughout the body; lack of drug specific affinity toward a pathological site; the necessity of a large total dose of drug to achieve high local concentration; non-specific toxicity and other adverse side-effects due to high drug doses[17]. To address this issue, it is essential to transport the therapeutically active molecule mainly to the target where it is needed and at the required time and level[18]. This could be achieved by embedding the drugs into nontoxic and biodegradable polymers from which the drug will be released in a sustained manner[19].

The performance of a polymeric material relies greatly upon the properties of the boundaries in many applications because interactions between the material and its environment occur chiefly at its surfaces. For blood contacting implant devices, it is very important that surface show minimal protein adsorption and it can be achieved by increasing the hydrophilicity of the surface because it reduces protein fouling and improve biocompatibility[20]. PHEMA is particularly attractive for biomedical engineering applications because of their high water content, non-toxicity and favorable tissue compatibility and its physical properties can be easily manipulated through formulation chemistry and it has been extensively used in medical applications such as contact lenses[21], keratoprotheses, and as orbital implants[22]. The presence of a hydroxyl and carboxyl groups on each repeat unit in PHEMA makes this polymer compatible with water and the hydrophobic α-methyl groups and backbone imparts hydrolytic stability to the polymer and support the mechanical strength of the polymer matrix[23].

TECHNIQUES OF SYNTHESIS OF PHEMA BASED NANOPARTICLES

Atom transfer radical polymerisation (ATRP) method

ATRP is a versatile technique for the controlled polymerization of low to moderately high molecular weight polymers with well-defined architecture and controlled dimensions[24,25], has been successfully employed for the polymerization of a variety of acrylate and methacrylate monomers, such as methyl acrylate[26,27], methyl methacrylate[28] and *n*-butyl acrylate[29,30] with a high tolerance of growing species to many functionalgroups including acids, hydroxy- and amino groups[31]. ATRP has been used to tailor polymers with specific functionalities along the chain. Hydroxyl functional monomers such as 2-hydroxyethyl acrylate (HEA)[31,32] and 2-hydroxyethyl methacrylate (HEMA)[33,34] have been polymerized using this technique, too. With these monomers, different controlled polymer architectures and microstructures can be obtained, such as block copolymers[33] gradient

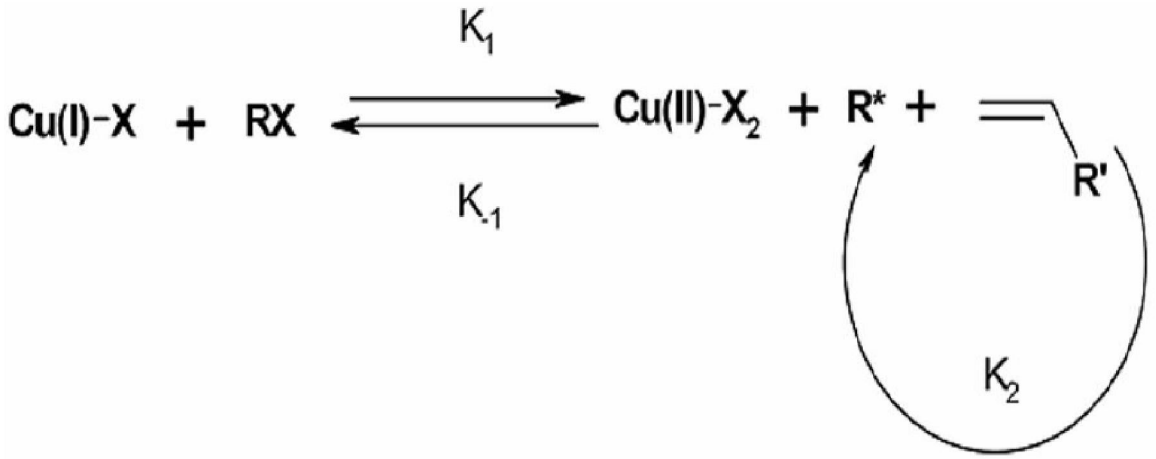

Figure 2 : Mechanism of atom transfer radical polymerization (ATRP)[69]

copolymers[35,36] or statistical copolymers[37].

The name ATRP originates from the atom transfer step, which is the key elementary reaction responsible for the uniform growth of the polymer chains. In ATRP the polymerization is typically started with α-halogenated esters (Figure 2). Typically, In ATRP chain growth is initiated by an alkyl halide (R–X) and catalyzed by a transition metal complex, such as CuX/2,22 -bipyridyl., it is generally believed that the pseudo-living nature of the polymerization is due to the relatively low concentration of polymer radicals, which leads to the suppression of classical termination relative to propagation[38, 39].

