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REVIEW ARTICLE

Applications of Synthetic Aromatic Polymers in the Biomedical Field: A Review

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ABSTRACT

The use of polymers as biomaterials has greatly influenced the advancement of the biomedical field. Various types of natural and synthetic polymers have been developed and modified to meet the requirements to be used in modern medicine. Among them, synthetic aromatic polymer such as polyetheretherketone (PEEK), polyethersulfone (PES), polyetherimide (PEI), polyurethane (PU), and polyaniline (PANI) have been widely used in tissue engineering, therapeutics, surgical sutures, drug delivery, diagnostics, implants, and dentistry. These polymers had excellent thermal and mechanical stability, but they still needed to be modified to enhance certain properties. Therefore, polymers with the desired physical, biological, chemical, biomechanical and degradation properties must be considered in order to meet functional requirements. This review briefly discussed the use of synthetic aromatic polymers in biomedical applications in terms of their properties, material design and use, as well as developments, current progress and challenges based on previous research reports.

Keywords: Synthetic, Aromatic polymer, Biomedical, Medical device, Biocompatible

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INTRODUCTION

The term polymer comes from two combinations of Greek words which are poly and meros which refer to 'many' and 'many parts' respectively (1). Polymers had given a new dimension in biomedical applications as well as the largest and versatile class of biomaterials. Generally, aromatic polymers are aromatic compounds that consist of conjugated planar ring systems with delocalized pi-electron clouds in terms of individual alternating double and single bonds. The aromatic polymer is also known as arenes and the examples of this compound are benzene and toluene. This type of polymer usually had excellent mechanical (high toughness, strength, and ductility) and thermal stability (able to stand operation temperature) because of the close loop of electrons (2). Therefore, the aromatic polymers widely used in several application such as related to construction, automobile, electronics, aviation, and packaging industries, where acts as a medium for energy storage, energy transmission, or energy converter.

The polymers are divided into natural and synthetic classes where each of them provides different benefits for biomedical applications. In this review, the focus was only on synthetic aromatic polymers which are PEEK, PES, PEI, PU, and PANI. Synthetic polymers are more preferable in many industrial and research area it can be modified, designed, and synthesized with a large variety of structures and require physicochemical properties, which contribute to increasing interest in biomedical applications such as tissue engineering, bone implant, diagnostic media, drug delivery, and therapeutics (3). Besides, this polymer also offers ease of processing, flexibility, and lightweight, It is commonly human-made polymers, where often develop from petroleum oil. There are four main categories of synthetic polymer which are thermoplastics, thermosets, synthetic, and elastomers fibers were consist of a backbone made of carbon-carbon bonds and heterochain (oxygen, nitrogen, and sulfur). The common backbone of these polymers is polysulphone, polystyrene, polysulfides, polyetheretherketone, and polyamides.

The usage of synthetic aromatic polymer in biomedical had increased from year to year to treat and support patients with various diseases using their utilization in blood and tissue interacting medical devices and drug delivery systems. The first utilization of polymer in the biomedical field starting in the 1960s. Until recently, there are numerous successful synthetic aromatic polymer designs but challenges still exist, especially the degradation time (3). Usually, the polymer used for medical material degrades over time, thus, several strategies had been introduced to improve the stability and some properties. Therefore, deep research on selecting and modifying the polymer had been made by researchers through combining biology, chemistry, materials, clinical and engineering practice to produce advanced polymer-based biomaterial. The polymer utilized for biomedical application should be non-toxic, biocompatible, biodegradable, and meet specific requirements due to it has direct contact with the human body.

The application of synthetic aromatic polymers in the biomedical field was extensively reviewed based on the reported studies. Besides, the requirement and properties need to be fulfilled in selecting and designing the polymeric-based material and the type of synthetic aromatic polymers were briefly discussed on their properties, usage, and application in the medical field.

PROPERTIES REQUIREMENT OF POLYMER FOR BIOMEDICAL APPLICATION

The safety of polymer biomaterial is crucial because of the direct interaction and contact with the human body. The specific requirement should be fulfilled to avoid any disaster toward a human. Three basic properties need to achieve before used in a biomedical application which are self-healing, adhesion, and superhydrophobicity (4,5). A lot of studies have been carried out to obtain the mentioned properties.

