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RECENT TRENDS IN DIFFERENT TYPES OF SYNTHETIC HYDROPHILIC POLYMER NANOPARTICLES, METHODS OF SYNTHESIS & THEIR APPLICATIONS

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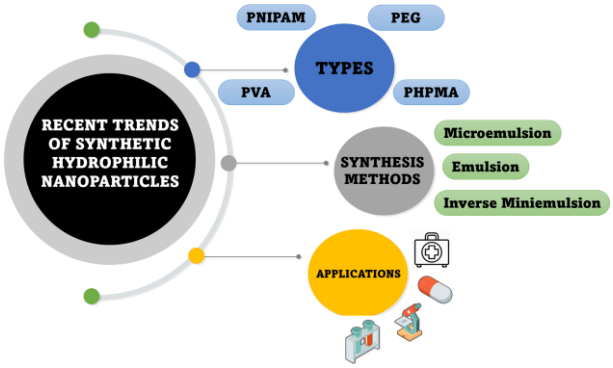
Graphical abstract



Abstract

Numerous types of hydrophilic polymer nanoparticles (NPs) have recently become research hotspots because of their ability to dissolve in water and can be adapted with respect to physical, chemical, and biological properties to meet the requirements of different applications. Synthetic hydrophilic polymeric NPs had successfully gained much attention because of their unique physicochemical properties, such as low toxicity, biodegradability, bioavailability, and support material for extensive swelling in water. These synthetic hydrophilic polymers NPs create new opportunities to produce water-soluble polymer types that would be able to imitate the structure and function of biological polymers. Several synthetic hydrophilic polymer NPs that gain high interest recently including poly(N-isopropyl acrylamide) (PNIPAM), poly(ethylene glycol) (PEG), poly(vinyl alcohol) (PVA) and poly(N-(2-hydroxypropyl) methacrylamide (PHPMA) are reviewed in this paper. Furthermore, various synthesis methods to produce synthetic hydrophilic polymer NPs for instance emulsion polymerization, microemulsion polymerization and inverse miniemulsion polymerization are highlighted, and a brief overview on their recent applications especially in medical applications are also be discussed thoroughly in this review.

Keywords: Hydrophilic polymer, polymeric nanoparticles, polymerization, medical, synthetic polymer

Abstrak

Pelbagai jenis partikel nano (NP) polimer hidrofilik telah menjadi tumpuan penyelidikan kerana kemampuannya larut di dalam air dan dapat disesuaikan dengan sifat fizikal, kimia dan biologi dalam julat lebar untuk memenuhi keperluan bagi penggunaan yang berbeza. Partikel nano polimer hidrofilik sintetik telah berjaya meraih banyak perhatian kerana sifat fizikokimianya yang unik, seperti ketoksikan yang rendah, biodegradasi, bioavaibiliti dan bahan sokongan untuk pembengkakan yang meluas di dalam air. Partikel nano polimer hidrofilik sintetik ini telah mencipta peluang baharu untuk menghasilkan jenis polimer larut air yang berupaya meniru

struktur dan fungsi polimer biologi. Beberapa partikel nano polimer hidrofilik sintetik yang mendapat tarikan tinggi baru-baru ini termasuk poli(N-isopropil akrilamida) (PNIPAM), poli(etilena glikol) (PEG), poli(vinil alkohol) (PVA) dan poli(N-(2-hidroksilpropil) metakrilamida (PHPMA) dikaji dalam manuskrip ini. Tambahan pula, pelbagai kaedah sintesis untuk menghasilkan partikel nano polimer hidrofilik sintetik seperti pempolimeran emulsi, pempolimeran mikroemulsi dan pempolimeran miniemulsi songsang ditekankan, dan, gambaran ringkas mengenai aplikasi terkini terutamanya dalam aplikasi perubatan juga dibincangkan secara menyeluruh dalam ulasan ini.

1.0 INTRODUCTION

Nanotechnology and nanoscience are one of the most popular areas for current research and have been identified as the dominant and most commercially successful technologies that aim to improve health care strategies. Despite some limitations, medical nanotechnology is already used by several pharmaceutical and medical equipment companies. Some cancer drugs, which have a high toxic potential, can be administered with an improved safety profile using nanotechnology [1]. The synthesis of polymer nanoparticles (NPs) with controlled characteristics has become an appealing research topic lately, particularly in biomedicine, because of the wide variety of applications they reveal.

NPs are solid and colloidal particles of macromolecular substances within the size range from 1 to 100 nm and can be loaded with active compounds entrapped within or surface-adsorbed onto the polymeric core. Polymeric NPs have shown great potential for targeted delivery of drugs for the treatment of several diseases [2]. The rapid advancement of this technology over the past decade has allowed the design of specific and multifunctional polymer nanoparticles for the delivery of drugs, medical imaging, therapeutics, medical diagnostics, implantable materials, and tissue regeneration [3]. NPs have gained much attention due to their eccentric properties, for example more potent, less toxic and smart outcomes [4]. NPs are classified into different groups based on their properties, shapes, or sizes. The examples of nanoparticles are fullerenes or carbon nanotubes (CNTs), metal NPs (such as gold, silver and copper), ceramic NPs (such as calcium, titanium and silicon) and polymeric NPs (such as cellulose, gelatine and chitosan) [5].

Of all the types of NPs, polymeric NPs are widely used in many fields especially medicine because they have unique physicochemical properties, such as good biocompatibility, broad-structure variety and also notable bio-imitiative characteristics. This is proved by the ability of polymeric NPs as drug delivery to send the drug into the predetermined area in the human body with good efficiency [6]. Recently, research has succeeded in discovering that polymeric NPs can precisely engineer materials at a molecular level [7]. Polymeric NPs can be obtained by processing in the lab (synthetic polymeric NPs [8] and nature (natural polymeric NPs) [9]. There are several natural polymeric NPs that have been widely used, such as alginate, albumin and chitosan, which have scientifically proved as ocular nano delivery agents. Poly lactic acid (PLA), poly glycolic acid (PGA) and hydroxypropyl methyl cellulose (HPMC) are few examples of synthetic polymeric NPs, which have been studied as delivery agents through the ocular route [8, 10, 11].