ATRP is based on the generation of radicals by a reversible redox reaction of transition metal complex (M_t^n-Y/Ligand, where Y is a counterion). Transfer of an atom (usually halogen) from a dormant species to the metal results in an oxidized metal complex (X-M_t^{n+1}-Y/Ligand which is persistent species) and free radical ($R^{'''}$).

HEMA can not be polymerized by anionic and group transfer polymerizations due to the labile proton on the hydroxyl group. Little success has been accomplished in polymerization of methacrylates by NMP. Beers et. al. reported the controlled linear homopolymerization of HEMA and the preparation of a block copolymer with a MMA by ATRP[33]. Gao and Matyjaszewski[40] synthesized linear poly(2-hydroxyethyl methacrylate) (PHEMA) by ATRP at first. After esterification with pentynoic acid, click reaction

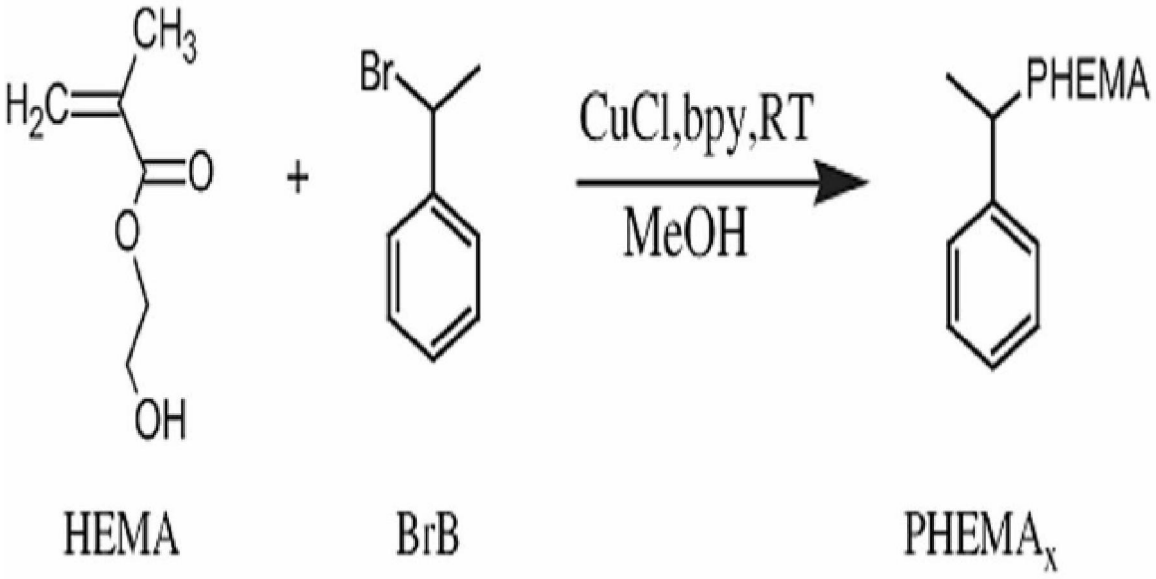

Figure 3 : ATRP synthesis of PHEMA

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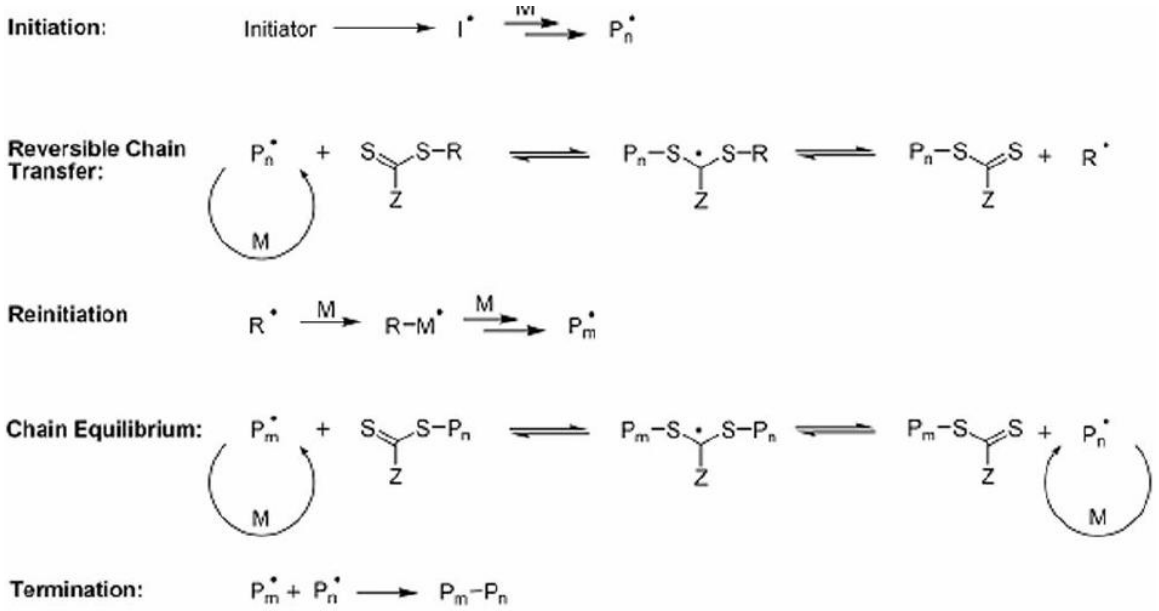