Self-healing

The human body is a unique creature where when the injury occurred the repairing or replacing are take place to heal the damaged tissues that known as self-healing. However, this condition happens for non-serious tissue damage. Meanwhile, the serious damage or injury beyond self-healing the alternative 'material' is required to help the healing process through an implant. The main factors that affected the implant are aging, load, and wear. Therefore, the researchers aim to develop a material that can self-heal. The 1st generation of self-healing employs polymer and its composite material to irreversibly repair without restore the damaged matrix. The 2nd generation reversibly restores the damaged matrix. Several polymers and their composites were largely developed and used due to their advantages and ability to solve the drawbacks associated with the polymer matrix. In summary, the polymeric based materials should obtain the following properties:

a. The material had self-healing properties where it able to heal the damaged or injured part several times.
b. Managed to automatically heal the material.
c. Able to treat and heal any size of a material defect.
d. Affordable maintenance cost.
e. Exhibit excellent mechanical, thermal, and performance.
f. Economy than commercial material

Besides using pristine polymer, composite materials such as nanoparticles and another modifier are also added to improve the mechanical, thermal, and other physical properties of polymeric-based self-healing materials. The pristine polymers have lower modulus and strength than metal and ceramic where improvement is necessary.

Adhesion

Adhesion is classified as a factor obtained by animals and plants as well as other organisms for living. This facilitates the organism to attach to the host or vice versa permanently or temporarily. There are many ways are adhesion is necessary and utilized by plants, animals, and bacteria as described in the Bassas-Galia study (5). The polymeric-based material with adhesion has been produced and utilized in biomedical applications.

Superhydrophobicity

Polymeric-based material with superhydrophobic surfaces achieves high mechanical stability due to low ability in absorbing water as well as less swelling degree. This characteristic is always obtained in many plants and insects. Therefore, the polymer should have superhydrophobic properties to make it useful for biomedical application in reducing the chance of blood coagulation contribute from platelet adhesion.

TYPES OF SYNTHETIC AROMATIC POLYMER

This part describes the characteristic of commonly used aromatic synthetic polymer in biomedical applications. The PEEK, PES, PEI, PU, and PANI-based material were selected to deeply discover their properties, benefits, and their performance.

Table I : Application of synthetic aromatic based polymer for biomedical areas

Modified Polymer	Applications	Type of experiment	Remarks	References
			Polyetheretherketone	
Hydroxyapatite (HA) whisker-reinforced polyetheretherketone	Bone ingrowth scaffolds for orthopedic implant fixation and interbody spinal fusion	In vitro	- The Hydroxyapatite whisker-reinforced polyetheretherketone was prepared using a combination of powder processing, compression molding, and particle leaching methods. - Has porous structure with 75–90% porosity and 0-40 vol. % HA reinforcement. - The Micro-CT showed that the scaffold porosity was interconnected and within the size range needed for bone ingrowth.	(6)
Nano-titanium dioxide/ polyetheretherketone (PEEK)	Bone substitute material or metal implant material in dental and orthopedic applications	In vitro and in vivo	- The composite polymer was prepared by powder mixing and compression molding methods. - The titanium dioxide dispersed uniformly in PEEK matrix and the smooth and rough sample surface. - Finding from in vitro bioactivity showed that the material combination promoted cell attachment and improved osteoblast cell spreading. - Finding from in vivo showed that the enhanced bone regeneration around implants by titanium dioxide resulted from higher bone/tissue volume and vivid visualization in 3D and histologic images.	(7)
PEEK – Optima (Invibio)	Maxillary obturator prosthesis	In vivo	- Commercial PEEK – Optima (Invibio) was used in this research. - The PEEK – Invibio had high biocompatibility, low specific gravity (1.31 g/cm^3) similar to polymethyl methacrylate, ease of polishing, resistance to cracking, flexural bonelike modulus, and machinability. - The procedure from this study is better than traditional techniques where the use of PEEK facilitate the fabrication of the antral section of the palatal prosthesis and led to more lighter obturator prosthesis. - PEEK-Invibio provided the patient with a more functional, better-adjusted, and lighter prosthesis.	(8)
Carbon fiber reinforced (CFR) PEEK composite	Orthopedic and dental implant material in tissue engineering, bone repair, and regeneration applications	In vitro	- The fused deposition modeling (FDM) was used to fabricate CFR PEEK composite. - The result showed that the CFR PEEK obtained better mechanical strengths than the printed pure PEEK. - FDM-based composite PEEK had highly rough topographies, high biocompatibility, and non-toxicity.	(9)
			Polyethersulfone	
Hydrophobic PES blended with fluorinated polymer membrane	Venting and sterile barrier	In vitro	- The hydrophobic PES was fabricated by modifying the inner and outer surfaces. - A fluorinated polymer was composited to the hydrophobic PES via surface crosslinked using a continuous thermal process. - The membrane had high mechanical stability and a rigid surface.	(10)
Isothermal nucleic acid amplification – Porous PES	Paper-based molecular diagnostic devices for point-of-care applications	In vivo	- The PES based materials are less expensive than typical used LFD membrane - This material yielded statistically significant amplication using LAMP when excess liquid was available. - The porous PES materials had the potential to be used as paper-based molecular diagnostic devices as its success in amplication reactions of all tested materials (four separate DNA and RNA targets – Bordetella pertussis, Chlamydia trachomatis, Neisseria gonorrhoeae, and Influenza A H1N1).	(11)