Synthetic polymeric NPs are broadly explored by scientists because of the biocompatibility and biodegradability characteristics even though they are produced synthetically [12, 13]. In addition, synthetic polymeric NPs are preferably used as drug delivery rather than natural polymeric NPs because natural polymeric NPs (such as polysaccharides and proteins) have different purity and mostly need the addition of cross-linker. Cross-linker has the possibility to denature the embedded drug, which makes natural polymeric NPs not suitable for drug delivery [14]. Generally, the structure of synthetic polymeric NPs can either have the characteristics of hydrophilic or hydrophobic or both, which are referred to as amphiphilic. For example, the presence of hydrophilic functional groups, such as –OH, –COOH, or $–NH_2$ can increase the hydrophilicity of the NPs, making them more water soluble in aqueous solutions. On the other hand, the presence of the hydrophobic functional groups like $–CH_3$ or $–C_6H_5$ increases the hydrophobicity of the NPs making them less soluble and more likely to aggregate in the aqueous medium. Polymeric NPs that are categorized as hydrophilic polymeric NPs have surface and core that are hydrophilic. Besides, polymeric NPs have a hydrophilic surface, but hydrophobic cores are also classified as hydrophilic polymeric NPs. Water soluble and insoluble drugs can be entrapped into the hydrophilic polymeric NPs by modifying the hydrophilicity and hydrophobicity of the core of the NPs [15]. A wide range of hydrophilic polymers NPs are available but natural and semi-synthetic hydrophilic polymer NPs were not always suitable because of their properties that are not imitable for many applications. Thus, many biodegradable and biocompatible synthetic polymers were designed including poly(ethylene glycol) (PEG), poly(vinyl alcohol) (PVA), and poly(DL-lactic-co-glycolic acid) PLGA).

Additionally, they could easily be modified to fit biological, physical, and mechanical requirements [1].

Furthermore, there are numerous techniques that can be considered to synthesize hydrophilic polymeric NPs. These techniques are subdivided into two different groups, which are methods for preparation of hydrophilic polymeric NPs from the polymerization of monomers and methods for preparation of hydrophilic polymeric NPs from the dispersion of preformed polymer. Emulsion polymerization, micro-emulsion polymerization and inverse miniemulsion polymerization are several example techniques to produce hydrophilic polymeric NPs that are synthesized from the polymerization of monomers, while solvent diffusion and solvent evaporation are few examples of methods to produce hydrophilic polymeric NPs from the dispersion of preformed polymer [2, 16]. The choice of an appropriate method for producing hydrophilic polymeric NPs depends on many factors, such as particle size, type of solvents, methods to produce hydrophilic polymeric NPs, polymers used to synthesize and area of application [2, 16, 17]. Particle size is one of the crucial considerations because different synthesis methods used to produce NPs could lead to a different size range of NPs. The types of solvent used also play a critical role in determining the hydrophilicity of the NPs. The selection of an appropriate solvent is necessary to ensure the resulting NPs have the desired properties. The selection of methods to produce hydrophilic NPs is another vital factor as different methods can lead to varying levels of hydrophilicity in the NPs. Additionally, different polymers have varying chemical and physical properties that can affect the hydrophilicity of NPs, and finally, the area of application for the NPs is also an important consideration when selecting a suitable synthesis method. Synthetic hydrophilic polymers create new opportunities to produce water-soluble polymer types that would be able to imitate the structure and function of biological polymers [18]. Nevertheless, this review will discuss and focus on the different types of synthetic hydrophilic polymeric NPs, the methods of synthesizing synthetic hydrophilic via polymerization of monomers and some of their applications especially in medical applications.

2.0 TYPES OF HYDROPHILIC POLYMER NANOPARTICLES

Poly (N-isopropyl acrylamide) (PNIPAM)

Currently, smart polymers have received lots of attention especially in the field of controlled drug delivery systems [19]. Smart or intelligent polymer are polymers which adjust their properties and response drastically towards environmental factors or external stimuli such as pH, temperature, humidity, electrical field, ionic strength, light, electric effect, specifics ion or molecule and solvent and ionic strength [20]. Among the external stimuli, temperature and pH are the most studied by researchers during the past decades and found to be relevant in biomedical application and tissue engineering because their parameters change naturally and can be easily controlled [19]. PNIPAM is one of the smart materials that offer huge interest and is known as thermo-responsive smart polymer which is a polymer that adjusts its properties when temperature changes. PNIPAM has a well-defined structure and is soluble in cold water, but it is precipitated when heated above the lower critical solution temperature (LCST) [21]. PNIPAM LCST transition phase lies in the range of the human body temperature which is at 32℃. The absolute temperature depends on other factors such as degree of polymerization and the concentration of polymer [22].

PNIPAM has a remarkable molecular architecture which its chain comprises both hydrophobic and hydrophilic regions, hydrophilic amide group (-CONH-) and hydrophobic iso-propyl (-CH $(CH_3)_2$). The chemical structure of PNIPAM is shown in Figure 1.

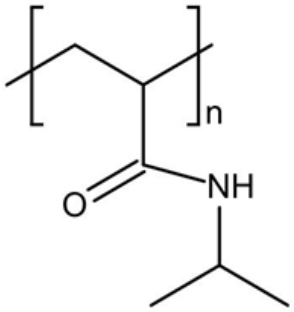


Figure 1 The chemical structure of PNIPAM

This polymer will undergo sudden change in its microstructure from hydrophilic to hydrophobic state caused by temperature change. When the temperature is below LCST, the hydrophilic amide group dissolved by the water molecules resulting in the PNIPAM soluble in water caused by a highly structured hydration shell made by hydrogen bonding and made it remains in a coil-like conformation. While it will collapse into coil-to-globule when the temperature is elevated because the hydrogen bonding is weakened and following that the interactions among the hydrophobic group become strong and result in the release of water from structure [27, 23]. On top of that, it is often misinterpreted that PNIPAM is hydrophobic above LCST, although it contains both hydrophobic and hydrophilic moieties [22]. In several studies, chain-end functionalization with different functional groups or copolymerization was shown to improve PNIPAM's thermal responsiveness (LCST) or pH sensitivity [24]. In addition, recently, the extensive research interest in PNIPAM-based smart hydrogels has been aroused owing to their fascinating properties and functions where it could permit various smart functions such as shape change, self-regulation, and rupture, similar to a cell and some smart biological systems [25].

Poly (ethylene glycol) (PEG)

PEG is a polyether linear-chained polymer made up of repeated ethylene glycol units [-(CH_2CH_2O)n] [26] that have already been used for a large number due to their high latent enthalpy, non-corrosive, and good biocompatibility [27]. Figure 2 shows the molecular structure of PEG. PEG is considered as a favorable material for drug delivery because it comes with different molecular weights despite sharing the same basic structure [28]. The linear PEG material already exhibits thermos-responsive properties with LCST values ranging from 100-176 °C [29]. The common method used to synthesize PEG is by an anionic or cationic polymerization that can produce very low polymers with a broad range of potential molar masses [26]. PEG is usually synthesized by polymerizing ethylene oxide and any hydroxyl initiator ionically. A hydrogen group could come from water, ethylene glycol, and diols. The polymers can also be synthesized from epoxyethane by means of ring-opening polymerization [30]. A range of molecular weights are available for PEG based on the number of repeating subunits [28,31]. The high molecular weight of the PEG is one of the reasons for its higher melting enthalpy [32].