Figure 4 : Mechanism of reversible addition-fragmentation chain transfer (RAFT) polymerization

of the obtained PHEMA-alkyne with azide-terminated PEO afforded homopolymer brushes with a grafting efficiency up to 88%. Gao and coworkers41 fabricated amphiphilic copolymer brush-functionalized carbon nanotubes by coupling ATRP grafting-from and click grafting-to techniques. The synthetic routes of PHEMA homopolymer is shown in Figure 3.

Chen et al.[41] prepared well-defined multiarm star block copolymers poly(glycerol)-*b*-poly(2-hydroxyethyl methacrylate) (PG-*b*-PHEMA) with an average of 56, 66, and 90 PHEMA arms with large amount of hydroxyl groups in the side chain of the arms, respectively by atom transfer radical polymerization (ATRP) of HEMA in methanol by a *core-first* strategy, initiated by a hyperbranched polyglycerol (PG)-based macroinitiator.

Reversible addition-fragmentation chain transfer (RAFT) method

Reversible addition fragmentation chain transfer is another successful technique to avoid the use of toxic organometallic catalysts, and to attain narrow polydispersity indices (PDIs). It utilizes dithioesters as chain transfer agents for the living character of polymer. Rates of addition and fragmentation are fast relative to the rate of propagation. RAFT agent deactivates the polymer chains to form a dormant species, resulting in a controlled polymerization. In RAFT polymerization, the product of chain transfer is a chain transfer agent with similar activity to the precursor transfer agent. This process is also referred to as degenerative chain transfer. The polymeric starting materials and the products have equivalent properties and differ only in molecular weight[42]. The key elementary mechanism of RAFT polymerization is a sequence of addition-fragmentation equilibria as shown in Figure 4[43,44].

After the production of a propagating radical by a conventional way, a chain transfer agent (CTA) reacts with a propagating macroradical and form transient radical. This transient radical can fragment back to the original form or to the direction of another dormant chain and produce a living group, R•. This leaving group should react with the monomer to reinitiate the polymerization, then a series of addition-fragmentation steps occur. The equilibrium between the active propagating species and the dormant polymeric RAFT species allows all chains to have an almost same opportunity to grow and controlled polymerization takes place. When the polymerization is complete, the end groups of the chains contain the thiocarbonylthio moiety[45].

In 1998, Chiefari and coworkers[46] reported the copolymerization of HEMA with MMA by the RAFT process in ethyl acetate at 60°C. Chong et. al.[47] also stated that in the absence of chain transfer (to solvent, initiator, or monomer), the total number of chains formed will be equal to (or less than) the moles of the dithio compound employed plus the moles of initiator-derived

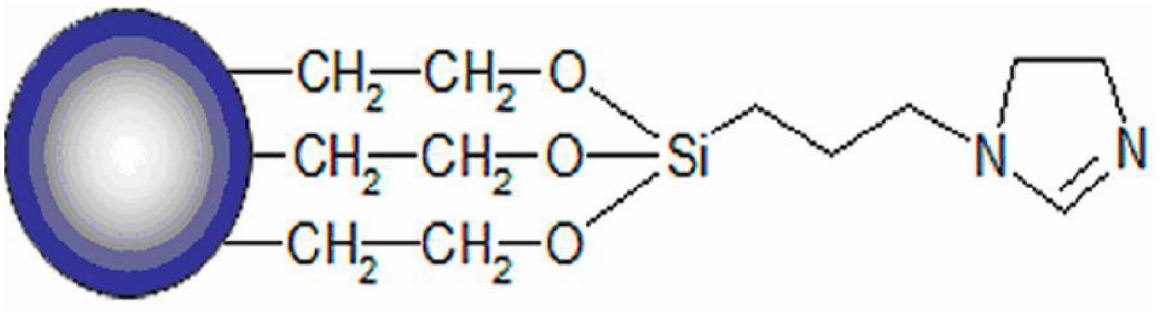

Figure 5 : Structure of the PHEMA-IMEO nanoparticles

radicals. In block copolymer synthesis, these additional initiator-derived chains are a source of homopolymer impurity. For maximum purity, it is desirable to use low concentration of initiator and to choose solvents and initiators which give minimal chain transfer. As with conventional radical polymerization, the rate of RAFT polymerization is determined by the initiator concentration.

