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REVIEW ARTICLE

SYNTHETIC POLYMERS AND THEIR USE IN CLINICAL MEDICINE: A NARATIVE REVIEW

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ABSTRACT

A plethora of synthetic, hybrid and biological polymers are widely being used in medical applications. Many polymers are helpful in our civic activities. Their peculiar chemical, physical, and biological properties are applicable in multiple domains of life from engineering to medicine. This review specifically addresses the novel polymers and their applications in clinical medicine. It has been reported by the researchers that, synthetic polymers are not only playing tremendous roles in micro and macro medical-industry but these also play a remarkable role at nano levels as nano-drug carriers in pharmaceuticals. In this review, we will give a brief introduction of polymers and how they are widely being used in medicinal interventions. We will further shed light on the future prospects of polymers with an updated version.

KEYWORDS: Clinical Medicine; Biomedical Polymers; Nanoparticle-Drug Delivery Systems; Synthetic Polymers; Polymers.

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1. INTRODUCTION

Almost everything which is around us is made up of any kind of polymer i.e; natural, synthetic and hybrid polymers.[1] Humans are using natural polymers like hairs, cellulose or horns since the beginning of man-kind. They have successfully mastered in their medical applications like suture materials are being used since thousands of years and dental implants are also being reported since Egyptian civilization and the list goes on.[2]

Human-made synthetic polymers are also multifarious as of natural polymers, even though, their progress and extensive use are reported during and after the advent of World War II.[3] Freshly developed polymers spontaneously took their entry in medical domain, like polyamides and polyesters as man-made suture materials.[4]

Synthetic polymers received spotlight for various reasons; their peculiar chemical and physical properties make them a strong candidate in today's era.[2] For instance, their peculiar characteristics can be attained based on simple monomer units, their polymerization reactions are easily adjustable and controlled.[5] They possess contemporary mechanical properties like shape memory polymers, they can readily deform and attain their original shape with particular stimulus such as temperature, light, magnetic field or PH.[37] There are widely being used in biomedical domain as in vascular stenting, suturing, drug-delivery devices or agents, dental implants, clot removing agents etc.[6] Despite their mechanical properties they also elicit specific functional characteristics. For instance, the cellulose biopolymers are used as drug delivery agents.[21] Possessing organic chemistry, the polymers show allegiance with biological components like cells and tissues.[7] These peculiar properties support them to be widely used in human bodies.[9] Apart from ascendancy, they can also pose a serious threat to human health.[8]

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2. METHODOLOGY

This narrative review was conducted in School of Pharmacy & School of Medicine, Changzhou University, Jiangsu, China from January 2022 to May 2022. In order to assess the applications of synthetic polymers in clinical medicine, this review analyzed all articles published during 1999 to 2022 in both local and foreign journals. To answer this question, different keywords "Clinical medicine", "Biomedical polymers", "Nano-drug delivery carriers", "Synthetic Polymers", "Polymers'' separately and in combination were searched in different electronic databases such as CINAHL, PubMed, Scopus, Web of Science, HEC digital library, and eMedicine. The articles' inclusion criteria were based on the article which contained relevant data regarding applications of synthetic polymers in clinical medicine. Articles with copyright, irrelevant information and lacking the full text were excluded. In the screening step, 93 articles were selected after review of abstract; according to criteria the duplicate and incomplete articles were removed. In last step, 57 articles were selected for the final analysis.

3. DISCUSSION

3.1 Intrinsic properties and application of polymers

3.1.1 Polyolefins

Polyolefins Polyethylene (PE) and polypropylene (PP) are hydrophobic polymers, which do not degrade in-vivo.[1] The low-density PE are mainly used in packings.[33] And high-density PE are mainly used in implantology such as artificial joints. Because of their biological inertness, they are also used in meshes and sutures.[9]

3.1.2 Polyvinyl chloride (PVC)

PVC is an important polymer used in medicine industry.[7] It needs plasticizers and stabilizers for its application and fabrication, which are reported to be prime medical concerns for its therapeutic use.[10] The Calcium/ Zinc stabilizers help them to prevent from autocatalytic breakdown of hydrochloric acid and disintegration of polymer upon thermal processing.[27] The most commonly used plasticizers i.e. phthalate converts hard/ rigid PVC into soft polymer which is then used for blood storage bags and extracorporeal tubings.[11] Studies reported the cytotoxicity of PVC which are manufactured with plasticizers like phthalate and tin.[12]