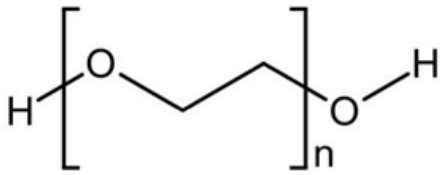


Figure 2 The molecular structure of PEG

PEG was already approved by the U.S Food and Drug Administration (USFDA) for various applications including cosmetics, foods, pharmaceuticals, and clinical uses [30,33]. This polymer is highly soluble in water even at higher molar masses due to the oxygen molecule that it has within the backbone [32]. PEG that has low molecular weight has widely been used in solid polymer electrolytes (SPEs) due to its desirable properties of low cost, low viscosity, low toxicity and high dielectric constant that have historically made it a popular plasticizer [34]. PEG is not biodegradable when unmodified but can be copolymerized with degradable polymers to allow biodegradation [38]. These properties make PEG a beneficial synthetic polymer that is often used as a hydrogel and sometimes an injectable hydrogel in preparation of sensing devices, advanced medical devices, and drug delivery systems [35].

Poly (vinyl alcohol) (PVA)

PVA is a semi crystalline hydrophilic vinyl polymer [33] that has been used since the early 1930s as the first synthetic colloid in a wide range of applications [36]. PVA is linked by only carbon-carbon linkages, and it can be chemically modified by simple reaction because of its straightforward chemical structure [37]. The molecular structure of PVA is shown in Figure 3. When PVA is dissolved in water, the hydrophilic ether groups interact with water, whereas the ethyl chains resist water [29]. Since -OH groups are presented in abundance in this compound, it is able to observe large quantities of water [38]. This weakness can be overcome by combining PVA with a more hydrophobic filler [39]. The water-soluble properties, biodegradability, biocompatibility, non-carcinogenicity, non-toxicity, bio-adhesiveness, high chemical, and oil reactivity of PVA make it an attractive polymer for bioplastics [37,39]. The pH value, viscosity, drying point, melting point, refractive index, and residue on ignition of PVA are determined by molecular weight and hydrolysis rates [40]. In order to formulate PVA, vinyl acetate monomer is polymerized into polyvinyl acetate (PVAc), followed by the hydrolysis of the acetate group of the PVAc [41]. Most of the molecular weight of PVA depends on the initial vinyl acetate polymer and the degree of hydrolysis [44]. PVA powder can be white to cream coloured, and it has no odour and taste [42,47].

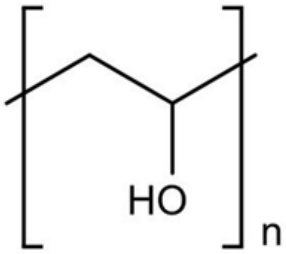


Figure 3 The molecular structure of PVA

PVA can be blended with different synthetic or natural polymers [42]. It can be blended with chitosan to form stable and complexes due to the polarity and tendency to create intermolecular and extra molecular hydrogen bonds [43]. It has been demonstrated that PVA and its copolymer can be used to build novel biologically active composites such as hydrogels, microparticles, NPs and nanocomposites for use as therapeutic agents in cancer. PVA is soluble in water, slightly soluble in ethanol, but insoluble in other organic solvents [44]. The fact that this polymer can be broken down into water and is biodegradable makes it useful in a variety of industrial application fields, such as medical, food, cosmetic, pharmaceutical, and packaging [45]. Its high swelling in water or biological fluids, combined with its elastic or rubbery nature, makes PVA gels suitable for the imitation of natural tissues [37]. Due to its low hazard, non-hazardous, safe handling and excellent film forming characteristics, PVA proves to be an excellent choice for tissue engineering [41]. A recent research interest has been developing mechanically robust PVA materials for use in high performance films, fibers, and synthetic ligaments and muscles [46]. The absence of chemical crosslinkers in PVA's structure allows it to form low-

toxicity physical hydrogels by successive freezing [47]. The suitable melting point, chemical stability, and high phase change enthalpy of PVA make it suitable as solid-liquid phase change materials [48].

Poly (N-(2-hydroxypropyl) methacrylamide (PHPMA)

PHPMA is a hydrophilic synthetic polymer often used as a replacement to PEG because of its high polymerization and conjugation dimensions compared to PEG [49,50]. In polymeric systems, PHPMA has achieved great significance and is one of only a few synthetic polymers to have undergone clinical study [51]. PHPMA has been found in various applications including nanomedicine and biomedical due to their high solubility in water, biocompatibility, non-toxicity, and non-immunogenicity [50,52]. This polymer has been proving its efficiency in lipophilic therapeutics and does not cause any accelerated blood clearance, allergic reaction and minimal side effects compared to PEG [53,54].

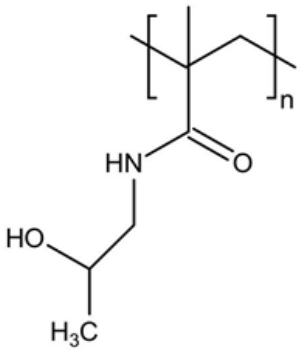


Figure 4 The molecular structure of PHPMA

It has a good hydrolytic stability due to the presence of an OH group attached to an alkyl carbon and an N-substituted amide bond in the side chains [50,55]. Figure 4 shows the molecular structure of PHPMA. The presence of an end OH group as a secondary alcohol in its molecular structure can be utilized for the conjugation and installation of various chemicals [50, 56] pendent group [51] or targeting molecules [52] via ester linkage [49]. PHPMA can be synthesized via conventional free radical polymerization or by controlled radical polymerization techniques that are often used which are atom transfer radical polymer (ATRP) and reversible addition fragmentation chain transfer (RAFT) [51,56]. PHPMA solubilization properties can solubilize hydrophobic drugs. The conjugation of drug to PHPMA enhances drug solubility, stability and increases its half-life [55]. However, PHPMA is a non-biodegradable polymer. Hence, it limits their utility for some pharmaceutical applications [56].

Figure 5 summarizes the connectivity of the discussed synthetic polymer NPs and their contributions to various applications.