Merkel et.al[48] Synthesized Low Molecular Weight pDMAEMA-*block*-pHEMA Block-Copolymers via RAFT-Polymerization in a molecular weight (Mw) range of 17–35.7 kDa and analyzed using 1H and 13C NMR (nuclear magnetic resonance), ATR (attenuated total reflectance), GPC (gel permeation chromatography) and DSC (differential scanning calorimetry).

Surfactant free emulsion polymerization method

Denizli et al.[49,50] synthesized poly(hydroxyethyl methacrylate) (PHEMA) nanoparticles with an average size of 150 nm in diameter and with a poly-dispersity index of 1.171 by a surfactant free emulsion polymerization. Reactive imidazole containing 3-(2-imidazoline-1-yl)propyl(triethoxysilane) (IMEO) was used as a pseudo-specific ligand. IMEO was attached covalently onto the nanoparticles. PHEMA–IMEO nanoparticles were used for the affinity binding of immunoglobulin-G (IgG) from human plasma. In this method, the HEMA/EGDMA mixture was added to aqueous solution of polyvinyl alcohol (used as the stabilizer for the preparation of the continuous phase) an ultrasonic bath for 30min. Prior to polymerization, KPS was added to the monomer phase and nitrogen gas blown through the medium for about 1–2 min to remove dissolved oxygen. Polymerization was carried out in a constant temperature shaking bath at 70°C, under nitrogen atmosphere for 24 h, the PHEMA nanoparticles formed.

Silane is a coupling agent and its bi functional molecule binds to both the exposed composite filler particles and bonding resin. The silane compounds readily reat with the surface hydroxyl groups of the different supports. It is assumed in the literature that the silane molecules are fast hydrolyzed by the trace quantities of water present either on the surface of the support or in the solvent followed by the formation of a covalent bond with the surface. For the silanization, PHEMA nanoparticles and IMEO (mol ratio 1:10) were mixed and stirred at 25 °C for about 4 days. At the end of this period, stirring was stopped. The silanization reaction takes place at 25 °C without any catalyst as shown in Figure 5[51].

Suspension polymerization method

Bajpai and coworker prepared PHEMA nanoparticles by a modified suspension polymerization technique, as published by Kaparissides et. al.[32]. In brief, In this technique, polymerization was carried out in an aqueous phase containing PVA, which was used as the stabilizing agent. The mixture containing the monomer HEMA, the cross-linker EGDMA and the initiator Bz_2O_2 dispersed in toluene was added into 500mL conical flask containing the suspension medium (200 mL aqueous PVA solution (0.5% W/V)). The reactor was flushed by bubbling nitrogen and then sealed. The reaction mixture was 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[53].

Photochemical polymerization method

Hoffmann[54] and Stroyuk[55] found that quantum-sized semiconductor particles were efficient

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photoinitiators to initiate polymerization of monomers in high quantum yields and proposed the mechanisms of polymerization. SiDe et al.[56] synthesized poly(2-hydroxyethyl methacrylate)(PHEMA) magnetic nanogels by *in-situ* polymerization of 2-hydroxyethyl methacrylate (HEMA) and N,N'-methylene-bis-(acrylamide)(MBA) in Fe_3O_4 aqueous suspension under UV irradiation. When Fe_3O_4 nanoparticles are dispersed in aqueous solution containing HEMA and MBA, monomer and cross-linker molecules will be adsorbed on the surface of Fe_3O_4 due to its high surface energy. The photon section of Fe_3O_4 nanoparticles is far larger than that of monomer or cross-linker. As the system was exposed to UV light, overwhelming quantities of photons were absorbed by vinyl molecules on the surface rather than those in solution. Photopolymerization is primarily induced on the surface of magnetites before polymer networks are formed by free radical reactions and polymer chains propagate spontaneously. At the same time, a few of monomer in solution may absorb a tiny proportion of photons and be converted into monomer radicals. These radicals are involved in the reactions such as chain propagation and termination of the polymer shell as well as homopolymerization of monomer occurring in solution.