Nanozeolite and vitamin E D-α-Tocopherol polyethylene glycol succinate based PES	Hemodialysis	In vitro	- The Hollow fiber membrane (HFM) of PES was composited with Tocopherol polyethylene glycol succinate as additive and Nanozeolite as a filler. - The membrane was prepared via spun of dry-wet spinning approach based on liquid-liquid phase separation. - The HFM composite PES showed improved hemocompatibility where lower hemolysis percentage (0.28%: batch mode; 0.32%: continuous mode), higher coagulation time, lower platelet adhesion, and lower protein adsorption (16.34 μg//cm^2) than commercial HFM membrane.	(12)
		Polyetherimide		
Photosensitive PEI	Implantable medical device	In vitro	- The photosensitive PEI film was prepared through spin-coated material on silicon wafers, cured at temperatures ranging from 150 to 450 ˚C, and sterilized by autoclaving. - The result showed that the film was noncytotoxic than the negative control of polyethylene and the conventional PEI. - The film also obtained good and better spreading, morphology, and fibroblast adhesion.	(13)
PEI	Biological cell culture	In vivo	- The research compared the cultivation of stromal marrow cells (OP9) on transparent PEI, PEEK, and paralyne (PA). - The micro trenches were fabricated on polymer films by hot embossing with a depth and width of 5 μm. - The cultivation evaluation of OP9 was performed via mold fabricated with micromachining process technology. - The transparent PEI film obtained the most optimal structure for cell culture, and the cell grew able to be observed using an optical microscope compared to PEEK and PA.	(14)
PEI-modified magnetic Fe_3O_4 nanoparticles	Delivery therapeutic small interfering RNA	In vivo	- The research aimed to prepare PEI-modified magnetic Fe_3O_4 nanoparticles for siRNA delivery into Ca9-22 oral cancer cells. - The Fe_3O_4 nanoparticles were synthesized based on the oxidative hydrolysis method. - The Fe_3O_4 and PEI were further synthesized in acid and alkaline solution, precipitated, and ultrafiltration process. - The results showed that this material is suitable for siRNA delivery as it providing satisfied siRNA dispersibility and adsorption capacity.	(15)
PEI decorated with iron oxyhydroxide (FeOOH)	Small interfering RNA	In vitro and in vivo	- This research developed a novel FeOOH nanoparticle with the surface was altered with branched PEI for delivering siRNA into the cancer cells. - The material was synthesized via heated continuous stirring. - The result showed that PEI-FeOOH achieved efficient complex siRNA, mediated endosomal escape, and effective cellular uptake. - PEI-FeOOH/siRNA formulation incorporated with anti-RRM2 siRNA effectively activated the growth of tumor tissues, and obtained excellent safety profiles in vivo.	(16)
		Polyurethanes		
PU – pH sensitive macrodial, L-lysineethyl ester-diisocyanate and L-lysine derivative tripeptide as chain extender	Drug delivery	In vitro	- Introduce novel methods in preparing amphiphilic multiblock PU with pH sensitivity and biodegradability. - This material had high microphase separation, able to be cleaved in acid media, degraded in enzymatic solution, good biocompatibility, able to be self-assembled into micelles.	(17)