3.1.3 Silicones

Silicones are biostable and hydrophobic elastomers which do not need any assistance of plasticizers, because of their peculiar physical and chemical properties they are strong contenders for several medical applications.[13] It is investigated that in ophthalmological applications they elicit more tolerance, reciprocally the formation of fibrous capsule in breast implants.[14]

3.1.4 Poly tetrafluoroethylene (PTFE)

PTFE is commercially known as Teflon is non-degradable and hydrophobic material.[41] It instigates less inflammation in the human body and manifests the ingrowth of tissue.[2] These are mainly used as vascular grafts in surgeries.[15]

3.1.5 Polyethers

Ether is biologically stable.[4] Polyether ether ketone (PEEK) are typically used in orthopedics for being hard in nature.[51] Polyether sulfone (PES) are used in dialysis membranes.[16]

3.1.6 Polyurethanes

They are synthesized with various properties. Polyethers, Polyesters, and polycarbonate-based polyurethanes with two components i.e; aliphatic or aromatic.[33] Their aromatic formulations elicit good stability.[12] Polyurethanes stents are effectively used as ideal drug carrier for local delivery system in humans.[47] Miscellaneously, possessing excellent mechanical properties they are used in tissue-engineering.[17]

3.1.7 Methacrylates

Methyl methacrylates are widely used in orthopedics and dentistry. They are suitable for use only with in situ polymerization, because this process is exothermic. It can pose a threat for tissue damage; hence its low amount is always recommended. Possessing special optical properties, they are used as intraocular lenses.[18] They are also used in hemo-compatible coatings like lubrication coating on contact lenses.[19]

3.2 Biomedical implications of synthetic polymers exterior to body

3.2.1 Hemodialysis membranes

These are typically manufactured as clusters of void fibers with a blood contiguity surface of 0.5-1.5 m^2. Blood interaction poses great threats on compatibility of blood with membranes, besides the requirements of substances which are much smaller than the albumin and to address the transit of contaminants of dialysate into the blood.[20] Conventional dialysis membranes were prepared from cellulose, its hydroxyl group surrogate by the acetyl derivatives with other helping supplements to avert initiation of complement system, associated leukocytes activation and damage to the lungs. Synthetic membranes are specifically made up of hydrophilic and hydrophobic polymers such as the membranes of polysulfone (PSf), polyarylsulfones, or polyvinylpyrrolidone (PVP), and PES. Other miscellaneous materials are also used, such as polycarbonate, polyester polymer alloy (PEPA), PMMA, polyacrylonitrile (PAN), ethylene vinyl alcohol copolymer (EVAL) and molecular nano-porous silicon membranes.[21] It is reported that the hydrophilic components of polyethylene glycol (PEG) or PVP in membrane improves the properties of blood compatibility and antifouling.[8]

3.2.2 Containers

Plethora of polymers is not biocompatible, hence used for packaging of medical devices and drugs. Syringes and plastic ampules are used to migrate drugs from one medium to another medium, but this phenomenon depends upon several factors such as drug-polymer interaction, oxygen permeation, the shifts in pH etc.[22] It is reported that the drug-polymer interaction not only affects the efficacy, distribution, bioavailability, nature of the drugs but also impairs the functions of polymer such as their physical, chemical, and mechanical properties. Polypropylenes, HDPE, and polyolefins are strong aspirants for the production of compressible vials, UV or oxygen resistant canisters because of their peculiar properties of inertness. Cyclic polyolefins and copolymers are widely used in prefilled polymer syringes because of their optical and mechanical properties along with their potential stability in steam sterilization. The tip-caps of these syringes are mainly made up of elastomers.[23]

Moreover, phthalate-based PVC plasticizers are used for several extracorporeal perfusion tubes to administer medicines, and also in blood leading tubes in extracorporeal oxygenation or extracorporeal dialysis. Additionally, the blood and its substitutes are also stored in the bags manufactured from aforementioned polymers. Researchers investigated that phthalate-based PVC plasticizer bags reduce the risk of hemolysis of red blood cells to 50% as compared to non-plasticized blood canisters. These materials are also effective to keep blood products safe for a longer duration of time.[24] The extracorporeal circulation tubes are frequently heparinized to minimize the effect of coagulation because of their continuous contact and increased thrombogenicity of PVC. To store platelets, polymers like polyolefins are used. Polyethylene and polyurethanes are used in tubings. The tubings are typically made up of silicone. To store platelets, several polymers such as polyolefins, polyurethanes and polyethylene are used for tubings. Silicone is a typical component for the tubings of peristaltic pumps.

3.3 In-vivo applications of polymers

Here we will introduce the in-vivo applications of synthetic polymers.