Dispersion polymerization method

Benes et al.[57] synthesized PHEMA particles by dispersion polymerization of HEMA in a mixture of toluene and 2-methylpropan-1-ol of a given composition using cellulose acetate butyrate as stabilizer. Dibenzoyl peroxide was used as an initiator of polymerization. Particles were cross-linked with ethylene dimethacrylate added at a later stage after the start of polymerization. The reaction mixture was stirred for 5 min, bubbled with pure nitrogen for 10 min, and then heated (typically at 70 °C) under stirring at 500 rpm. Two hours after the start of the polymerization, definite amount of EDMA was added; the overall polymerization time was 8 h. at least

CHARACTERIZATION OF PHEMA BASED NANOPARTICLES

FTIR analysis of PHEMA nanoparticles

The FT-IR spectra of HEMA and PHEMA are given in Figure 6. In the spectrum of monomer (Figure 6a) the –OH peak is broad in the range of 3300-3700 cm^{-1} indicating hydrogen bonding. It also was retained in the spectrum of polymer (Figure 6b)[53]. However, the shoulder at 3100 cm^{-1}; peaks at 1637, 933 and 816 cm^{-1} corresponding to –C=C– in the spectrum of monomer are not present in the polymer spectrum. The –C=O (1719 cm^{-1}), -C-O-C- (1321-1032 cm^{-1}), -CH2 (1404-1379 cm^{-1}) are present in both spectrum. Thus, polymerization proceeds via the opening of double bonds.

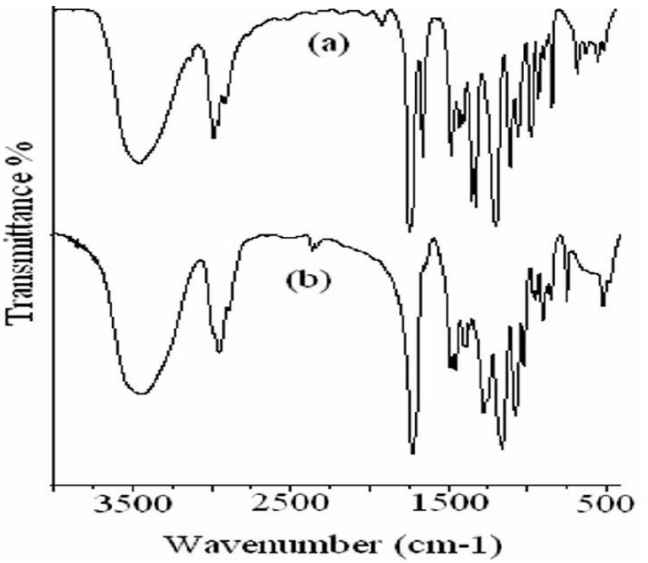

Figure 6 : FTIR spectrum of (a) HEMA and (b) polymer of HEMA

DSC analysis of PHEMA nanoparticles

The DSC thermogram of PHEMA is given in Figure 7. The detailed analysis of thermogram by a program showed that the Tg value is around 88ºC and peak at 110-160 (maximize at 140 ºC) corresponds to further polymerization which was not observed in the second run thermogram. The polymerization peak has the enthalpy of ΔH=-61.3 J/g. The poly-(HEMA) shows a distinct feature in the DSC curve, having an endotherm at about 303 °C, due to thermal degradation. An additional endothermic peak appears at around 477 °C [58]. Water in hydrogels is classified as free and bound water; bound water exits as freezing-bound water and nonfreezing-bound water (Figure 8)[59]. In DSC studies, freezing water exhibits a crystallization exotherm at about -20°C, where as freezing bound water associated with the matrix exhibits an exotherm at about -40 °C[60]. Nonfreezing water molecules are tightly associ-