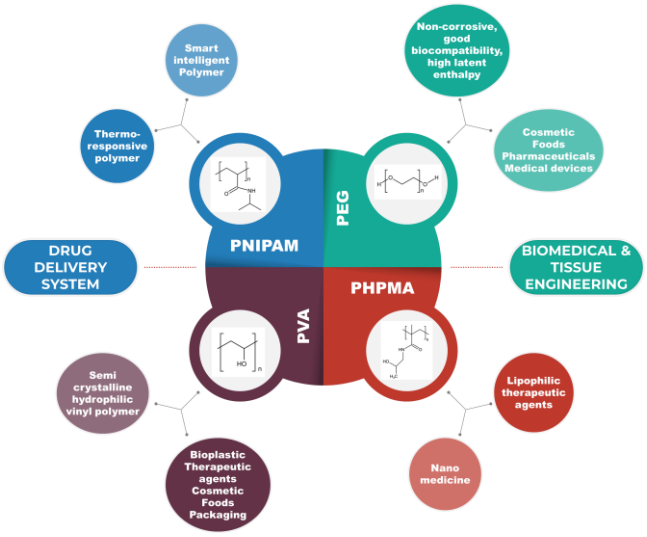


Figure 5 Schematic diagram of synthetic polymer NPs and their contribution to various applications

3.0 SYNTHESIS METHODS FOR SYNTHETIC HYDROPHILIC POLYMER NANOPARTICLES

Hydrophilic polymer NPs are broadly studied in the pharmaceutical sector, especially as drug carriers. Hydrophilic polymer NPs can be utilized as drug carriers because of the potential to control or assist the releasing of drugs into the system of living organisms [17]. Other than that, hydrophilic polymer NPs have attracted much attention from other nanoparticles because polymer NPs have unique properties, for instance biocompatibility, biodegradability, non-immunogenicity, and non-toxicity [57]. Hydrophilic polymer NPs can be synthesized by various methods, which depend on many factors, such as the requirement size of the NPs, area of application and polymeric systems [16]. Hydrophilic polymer NPs can be synthesized from the polymerization of monomers, such as emulsion polymerization, micro-emulsion polymerization and inverse miniemulsion polymerization.

Synthesis by Emulsion Polymerization

Emulsion polymerization is known as one of the fastest methods for the preparation of hydrophilic polymer NPs, which involves the propagation reaction of free radicals with monomer molecules in a very huge number of discrete polymer particles (range from 10^{16} – 10^{18} dm^{-3}) that dispersed into the continuous aqueous phase [58,59]. Emulsion polymerization is discovered during the World War II, which United States (U.S) advanced the emulsion polymerization to produce government-rubber-styrene (GR-S) rubber or styrene-butadiene rubber (SBR) [60]. It was during this time that Japanese discontinue taking natural rubber from the East.

Generally, emulsion polymerization system includes a monomer that is emulsified in water with presence of surfactant and polymerization initiated with a water-soluble initiator (Figure 6). At the beginning of polymerization, the monomer is presented mostly in droplets that have been dispersed in the continuous phase. A heterogenous reaction media is formed in which the monomer exists as dissolved molecules, clusters of a few molecules, nanodrops and large-size droplets. When surfactant is added, it facilitates the development of monomer droplets that coexist with monomer swelling micelles.

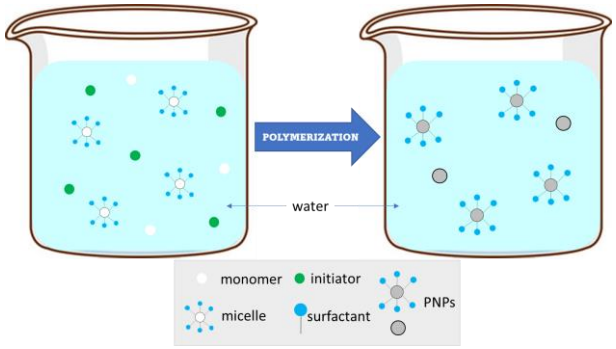


Figure 6 Emulsion polymerization process

Emulsion polymerization process is a complex process because free radicals control the nucleation, growth, and stabilization of polymer particles. The segregation of free radicals among the discrete monomer-swollen polymer particles is the most noticeable feature in the emulsion polymerization, in which it will reduce the probability of bimolecular termination of free radicals. Thus, it will increase the polymerization rate and produce polymers with a high molecular weight. This accomplishment cannot be achieved in bulk or solution polymerization [58].

Nowadays, emulsion polymerization is extensively used by others due to the ability to form a diversity of hydrophilic polymer NPs. In addition, emulsion polymerization is the common method to produce hydrophilic polymer NPs because it only deals with water, monomer of low water solubility and surfactant [58,61]. Besides, emulsion polymerization is favored by many researchers especially when synthesizing hydrophilic polymer NPs because of the ability to obtain higher rates of polymerization and generate higher molecular weight polymers. Other than that, emulsion polymerization also able to produce polymer without the existence of volatile organic compounds (VOCs), which are organic chemical compounds that have boiling point (range from 50 – 260 °C) and vapor pressure higher than 102 kPa at 25 °C [60,62].

Recently, the copolymerization between methyl methacrylate (MMA) and hydroxypropyl methylcellulose (HPMC) had succeeded in producing hydrophilic poly(methyl methacrylate-co-hydroxypropyl methylcellulose) P(MMA-*co*-HPMC) NPs. The hydrophilic P(MMA-*co*-HPMC) is synthesized via emulsion polymerization method with sodium dodecyl sulphate (SDS) and potassium persulfate (KPS) as anionic surfactant and water-soluble initiator, respectively. The study had proved that different molar ratios of MMA and HPMC monomers used in the copolymerization can affect the copolymer formation, morphology, thermal stability, and solubility. From the research, it can be concluded that different ratios did affect the characteristics of the P(MMA-*co*-HPMC) formed, which the higher the amount of MMA, the average particle size of the P(MMA-*co*-HPMC) NPs become bigger. However, the average particle size of the P(MMA-*co*-HPMC) will decrease if the higher quantity of HPMC is used in emulsion polymerization [63]. Regardless, the research succeeded in proving that emulsion polymerization can synthesize hydrophilic polymer NPs.

Poly(methyl methacrylate) (PMMA) is an example of hydrophilic polymer NPs produced via emulsion polymerization, in which PMMA is characterized as an important polymer material because it has many excellent properties, such as excellent chemical stability, relatively stable physical and mechanical properties and good optical properties [64,65]. The synthesis of PMMA was assisted with SDS and KPS which act as surfactant and initiator, respectively. The PMMA microspheres obtained had a diameter that ranged from 80 - 110 nm. By analyzing the PMMA microspheres obtained using scanning electron microscope (SEM), it is observed that the microspheres had consistent size and arranged in a three-dimensional periodic close array in long range [65]. However, the characteristics of the PMMA can be altered or improved with the addition of other polymer NPs [63,65]. Despite all of that, emulsion polymerization can synthesize hydrophilic PMMA. In addition, PMMA synthesis from emulsion polymerization also can be encapsulated with other NPs by using the same technique. The study has proved that drug loaded PMMA produced using this technique is highly suitable for effective, localized, and safe chemotherapy [66].