3.3.1 Urethral stenting and urinary catheters

The upper urinary tract phiz identical complications of microbial infections with polymer ureteral stents as catheters in lower urinary tract site.[25] Silicone is considered to be the most suitable material to address this problem, but it shows some resistance as well. It's high frictional and low mechanical stiffness properties make its application somewhat difficult.[23] The contemporary polyurethane formulations such as soflex, chronoflex, tecoflex, perculflex, PMMA/ pHEMA copolymers, polyesters (Silitek), Styrene/ ethylenebutylene/ styrene block copolymers are developed to address the problems which are being caused by silicones. But there is no any ambiguity in saying that silicones are more stable materials with revised mechanical properties. Urethral stents laminated with phosphorylcholine, PVP, hydrogels, glycosaminoglycanes (Heparin, GAGs) are used widely to hinder the microbial colonies and improve patients' safety.[26]

The urinary catheters are mainly manufactured from silicone, latex and polyurethane. Possessing higher pervasiveness of latex allergy, the latex is always blended with other polymers. The common complications such as catheter blockage, impudence and urinary tract infections are generally associated with urinary catheters. These catheters instigate the bacterial growth such as *Proteus mirabilis* which impairs the membranes of urinary tract.[27] These catheters must possess the ability of easy insertion, prevention from any occlusion or collapse, and easy removal. The surface of these catheters should be smooth with minimal friction. Therefore, the coating techniques are the primary concern in their production.[28]

PTFE coated latex catheters retain in patient for a period of three to four weeks approximately, but this duration is much longer for silicone and silicon-based catheters. A polymer named pHEMA is used as a hydrogel coating which allows the catheter to remain stable. Silver based hydrogel coatings provide anti-microbial fittings to the catheters. Studies reported that the use of these hydrogel coatings lower the risk of contamination.[29]

3.3.2 Dressing of wounds

Synthetic polymers possessing the characteristics of small pore size and high surface area are typically used for burn management and wound dressings. Polyurethane-dextran's nanofiber mats which contain an antibiotic named ciprofloxacin are widely used for dirty wound dressings.[30] A group of scientists find out that chitosan-based poly (N, N-diethyl-acrylamide) dressing is potentially used for various biomedical applications and wound dressings because of their interactive and thermo responsive inter-penetrating polymer network films.[31] Cellulose acetate, poly(lactide-co-glycolide), poly-l-lactide and water-soluble carrageenan hydrogels impenetrated with a natural material named shikonin are best candidates for wound healings, with antioxidant, antimicrobial, antitumor and anti-inflammatory activities.[32] Poly (ethylene glycol)/ chitosan polymers treated with ciprofloxacin hydrochloride antibiotic are used in contaminated/ clean contaminated wound dressings.[33] Another research reported that silver nanoparticles and chitin based bactericidal films are also used in the dressing of burns and wounds.[34] Polyethylene glycol in an association with heparin (low molecular weight), polyethylene glycol-protein conjugates are used as occlusive materials for wound dressings.[35] Polyurethane foams in combination with pH-sensitive bentonite hydrogels or alginate are also used as wound dressings for semi-clean wounds. Polyurethanes possess good antibacterial and absorptive properties. Polyvinylpyrrolidone-alginate based hydrogels containing nano silver are being widely used as dermatological bandages and dressings. Scientists found that silicone-coated non-woven polyester dressings strengthens the re-epithelialization of skin in sheep models in treating skin wounds/ scars.[36]

3.3.3 Vascular catheters

While considering the quality of vascular catheters, it is important to note that they must not be thrombogenic and inflammatory towards vascular wall.[37] These must possess the properties of non-collapsing, non-kinking and mechanically flexible. CVC's (central venous catheters) because of their long stay inside the body usually elicits antimicrobial properties which avert them from any bacterial adhesions.[37]

Polyvinylchloride (PVC) was the earliest polymer which was used widely for the production of catheters. Currently its long-term applications (peripheral venous catheters) are confined to short-term applications because of plasticizers.[38] Therefore, polyurethanes, having peculiar properties have replaced the PCV because they do not need plasticizers as catheters. Plethora of polyethenes, polyesters, and polycarbonate-based polyurethanes with their aliphatic or aromatic components has been manufactured for catheters.[39] Silicone-based catheters are now inserted for persistent applications in patients from few weeks to several months. Researchers have investigated that silicone is much softer material than polyurethanes, hence, their risk of vascular injury is also quite less.[40]