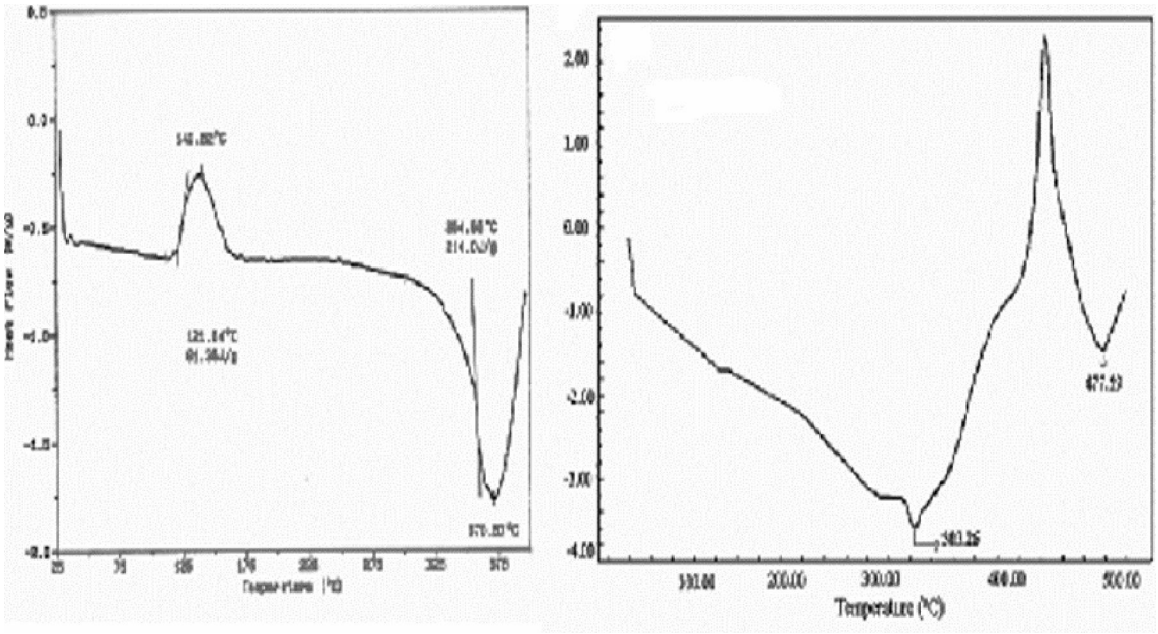

Figure 7 : DSC thermogram of PHEMA

ated with the hydrophilic groups on the polymer and cannot be detected by DSC. Nonfreezing water is, however, calculated from the intercept of plots of total exotherm area versus water content.

Kim et al.[61] determined the free and bound water content in the PHEMA gel by DSC techniques and explained that 21% and 19% bound water present in isotactic and syndiotactic PHEMA gel. similarly, Yishi et.al.[62] studied the state of water in the copolymer of poly(N-vinyl pyrrolidone- methylmethacrylate) and poly(N-vinyl pyrrolidone- hydroxylethyl methacrylate) gels by DSC. They determined that water content basically depands upon nature of monomer and its hydrophilicity.

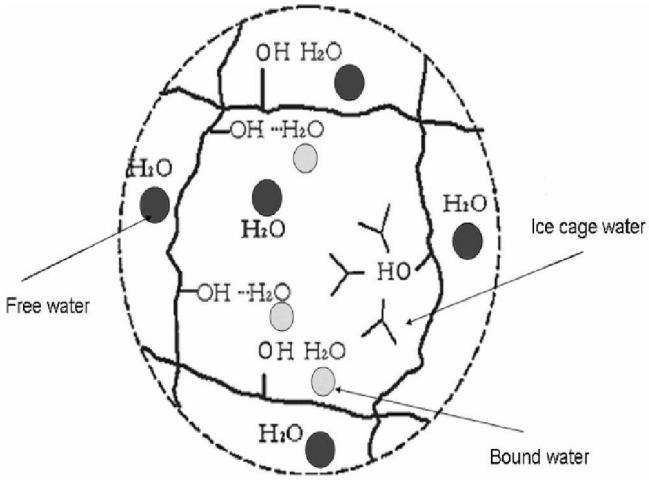

Figure 8 : Different type of water content in PHEMA

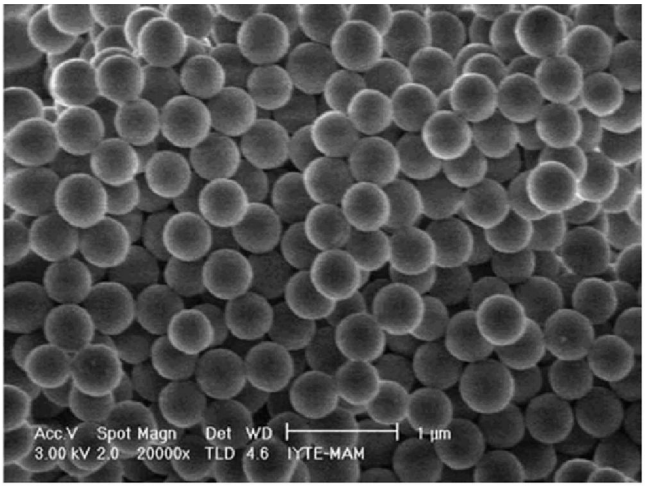

Figure 9 : SEM image of PHEMA nanoparticles[51]

Scanning electron microscopy of PHEMA nanoparticles

The surface topography of an implantable material is a significant parameter in the appreciation of biocompatibility. The surface roughness, for example, can notably influence the adherence of certain cellular types (fibroblasts, osteoblasts…). The surface roughness a biomaterial can be visualized by different methods like scanning electron microscopy (SEM)[63]. The SEM image of surfactant free emulsion polymerized PHEMA nanoparticles is shown in Figure 9[51]. The SEM image of nanoparticles clearly suggests for a non-smooth morphology of the PHEMA nanoparticlesa and uniform size of PHEMA nanoparticles.