Poly(ethyl 2-cyanoacrylate) (PECA) is a hydrophilic polymer NPs that can be obtained using emulsion polymerization. PECA belongs to the family of poly(alkyl cyanoacrylate) (PACA), in which is commonly practiced in medical because of its specialties, such as biocompatible, biodegradable and also muco-adhesive polymer that have strong interactions with cells and tissues [67]. In fact, recent innovations in nanotechnology have resulted in the production of numerous types of PACA polymers, which includes drug carrying nanospheres and ligand-decorated NPs [68]. The Tween 20 (non-ionic surfactant with 0.5% w/v) was dissolved in an aqueous solution of hydrochloric acid (HCl) (pH 2.5). This mixture will serve as medium for polymerization. The ethyl 2-cyanoacrylate (ECA) monomer was dripped into the medium while continuously stirring using magnetic stirring at room temperature. After all of the monomer was completely polymerized, the NPs formed was neutralized with sodium hydroxide (NaOH) in order to confirm the reaction has ended. This research had studied the effect of different concentrations of monomer and

surfactant on several parameters (particle size, dispersion homogeneity and polymerization rate). Based on the research, the best concentration for surfactant and monomer for the formation of PECA NPs are 1.0% w/v and 1.0% v/v, respectively [69]. Nonetheless, more research needs to be done on the synthesizing of PECA via emulsion polymerization.

Other than that, ABA type block copolymers of poly(ethylene glycol) (PEG) and poly(dodecyl vinyl ether) is a hydrophilic polymer NPs, which is produced to study the application of this hydrophilic polymer NPs as a surfactant. In this study, PEG based macroinitiator (MI) with the terminal chloride atom at both ends was synthesized by the reaction of PEG-400 with chloroacetyl chloride, which was used for the cationic polymerization of dodecyl vinyl ether (DVE) producing ABA type block copolymer. MI is uncrosslinked polymers that have initiating groups like azo, peroxy and disulfide which then will be integrated into the main or side chain. When a MI that consists of an initiating group in the main chain is decomposed due to the existence of vinyl monomers, block copolymers will be formed [70]. In the emulsion polymerization of styrene and vinyl acetate, the ABA block copolymer was used as surfactant and potassium persulfate as the initiator throughout the process. From this research, it can be proved that ABA block copolymer produced by emulsion polymerization can slightly improve the viscosity of polymer, decrease the size of the particle, and increase the viscosity of the final product if the concentration of ABA block copolymer surfactant was increased. This is because surfactant concentration is sensitive to certain parameters, such as viscosity, molecular weight, and particle size [71].

Poly(N-isopropylacrylamide) (PNIPAM) NPs is another example of hydrophilic polymer NPs that was successfully synthesized via emulsion polymerization. This research used SDS, KPS and N,N'-methylenebisacrylamide (MBAA) during the emulsion polymerization process as the surfactant, initiator and cross-linker, respectively. The research studied the effect of using surfactant at different critical micelle concentrations (CMC) towards the emulsion polymerization process. CMC is defined as the concentration of surfactant above the micellization becomes thermodynamically favorable and any additional surfactant added to the system forms micelles [72]. From the research, it can be proved that different CMC did affect the emulsion polymerization, in which different morphology detected by the scanning electron microscope (SEM) and different thermal stability was obtained via thermogravimetric analysis (TGA) [23]. Besides, it proves that the equivalent CMC for the surfactant showed more stability in terms of thermal degradation based on the highest onset temperature. Recently, PNIPAM was used in a surfactant-free emulsion polymerization by grafting other materials with better hydrophilicity onto the PNIPAM backbone, which this process required novel materials with better biocompatibility. From this method, poly(N-isopropylacrylamide)-g-poly(N-isopropylacrylamide-co-styrene) microspheres (PNNS-MSs) were produced [73]. The research succeeded in proving that PNNS-MSs have excellent blood compatibility and lack of cytotoxicity.

Synthesis by Microemulsion Polymerization

Microemulsion polymerization was discovered around 1980 as an outcome of the various studies done on the microemulsion systems after the 1974 oil crisis. From the day onwards, speedy development related to microemulsion polymerization can be seen. This was proved by the constant increase in the number of papers published relating to microemulsion polymerization [74]. Microemulsion polymerization is known as a new and advanced method, yet effective to produce nanosized polymer particles. Microemulsion polymerization may appear similar to emulsion polymerization, which is because both methods can produce colloidal polymer particles, but completely different when comparing both methods based on the kinetic. Microemulsion polymerization exhibits only two reaction rate intervals, while for emulsion polymerization three reaction rate intervals are detected. Besides, particle sizes and the average number of chains per particle of microemulsion polymerization are significantly smaller than in emulsion polymerization [75]. Microemulsion polymerization is a stable dispersion that contains two immiscible liquids (like oil and water stabilized by the interfacial film) and with the addition of surfactant and/or cosurfactant. The cosurfactant is not compulsory in the microemulsion polymerization method, in which it is mostly used to reduce the electrostatic repulsion forces between the adjacent surfactant molecules, assist in lowering the interfacial tension to be close to zero and decrease the persistence length of the interfacial film [76].

Microemulsion polymerization can be used to synthesize copolymerization of butyl acrylate (BA) onto poly(ethylene glycol) dimethacrylate (PEGDMA). The research utilized microemulsion polymerization to improve and alter the physical properties of the base polymer [77]. PEGDMA widely contributes in biomedical, such as cell encapsulation, tissue engineering and drug delivery. This may be due to its unique characteristics, which are highly hydrophilic and can be adjusted. For instance, the molecular weight and water content of the PEGDMA can be modified to obtain the predetermined polymeric NPs [78]. The monomers of BA and PEDGMA were used in the formation of copolymerization of BA and PEGDMA (BA-co-PEGDMA), which the weight concentrations of BA (50%, 60%, 70%, 80% and 90%) will serve as manipulated variables. Potassium persulfate (APS) and SDS were used as initiator and surfactant for the polymerization, respectively. The dispersion medium for the reaction is water. Based on the research, high conversions and polymerization rates obtained for microemulsion polymerization of BA and PEGDMA at different values of weight concentrations of BA. In fact, the conversions also occur at relatively low reaction times. Despite that, there is a drawback to produce BA-co-PEGDMA, in

which the stability of the BA-co-PEGDMA is influenced by the weight concentration of PEGDMA. The most stable BA-co-PEGDMA is the ones that contain less than 30 wt.% of PEGDMA (above 70 wt.% of BA) [77].