High-density polyethylene-based (HDPE) polymers are used in inner edges or linings of invasive catheters which provides assistance in sliding the guide wire. PEEK or polyimide-based catheters are also used in inner linings because of their higher mechanical resistance. Conversely, the block copolymers of polyamide are used in exterior linings of same catheter, as they enhance the stability and flexibility of polyurethanes with nylon.[41] The balloons of invasive catheters are manufactured from polyamides or polyesters because of higher tensile strength.[42]

3.4 Other miscellaneous implications of polymers

3.4.1 Suture materials

Surgical staples and sutures made-up of polymers are the most frequently used materials in surgical interventions. Stability, degradability, tensile strength, absorption etc. are the properties which are specifically considered for the selection of suture materials in wound closure after performing surgery.[43] A large number of biological suture materials are used today. Cellulose, catgut, silk etc. are the examples of degradable biological sutures. While, vicryl (polyglactic acid), PDS, PGA are synthetic resorbable sutures.[44] Polyethylene, polypropylene, nylon, polybutester, polyesters etc., are non-absorbable sutures. Inner tissues and organs are usually fast healing in nature and they are stitched with resorbable materials. Conversely, the slow healing tissues such as tendons are sutured with non-resorbable materials.[45] It is shown that biologically degradable materials are deteriorated from tissue response by proteolysis.[46]

3.4.2 Joint prosthesis

Join prostheses are extensively used materials in orthopedic surgery.[47] Ultra-high molecular weight polyethylene (HHMWPE) in nature is semicrystalline polymer with potential strength, and low resistance, therefore, it is still a weak contestant for fatigue fractures.[48] However, the free radicals in polymer induced gamma sterilization poses a stable ageing to ultra-high molecular weight polyethylene devices upon storing oxygen ambiance. Researchers found that still no any other polymer can replace UHMWPE for bearing heavy loads. For small joint replacements, flexible silicone spacers are preferred because of their biocompatibility and mechanical properties.[49] But, pyrocarbon with graphite are gaining attention of researchers because of their inertness, young's modulus closer to bone and low friction behavior.[50]

3.4.3 Vascular grafts

ePTFE based polymers are amply used in vascular grafting. It is reported that the graft patency of ePTFE is somewhat similar to Dacron, but still ePTFE have advantage in handling over Dacron.[51] The self-sealing vascular grafts of polyurethane punctures immediately as compared to ePTFE grafts. Hence, the infection rate of polyurethane is higher than ePTFE. It is found that vascular grafting of big vessels are more successful such as 5-year patency rate in contrast to small vascular grafting. Tissue engineering is introducing itself as a strong player in mini-vascular grafting.[52]

3.4.4 Contact lenses

In Ophthalmology, contact lenses are widely used biomaterials. Old polymer lenses were specifically designed from a polymer named rigid PMMA. PMMA is reported as harmful material for corneal epithelial cells because of being hard in nature and its oxygen impermeability.[53] Therefore, silicon acrylate-based polymers were introduced.[52] Currently, siloxane-based hydrogels are used to enhance the formation of soft oxygen permeability for up to duration of one-month permanent wear.[29] Therefore, these kinds of hydrogels are being used as drug delivery carriers such as in the treatment of glaucoma.[54]

3.4.5 Dentistry

Synthetic polymers are phenomenally used in the field of dentistry, all the artificial teeth and dentures are made up of polymers.[43] PMMA is the most widely used polymer in dentistry.[55]

4. CONCLUSIONS & FUTURE PROSPECTS OF SYNTHETIC POLYMERS

Polymers; a repeatedly heard word in our regular life is a large molecule or macromolecular, that is a joint-venture of number of small subunits. We are living in an era of industrial revolution where we cannot imagine life without polymers. They are salient part of our personal, domestic and commercial life from our DNA to giant spaceships. Many polymers are being used in almost every domain of medical sciences. The peculiar properties of polymers such as degree of crystallization, molecular weight adjustments, cross-linking degrees, tensile strengths, characterizations, blending abilities, biocompatibility, and toxicity make them adjustable according to situation and desired use. Biodegradation is a contemporary and well-studied property of many polymers; hence these are widely applicable for in vivo and in vitro practices. It is worth-mentioning that experts from all domains such as doctors, chemical engineers, textile engineers, mechanical engineers, pharmacists, technologists, chemists, research experts and technicians staff are directly or indirectly associated in several research projects related to biopolymer and polymers. Surprisingly, in biomedicine, biophysics, polymer biology, molecular biology and pharmacy the science of polymers have opened new horizons of researches for investigators. It is quite obvious that why the study of these giant molecules is catching the eyes of researchers in today's era.

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CONFLICT OF INTEREST
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Acquisition, Analysis or Interpretation of Data:	TH, SS, AA, FA, YA, SK
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All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.