Transparent PU dressing	Surgical dressing	In vivo	- A pilot study to evaluate the chlorhexidine-impregnated dressing with polyurethane dressing to avoid the colonization of the catheter tip through migration from skin of critically ill adult patients with a short-term percutaneous central venous catheter (CVC). - No significant difference was found in the two groups (chlorhexidine and polyurethane) for skin site colonization, catheter tip colonization, skin irritation, number of unplanned dressing changes, catheter insertion site infection, and catheter-related bloodstream infection. - The patients well tolerated both dressings.	(18)
		Polyaniline		
PANI mediated polymeric nanoparticles	Photothermal cancer therapy	In vitro	- Platinum nanoparticles based PANI was prepared using a modified thin-film hydration method - The prepared PANI showed a favorable morphology in water, targeting tumors via the high affinity between trastuzumab and the overexpressed Her2 in tumor cells. - The prepared nanoparticles showed exciting photothermal conversion efficiency induced by NIR light and provide significant cell inhibition efficiency (94%) in vitro.	(19)
Rectangular shaped hollow PANI tubes	Drug delivery	In vitro	- The PANI tubes were developed by in situ Acid Red 8 crystals as a water-soluble template. - The material had high water-soluble drugs properties. - The PANI tubes produced a sustained release of the entrapped dye, and the resulted behavior depend on environmental pH.	(20)
PANI composite silica nanoparticles	Near-infrared light response bioimaging	In vitro and in vivo	- Introduce a new synthesis approach for silica nanoparticles, which included combining these nanoparticles with targetable and non-targetable fluorescent dopamine conjugated hyaluronic acid using rational chemical dehydration. - The composite material obtained high fluorescence intensity, mono-disperse in solution, respond to near-infrared light, and was amenable to certain labeling of cancer cell lines.	(21)
Lanthanide-based upconversion nanoparticles/ PANI	Bioimaging and photothermal cancer therapy	In vitro and in vivo	- Introduced a nanosystem based on upversion nanoparticles coated with a layer of PANI nanoparticles. - The material does not toxic the cells even at a high concentration (800 μg mL^{-1}), nontoxic to mice, and efficacy in photothermal cancer cell ablation. - Practical effect in vivo tumor ablation after irradiation via the 808 nm laser.	(22)

Table I summarizes the past studies of synthetic aromatic polymers in biomedical applications.

Polyetheretherketone

The PEEK is classified as a polyaromatic semi-crystalline thermoplastic polymer (Fig. 1a). The chemical of PEEK is $(–C_6H_4–O–C_6H_4–O–C_6H_4–CO–)_n$ and it is inert, were insoluble in almost all solvents. However, the PEEK highly soluble in concentrated sulfuric acid. The melting temperature of PEEK is 334°C, Tg is 145°C and crystallization peak is 343°C. These thermal properties make PEEK compatible with the human body. The first commercialization of PEEK for an industrial field is in the 1980s, while for the biomedical field it started used in 1998 by Invibio Ltd. (Thornton-Cleveleys, UK). Similar year, the Victrex company (London UK) had introduced PEEK-OPTIMA that suitable for long-term implantable applications. The PEEK based on composite material was developed to replace the usage of conventional ceramic and metallic devices. Up to now, the PEEK-LT1, PEEK-LT2, and PEEK-LT3 were widely employed in the surgical field such as maxillo-facial surgery, spine surgery, and orthopedic surgery. The PEEK LTI consists of different amounts of β-tricalcium phosphate and hydroxyapatite. The first reported PEEK polymer devices were used for fracture fixation by utilizing carbon reinforcement in a PEEK matrix.

Polyethersulfone

The PES is one of the common polymeric material used in biomedical application because of it unique and promising properties such as excellent mechanical, thermal, and hydrolytic strength in both wet and hot conditions. Generally, the PES is chemically developed from bisphenol A and dichloro-diphenyl sulfone via a condensation reaction, and proceed with the aromatic nucleophilic substitution (Fig. 1b). Commonly, the polymeric-based material is amorphous and transparent in structure, besides, having high glass transition temperature (Tg) up to 225 °C. Several companies such as Ultrason Solvay (Radel), BASF (Ultrason E), Sumitomo chemical (Sumika excel) company had commercially produced the PES polymer. Among them, the Ultrason and Radel PES are always selected by researchers and scientists for synthesizing and designing purposes. The Ultrason PES has 58 kDa of molecular weight and Radel PES has 15 kDa molecular weight. The pristine PES has a moderate hydrophobic characteristic which is suitable to be used for biomedical applications. Among the usage of PES in clinical practice are venting, sterile barrier, cell culture bag, and reactor.

Polyetherimide

The PEI consists of aromatic rings coupled by imide linkages, where the linkages have two carbonyls (C=O) groups that attached with the same nitrogen (N) atom (Fig. 1c). The PEI product (Ultem 1000) from General Electric, Schenectady USA, is commonly used to design and fabricated as material for biomedical applications. Past studies found that the usage of PEI does not lead to cytotoxicity or hemolysis, but, permits the growth and interaction of cells. Therefore, it shows that PEI is biocompatible with the human body. Among the usage, PEI in biomedical applications are biosensors, oxygenators, intraocular lenses, and neuroprostheses. The PEI had considerable mechanical and thermal stability (Tg: 217 °C), excellent chemical resistance, and high dielectric strength, where make it a promising candidate for steam sterilization. Other than that, the PEI also good membrane-forming, and the backbone easy to be chemically modified (bonded with the functional group) which promotes its usage for contacting with tissue cells or blood.