Other than that, poly(methyl methacrylate) (PMMA) is also an example of hydrophilic polymer NPs that has obtained much attention in nanotechnology. There are various methods that can be used to synthesize PMMA, in which microemulsion polymerization is also included [65, 74]. PMMA is broadly used in biomedical, which is due to its being biocompatible and non-toxic. In addition, PMMA is also approved by the Food and Drug Administration (FDA) for medical [79]. The monomer used to produce PMMA is methyl methacrylate (MMA). There were three types of surfactants used to investigate the effect of different surfactants to produce PMMA. The surfactants are anionic surfactant (sodium dodecyl sulfate, SDS), non-ionic surfactant (phenol exthoxylate, NPE) and cationic surfactant (cetyltrimethyl ammonium bromide, CTAB). The potassium persulfate (KPS) was used as initiator for the polymerization [80]. Based on the research, SDS, NPE and PMMA can be used as surfactants in polymerization but have different rates of reaction. This is because of the differences in the head-group structure of the surfactants.

Polyaniline (PANI) NPs is one of the most deliberated conducting polymers, which is because of the presence of the -NH- group at either side of the phenylene ring. Apart from that, PANI is a famous NPs because of easily obtained, regenerability, porous texture, easy synthesis route and excellent environmental stability [81,82]. PANI is a hydrophilic polymer NPs, which is usually used to modify and improve the hydrophilicity of the other polymer [83]. Recently, scientists have discovered that hydrophilic PANI can be synthesized by using microemulsion polymerization. The cationic surfactants used during the microemulsion polymerization are octyl trimethyl ammonium bromide (OTAB) and dodecyl trimethyl ammonium bromide (DTAB). Based on the research, surfactant concentration, surfactant spacer length and polymerization temperature can be used to control the size of the PANI NPs. The monomer and redox initiator used in the microemulsion polymerization are aniline and ammonium persulfate (APS), individually. This research managed to discover and prove that increasing the concentration of the surfactant and decreasing the temperature will affect the diameter of the PANI. Besides, the synthesis of PANI using microemulsion polymerization can increase and improve the conductivity of PANI compared to the PANI produced from conventional bulk polymerization [84]. Recently, PANI synthesis using microemulsion polymerization can be applied in the food industry, which PANI obtained is used to remove azo dyes (such as sunset yellow and congo red) in the food dyes [85].

Polypyrrole (PPy) is mostly used by other scientists due to the PPy being biocompatible, non-toxic, stable and have pH-dependent permeability towards the small organic molecules. Besides, PPy NPs are mostly infused into the polymer capsules to act as drug carriers, which can be proved as gamma imaging and can be performed with the PPy microcapsules that are filled with gold NPs [86]. The synthesis of PPy was produced by using micro-emulsion polymerization with the different concentration of surfactant varied from 50 to 200 nm, while for the change in concentration of surfactant varied from 0.8 to 0.44 M [87]. This research obtained a similar result to PANI NPs, in which the diameter of the NPs will change with the increase in the concentration of surfactant and decrease in the temperature. There was also PPy NPs synthesized via microemulsion polymerization using SDS as surfactant. During the polymerization, polyvinyl alcohol (PVA) was added to alter the structure and properties of the PPy NPs [88]. In this study, the synthesis of PPy with and without PVA were compared. It can summarize that PPy NPs with the addition of PVA showed better orientation and conjugation length than the PPy NPs without the presence of PVA.

Synthesis by Inverse Miniemulsion Polymerization

Inverse miniemulsion polymerization is another broadly applied technology for the preparation of high molecular weight water immiscible macromolecules because of the high concentration of monomers can be gained within the aqueous droplets without disturbing the monomer or polymer [89]. In general, inverse miniemulsion polymerization is a two-phase system consisting of an aqueous dispersion of relatively small, stable, and narrowly distributed droplets within a size range of 50 – 500 nm (Figure 7). The major factors which distinguish between conventional emulsion polymerization and inverse miniemulsion polymerization are the monomer is dispersed in aqueous phase instead of non-polar phase, and it is involved the use of a high shear device and a liphophobe. The inverse miniemulsion polymerization involves the utilization of water-soluble monomer which is dissolved in a polar dispersed phase which consists of non-polar solvents. Usually, the hydrophilic monomer used in the inverse emulsion polymerization is in the form of aqueous solution. Then it is emulsified in a continuous phase by using a water-in-oil (W/O) emulsifier and the polymerization process is initiated either by an oil-soluble or water-soluble initiator. The average particle size that can be produced from inverse miniemulsion polymerization is as small as 0.05 microns [90]. There are many hydrophilic polymer NPs had been managed to be synthesized by other scientists, such as poly(2-hydroxyethyl methacrylate) (PHEMA), poly(methacrylic acid-co-acrylamide) (PMMA-co-Aam) and poly(acrylamide) (PAM).

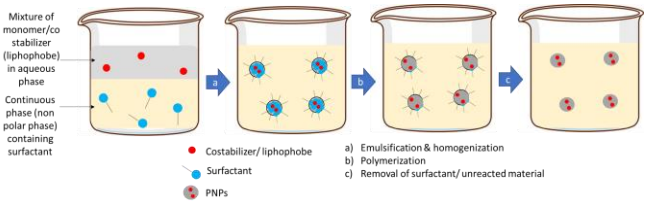


Figure 7 Inverse miniemulsion polymerization

Hydrophilic polymer PHEMA NPs can be synthesized using inverse emulsion polymerization because of unique characteristics, such as biocompatibility and biodegradability. Based on the study, the effect of sonication time and sonication amplitude of PHEMA produced via emulsion polymerization are used to determine the effect on the particle sizes of the PHEMA produced. The dispersed phase contains monomer (HEMA) while the non-polar continuous phase employs surfactant (Span 80). The sonication time used to analyze was from 10 to 30 min and sonication amplitude up to 60% [91]. The hydrophilic PHEMA NPs obtained from the experiment showed that sonication time and amplitude did affect the particle sizes of PHEMA and the solubility test proved that PHEMA can dissolve in the aqueous medium, yet the process was slow. In conclusion PHEMA can be produced by using inverse miniemulsion polymerization.