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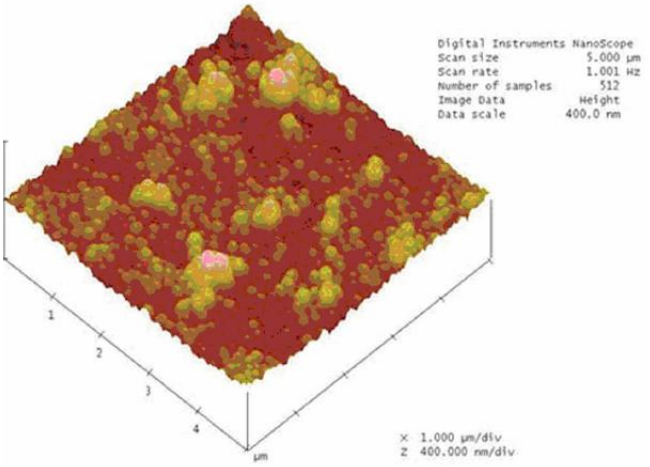

Figure 10 : AFM image of PHEMA nanoparticles[51]

Atomic force microscopy of PHEMA nanoparticles

Accurate size measurement during nanoparticle production is essential for the continuing innovation, quality and safety of nano-enabled products. Size measurement by analysing a number of separate particles individually has particular advantages over ensemble methods. In the latter case nanoparticles have to be well dispersed in a fluid and changes that may occur during analysis, such as agglomeration and degradation, will not be detected which could lead to misleading results. Atomic force microscopy (AFM) allows imaging of particles both in air and liquid, however, the strong interactions between the probe and the particle will cause the broadening of the lateral dimension in the final image[64]. The AFM image of PHEMA nanoparticles suggest that the PHEMA nanoparticles and perfectly spherical with a relatively smooth surface (Figure 10)[51].

APPLICATIONS OF PHEMA BASED NANOPARTICLES IN DRUG DELIVERY

Polymeric materials that respond to a stimulus are often called "smart" or "intelligent" due to their intrinsic ability to alter their physical or chemical properties. For the majority of the polymers that fall into this category, the response to a change in the surrounding environment is not only quick, on the order of minutes[65,66] to hours[67,68], but also reversible, mimicking the dynamics observed in natural polymers, such as proteins, polysaccharides, and nucleic acids in living organic systems[69]. Polyhydroxyethyl methyl acrylate(PHEMA) is anionic copolymer shows high swelling in neutral or high pH but do not swell in acidic medium. Therefore, the release kinetics of drug from PHEMA based nanoparticles can be triggered by changing pH of the medium.

The delivery of drug molecules through the carrier systems is assumed to avoid their unwanted effects because of controlled biodistribution. The ultimate goal of drug therapeutics is to increase the survival time and the quality of life of the patient. Nanoscale drug delivery systems have the ability to improve the pharmacokinetics and increase biodistribution of therapeutic agents to target organs, which will result in improved efficacy[70-72]. Biodegradable polymeric nanoparticles have been extensively used for cancer therapeutics[73]. The material properties of each nanoparticles system have been developed to enhance delivery to the tumor. For example, hydrophilic surfaces can be used to provide the nanoparticles with stealth properties for longer circulation times and positively charged surfaces can enhance endocytosis. The types of biomedical nanoparticles currently used in research for pharmaceutical purposes and more specifically for cancer therapeutic applications include dendrimers[74], liposomes[75], polymeric nanoparticles[76], micelles[77], protein nanoparticles[78], ceramic nanoparticles[79], viral nanoparticles[80], metallic nanoparticles[81], and carbon nanotubes[82].

You et al[67] synthesized pH-Sensitive poly(N,N-dimethylaminoethyl methacrylate (DMAEMA)/2-hydroxyethyl methacrylate (HEMA)) by forming an O/W emulsion followed by photopolymerization nanoparticles for the triggered release of paclitaxel within a tumor microenvironment. Tumors exhibit a lower extracellular pH than normal tissues. They found that paclitaxel release from DMAEMA/HEMA particles can be actively triggered by small, physiological changes in pH (within 0.2-0.6 pH units). In vitro results support that the drug would remain within the particle during circulation; upon exposure to a low pH environment, the particle would swell resulting in release of the drug. Monodisperse, pH-sensitive DMAEMA/HEMA nanocarriers encapsulating paclitaxel exhibited pH-dependent release kinetics.