Polyurethane

The PU is a unique polymer that consists of repeating urethane groups and alternating soft and hard segments, which was invented by Professor Dr. Bayer, O. in the 1930s. Generally, the PU is synthesized by the addition polymerization of an isocyanate (diisocyanate), derived from crude oil and a polyol (polyester and polyester), often in the existence of a catalyst and a chain extender to produce the desired polymer (Fig. 1d). Besides, the modifier and additives such as degassing agents, fillers, pigments, and moisture scavengers are added into PU for improvement. It was firstly introduced in biomedical applications in the late 1950s where had been used as breast prostheses and in-situ bone fixation. Therefore, the PU had been commercially produced by Bayer MaterialScience, BASF, Lubrizol with the most promising properties. The PU has excellent biocompatibility, mechanical, thermal, and durability stability, where widely used in medical devices such as artificial organs, wound dressings, and vascular stents. Many researchers continue the R&D of PEI to improve the properties and performance of various biomedical applications.

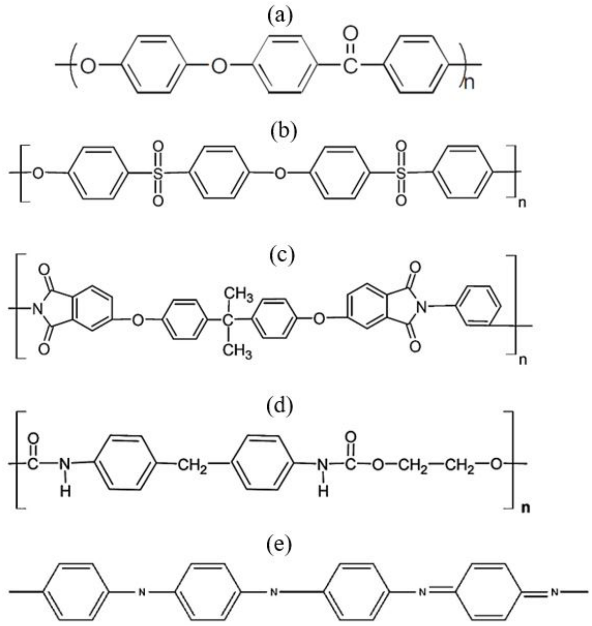

Fig. 1 : Chemical structure of synthetic aromatic polymer : (a) PEEK, (b) PES, (c) PEI, (d) PU, and (e) PANI

Polyaniline

The PANI-based material is one of the well-known synthetic polymers used for drug delivery, antimicrobial therapy, nerve regeneration, biosensors, and tissue engineering (Fig. 1e). Generally, PANI or also known as "aniline black" was introduced in the mid-19th century. Its molecular structure consists of quinonoid or benzenoid units or both types at different amounts. Commonly, the PANI is developed via both chemical and electrochemical oxidative polymerization in an acidic medium. Among the properties of PANI are highly thermal stability (Tg: 40 °C) chemical stability, high structural and chemical structure against alkaline and acidic solutions without suffering chemical degradation. To improve some properties of PANI, the nanomaterials such as chitosan, natural rubber, polyurethane, montmorillonite, and carbon nanotubes were to enhance the mechanical properties.

CONCLUSION

This review describes a comprehensive overview of synthetic aromatic polymers which are PEEK, PES, PEI, PU, and PANI based on their basic characteristic, development, and usage in biomedical applications. The development of various synthetic aromatic polymers has greatly influenced and contributed to the improvement of the biomedical field. Based on pieces of literature studies, the polymers fulfilled the basic properties such as self-healing, adhesion, superhydrophobicity, non-toxic, and excellent mechanical and thermal stability to achieve excellently biocompatible with the human body. Among the usage of these polymers in biomedical applications are the surgical field, medical devices, drug delivery, antimicrobial therapy, nerve regeneration, biosensors, and tissue engineering. The limitation of the pristine polymer can be overcome by modifying the surface structure of the material and compositing with nanocomposite elements such as chitosan, natural rubber, polyurethane, montmorillonite, and carbon nanotubes. Through these designs and modifications, certain properties such as thermal, mechanical, and performance can be improved. However, there is a remaining challenge in utilizing synthetic aromatic polymer in biomedical applications, especially that employed inside the human body, where the cytotoxicity occurs, low biocompatibility, processability, a significant difference of in-vivo and in-vitro research, and physicochemical properties, and it's modified based into biomedical applications that require further R&D from researchers and scientists.

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