Hydrophilic poly(methacrylic acid-co-acrylamide) P(MAA-co-Am) was also successfully synthesized using inverse miniemulsion polymerization. The polymerization of methacrylic acid (MMA) and acrylamide (Am) was crosslinked by methylenebisacrylamide (BIS) in the ultrapure water. N,N,N',N'- tetramethylethylenediamine was also added into the mixture. The co-surfactant (dioctyl sulfosuccinate (AOT) and Brij-30 with the molar ratio of 1:5) was used as a surfactant, which was dissolved in the hexane and served as a continuous phase. The ammonium persulfate (APS) in ultrapure water was used as initiator to initiate the polymerization [92]. The research used different values of crosslinker and MMA to identify their influences on the swelling ratio and swelling response. Increasing the amount of crosslinker will decrease the molecular weight between the crosslinker, which results in the decreasing of swelling ratio. Different values of MMA did not affect the swelling response but caused the shift of the hydrodynamic diameter. Consequently, the hydrophilic P(MAA-co-Aam) can be produced via inverse miniemulsion polymerization. However, there is a weakness detected from the NPs produced, which is low degree of polydispersity [93].

Polyurethane (PU) is also an example of hydrophilic polymer NPs that can be synthesized using inverse miniemulsion polymerization. Sodium chloride (NaCl) was dissolved in a hydroxyethyl starch solution. Then, it was added into the toluene polyglycerol-surfactant solution. The polymerization was initiated by the toluene-2,4-diisocyanate (TDI) [94]. The research discovered that increasing the concentration of the surfactant will result in the decreasing of the NPs size obtained. Other than that, hydrophilic poly(acrylamide) (PAm) NPs were also managed to be synthesized via inverse miniemulsion polymerization with the monomer acrylamide (in dispersed phase) and Tween 85 as surfactant was contained in the cyclohexane. The time taken for the acrylamide to be formulated in the cyclohexane (continuous phase) was very fast and achieved final conversion within several minutes [95]. Therefore, hydrophilic PAm also can be produced using inverse miniemulsion polymerization.

In summary, emulsion polymerization, microemulsion polymerization and inverse miniemulsion polymerization can produce hydrophilic polymer NPs. In addition, these methods also manage to improve the performance of polymers, such as increasing the solubility in aqueous medium and increase the stability of the polymer nanoparticles produced.

4.0 APPLICATIONS OF HYDROPHILIC POLYMER NANOPARTICLES

Polymeric NPs have been widely used and discovered in nanomedicine due to their unique advantages in the treatment of disease. Nanomedicine uses nanoscale materials, such as biocompatible nanoparticles and nanorobots for the diagnosis, delivery, or medication purposes in a living organism. In cancer treatment, nanomedicine produced from polymeric NPs can attack viral diseases and have higher treatment success rate when compared with other medicine [96]. Polymeric NPs are organic strategies for nanomedicine, in which nanomedicine can be used to determine the best and ideal nanosystem for more effective and specifically delivery of therapeutic applications. Regardless, there is an obstacle in this field due to the various combinations of intricate physiological systems and the massive feature considerations and corresponding effects. This has created a complex system to be analyzed [97]. Polymeric NPs function as drug carriers is a strategy, which aims to optimize therapeutic effects while minimizing the adverse effects. The selection of base polymers to prepare polymeric NPs are depending on numerous design and end application criteria, such as the size of the desired NPs, properties of the drug to be encapsulated in the polymer, surface characteristics and functionality [98].

Recently, there are numerous studies starting to utilize hydrophilic polymer NPs for drug delivery. Polyvinylpyrrolidone (PVP) is a hydrophilic polymer NPs that has been used in biomedical fields to form different drug delivery systems, such as oral, topical, transdermal, genes and ocular administration. The use of PVP alone or combined with other polymers has succeeded in improving drug dissolution, and disintegration properties [99]. In addition, scientists discovered that PVP had the longest mean residence time (MRT) of all polymers with the same molecular size. This can be proved as tumor necrosis factor-a (TNF-a) bioconjugated with PVP (PVP-TNF-a) can circulate longer than TNF-a bioconjugated with polyethylene glycol (PEG-TNF-a), in which the same molecular size is used [100]. Generally, MRT is defined as the average total time a drug molecule spends in the introduced kinetic space, which is influenced by the site of input and the site of elimination [101]. Apart from the fact that PVP had been widely used in medical field, there are still some significant weaknesses, such as can be used at certain levels, allergic reaction to some people, subcutaneous granulomas, pulmonary vascularization, and reticuloendothelial system (RES) deposition [102].

Consequently, more research needs to be done to discover ways to minimize or eliminate the weakness of PVP.

Other than that, polylactic acid (PLA) is also one of the polymer NPs that is broadly used as a drug carrier, yet PLA must undergo polymerization with another polymer to improve the hydrophilicity of the surface of PLA. Thus, it can function as a hydrophilic polymer NPs drug carrier. Polyethylene glycol (PEG) is one of the common hydrophilic polymers for surface modification and has been utilized to alter the hydrophobic PLA to form amphiphilic copolymer PLA-PEG, in which can be used to deliver both hydrophilic and hydrophobic drugs [103, 104]. PLA has many unique properties that made PLA widely used in biomedical applications, such as in dermatology, cosmetics, and tissue engineering [105]. PLA-PEG consists of PLA as the core, which serves as reservoir for the active pharmaceutical ingredients (APIs) and PEG as the surface, which serves as a stealth corona to avoid macrophage. Polymeric NPs can allow for higher drug content than convention formulation. PLA-PEG can be treated as a drug carrier whose size and shape are influenced by the proportion of PLA and PEG blocks and the polymer-solvent interactions [106]. In addition, the excellent biocompatibility between PLA-PEG has caused the surface layer, which is PEG can increase the solubility of insoluble drugs, prevent the absorption of protein on the NPs surface and also made NPs unidentifiable by the reticuloendothelial system as foreign bodies [107].

Therapeutic devices and scaffolds were designed using PNIPAM-based thermoresponsive hydrogels for drug delivery and tissue engineering. From a physiological standpoint, the negative swelling transition that PNIPAM exhibits at 34 °C makes it an appealing system for many applications in which research publications are continuously increasing. There have been several additional PNIPAM co-networks that have been synthesized with medical devices designed to deliver antimicrobial agents [108]. In cell sheet and tissue engineering, PNIPAM provides an excellent substrate for attaching, proliferating, and aggregating cells at 37°C, and allows cells to be detached just by switching the temperature, without the use of trypsin. The culture of cell spheroids within PNIPAM hydrogels has previously been performed, and at temperatures below LCST, the hydrogels liquified and the cell spheroids were released [109]. Bioengineering of bone tissue with PNIPAM-HAp scaffolds offers many advantages. Rather than acting passively as hydrogel composites, they will interact and respond to the biochemical environment as gates [110]. A new smart hydrogel with patterned structures based on PNIPAM is opening opportunities for the design and production of soft bionic actuators that take inspiration from the structure and movement of various plants and animals. Due to their temperature-responsive transparency, PNIPAM-based smart hydrogels may be used as smart windows to control the amount of sunlight to be admitted to the building. PNIPAM-based smart hydrogels exhibit injectability, biocompatibility, and biodegradability when combined with various monomers incorporated into the polymer structure to be useful in biomedical applications, such as drug delivery and cell delivery. A uniform coating of PNIPAM-based hydrogels on the surface of cell culture dishes permits the formation of a tissue-like cell layer, known as a "cell sheet", as well as the detachment of this cell sheet by controllable hydrophilic surfaces. Hydrogels based on PNIPAM have great potential for promising reconfigurable smart materials with many applications [111].