Therapeutic gene delivery is based on the concept that recombinant DNA and RNA interference technologies can be used to regulate disease at the molecular

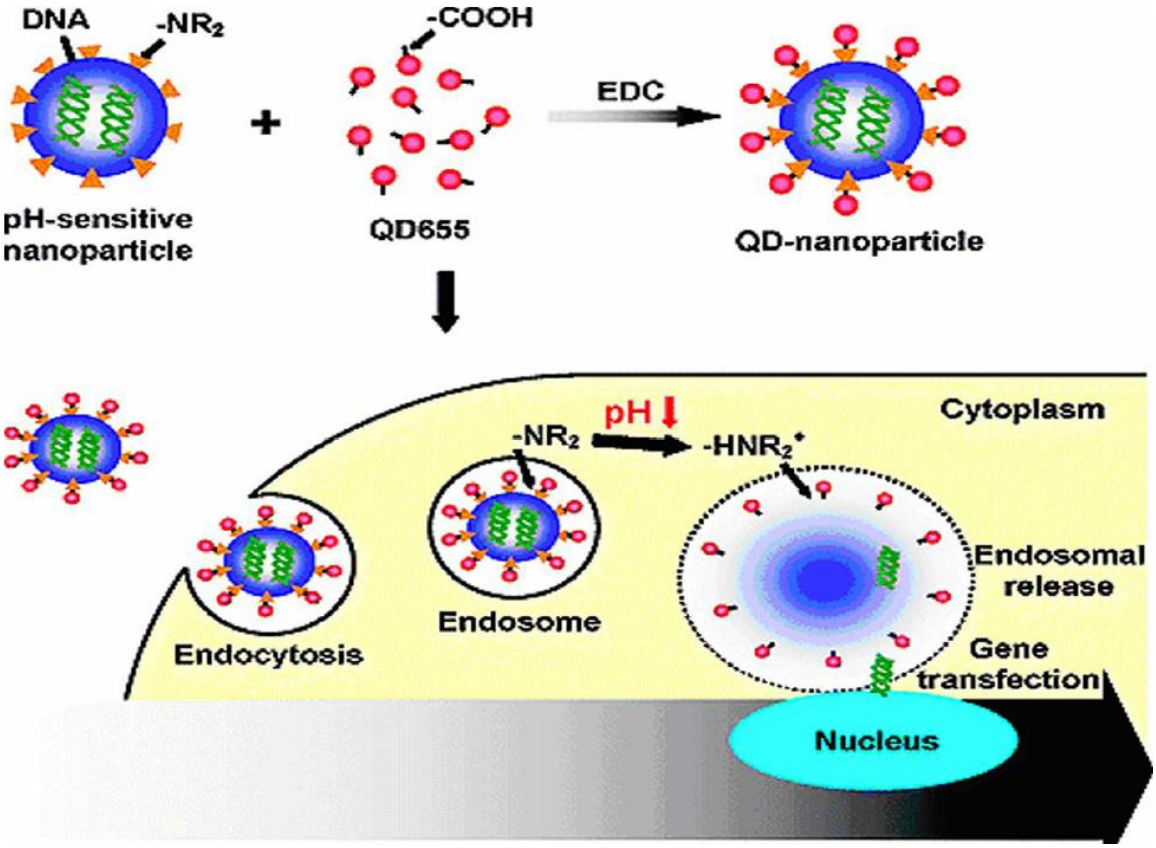

Figure 11 : Schematic illustration of the delivery of pH-sensitive gene carriers. For example, the DMAEMA/HEMA nanoparticle releases DNA in the low pH endosom[70]

level. Nonetheless, treatment of human diseases by genetic material instead of drugs has been limited by effective delivery without cytotoxicity. It is widely accepted that pH facilitates endosomal delivery. Endocytosis generally occurs by engulfing molecules or therapeutic vehicles by the plasma membrane. Plasma membrane invaginations evolve into endosomes that become lysosomes, acidic compartments responsible for degrading foreign agents. Therapeutic agents (i.e. pDNA) are delivered to the cytoplasm by disrupting endosomes (Figure 11). You and co-workers[83,84] studied the triggered release of DNA for gene transfection from poly(N,N-dimethylaminoethyl methacrylate (DMAEMA)/2-hydroxyethyl methacrylate (HEMA)) nanoparticles. Plasmid DNA for green fluorescent protein was encapsulated. It was also noticed that HeLa cells (cancer cells) were successfully transfected with a dependence on the swelling ratio and crosslinking density.

Bajpai and co-workers[85] also evaluated in vitro release of cancer drug from PHEMA nanoparticles and they found that release profiles show a fast release rate followed by a slow delivery of drug into the release medium. This biphasic nature of release profiles is due to two fact firstly surface drug is flushed into the release medium (fast release) and after that the remaining amount of drug passes slowly into the release medium because of the fall in concentration of drug within the nanoparticles.

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