Furthermore, PEGs with high molecular weights have been widely used to microencapsulate active pharmaceutical ingredients. PEGs reduce the need for harsh solvents during encapsulation. Occasionally, eye drops contain PEG to lubricate the eye. PEG is an ideal excipient for liquid dosage forms because of its resistance to mold growth and rancidity. Liquid PEGs (up to 1000 moles per liter) are generally used as suspension agents or stabilizers in emulsions. As well as being used as a solubilizer for drops ophthalmic or optic preparations, it is also used as part of liquid-filled gelatin capsules. Several drugs have been encapsulated with PEGylated biodegradable polymers to extend their half-life and reduce dosing frequency. Additionally, PEG coatings have been applied to biomedical devices to prevent or reduce the possibility of non-specific or immunogenic interactions with surrounding tissues while simultaneously maintaining their functionality. With PEG coatings, the device's functionality and biocompatibility can be improved and its thrombogenicity can be minimized [30]. Hydrogels based on PEG can easily encapsulate chemical drugs or active macromolecules by simply mixing them with solution at room or low temperature, and this process yields little drug loss, facilitating high dosage efficiency (nearly 100%) [112]. PEG has been employed in therapeutic strategies for many years. Using PEGylation to modify therapeutic proteins or liposomes, one can reduce immunogenicity and toxicity, prolong the blood circulation time, alter biodistribution, and increase protein activity [113].

Besides, PEG has been suggested for use in nanocellulose films as a plasticizer. When PEG is added, the top side of the film becomes rougher. PEG also has a positive influence on the dressing, permitting it to be more flexible and conformable in a wound bed. This implies that the PEG has a positive impact on the mechanical properties of the dressing, making it more flexible, ductile, and potentially conformable [114]. A PEG-coated nanoparticle showed mucus-permeability and will easily penetrate the gut epithelium and move down the gastrointestinal tract more rapidly. The nanoparticles reached the cecum two hours after administration [115]. PEG showed excellent hydrophilic and lubricative properties. Further, polymeric biomaterial surfaces have been immobilized with PEG to prevent protein absorption and adhesion to cells [116]. PEG has been studied for many years to enhance dispersion and mechanical properties of materials. PEG was proven to have excellent friction-reducing and anti-wear properties and can be used as a nano additive for water-based lubricants that are

environmentally friendly and safe [117]. PEG has been extensively used to modify the surfaces of nanoparticles. Nanoparticles decorated with PEG are able to circulate well and accumulate in the tumor site over time, because PEG has the properties of biodegradability and non-immunogenicity.

PEGylation prevents nanoparticles from adhering to macrophages and, therefore, prevents their opsonization. Many opsonized nanoparticles could circulate in the blood for a long period of time, eventually accumulating in the body. Alternatively, the PEG-attachments to hydrophobic polymers have improved both the amphiphilicity and the self-assembling properties of the synthesized block copolymers. In the treatment of breast cancer, PEGylated N-(2 hydroxypropyl) methacrylamide polymeric micelles were developed for doxorubicin delivery [118]. Plasmid DNA can be very efficiently encapsulated into PLA-PEG nanoparticles leading to rapid or controlled release of plasmid DNA depending on the conditions under which the NPs are processed [119].

Another effective small molecule delivery system is HPMA. There have been no negative reactions reported after using PHPMA in vivo [120]. Moreover, it is used in the form of NPs to expand the blood but because of its high biocompatibility, it is used to deliver drugs in medical application [45]. PHPMA brushes have shown to maintain antifouling properties when subjected to different shear stresses, like those found in the human body. In use of a citrate buffer, it was shown that the PHPMA brush reduced *E. coli* adhesion by as much as 90% compared to bare glass, and this effect lasted for only 30 minutes following biofilm formation [121]. HPMA has also been reported to have fewer negative effects than PEG, which suffers from accelerated blood clearance and allergic reaction. HPMA also solubilizes hydrophobic drugs, and it shows great stability as well as high drug loading capacity. Aside from stabilizing proteins, HPMA can also enhance catalytic or biological activity, enhance resistance to proteolysis, increase biodistribution and modify pharmacokinetics and pharmacodynamics [126]. The main method of excretion of PHPMA from the body is through the kidneys since it is largely water soluble. By conjugating a drug to the HPMA polymer backbone, the drug becomes more solubilizing and stable, with a higher half-life in blood circulation [50]. Polymerized PHPMA polymer is useful for fabricating nanoparticles that are encapsulated with drugs of interest via cleavable units, allowing the medication to be released or delivered in the body [122].

5.0 CONCLUSION

The convenience of synthesizing and designing synthetic polymers with a broad variety of physical properties and chemical properties made them particularly attractive in a wide range of technical and medical applications. In virtually all areas of research and practice, synthetic hydrophilic polymers are in widespread use in biomedical applications such as tissue engineering, drug delivery, therapeutics, and orthopedics fixation. In addition, even though the hydrophilic polymer NPs are produced synthetically, the performances are more excellent from the natural hydrophilic polymer NPs. For example, synthetic hydrophilic polymer NPs are biodegradable, biocompatible, and also low toxicity. These qualities have made hydrophilic polymer NPs a great deal for many applications. The primary features to take into consideration when selecting a polymer are stiffness, tensile strength, and elasticity, but also biocompatibility and toxicity. Synthetic hydrophilic polymers such as PNIPAM, PEG, PVA and PHPMA have led to immense advances in chemical synthesis and analysis in recent decades. Synthetic hydrophilic polymer NPs also managed to be produced from the polymerization of the monomers, such as emulsion polymerization, microemulsion polymerization and inverse miniemulsion polymerization. However, more research needs to be done on the production of hydrophilic polymer NPs by inverse miniemulsion polymerization. This is because less research has been done on this method compared with the other two methods. Other than that, this review proves that hydrophilic polymer NPs are suitable to be used in a broad range of applications particularly in medical and drug delivery.

Conflicts of Interest

The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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