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Changing paradigms of porous polymers in biomedical applications

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Abstract

Porous polymers have evolved as an exciting platform for diverse biomedical applications and have provided essential technical support to industries related to pharmaceutical and biomedical engineering. The constantly expanding toolbox of polymerization reactions is continuously supplying new methods applicable for synthesizing macromolecules and providing novel macromolecular architectures. Porous polymers, both from natural and synthetic origins, have unique physicochemical properties that make them ideal for drug delivery, tissue engineering, wound healing, etc. The current review aims to investigate the various types of porous polymers for potential biomedical applications and evaluate their contributions to the various innovations made in the field of application.

Keywords: Polymers, Porosity, Biomedical application, Drug delivery, Tissue engineering, Wound healing

1. Introduction

In recent times, the developing field of porous polymers has gained significant attention in various areas due to its advantageous and unique physiochemical properties, including its large surface area. The combined properties of a porous material and a polymeric material make porous polymers a wonderful technological platform for diverse applications [1]. During the early 19th century, Staudinger reported his classical work on polymerization and introduced the term “macromolecule” [2, 3]. Later in the year 1953, Staudinger was awarded the Noble Prize in Chemistry and this initiated the evolution of today’s macromolecular science.

Subsequently, porous polymers drove their way into the research arena with the high-quality mixture of polymers and air that started with the advent of rubber tyres and endured with the advent of froth rubber [4-6]. The capacity to generate pore-crammed polymers has brought about several large applications. The innovative Loeb-Sourirajan segment separation process, presented in the early 1960s, produced defect-free, uneven opposite osmosis cellulose membranes such as an ultrathin, selective film on porous support making industrial-scale manufacturing and its practical applications [7, 8]. These examples exhibit that it can take a long time to locate the proper mixture of polymerization, macromolecular shape, and processing to obtain feasibility for industrialized applications. For a long time, the range of porous polymeric systems was limited. On one facet of the spectrum’s size, rigid co-polymerizations, and multifunctional crosslinking comonomers have been engaged for the synthesis of glassy polymers with inherent microporosity. Recently, the field of porous polymers is constantly developing due to their enormous relevance towards different regions like gas adsorption and storage, gas partitioning and particular permeation, adsorption of natural pollutants, catalysis, photoconductors, sub-atomic motors, and clean energy storage [9]. Such colossal materiality is due to the consolidated properties of the permeable materials and polymers. As a result, membranes can be classified based on their nature, geometry, and separation regime, which are all influenced by the properties of the pores. These porous polymers have been exploited by diverse technological sectors, including biomedicine (Figure 1).

One of the outstanding areas in which porous polymers are beginning to be vital is the sector of tissue engineering [10-13]. Tissue engineering is the process of creating bioartificial tissues in vitro as well as altering cell growth and function in vivo through the implantation of suitable cells isolated from donor tissue and biocompatible scaffold materials [14]. Depending on the size of the pores of this porous polymer, they are classified as micro, meso, and macroporous polymers having pore sizes of <2 nm, 2-50 nm, and >50 nm, respectively. A higher degree of crosslinking and their porous nature are the two main features that help to differentiate gel-type particles of polymer. Porous substances, having tailored functionalities and being constructed from easy molecular synthons at the moment, are a primary factor of exploration in substance science. Such substances, particularly microporous polymers, provide a wide range of studies due to the unique feature of their pore size, allowing for the utilization of the inherent large interior areas and thus the noticeably large floor area.

Polymeric substances have been extensively used in biomedical and pharmaceutical product development including controlled or sustained-release drug delivery systems [15], transdermal drug delivery systems [16-18], nanotherapeutic systems[19-25], etc.

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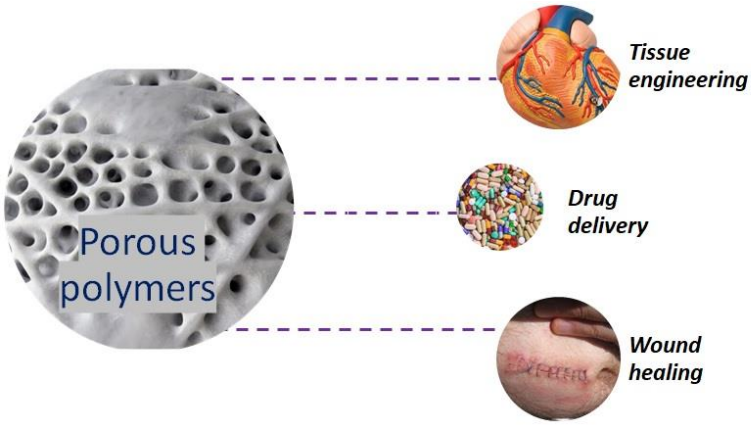

Figure 1 Porous polymers in biomedicine

2. Classification of porous polymer

Plenty of research has been done on polymeric materials that show various levels of porosity. Porous substances are generally identified by their distribution of size, texture, pore size, connection size, and total porosity value. Depending on the material used, the size and characteristics of the pores vary [26]. The pores are divided into macro-, meso-, and micropores based on the various mechanisms that occur in these pores during the nitrogen adsorption isotherm (Figure 2). Multilayer adsorption, capillary condensation, and micropore filling are the processes that relate to macropores (pore size above 50 nm), mesopores (pore size: 2-50 nm), and micropores (pore size: about 2 nm), respectively [27]. Since "nano" represents a size range of 1 to 100 nm, all three of the above types of porous materials can be called nanoporous. However, in most of the literature, nanoporous substances are mentioned as mesoporous and/or microporous substances [28].

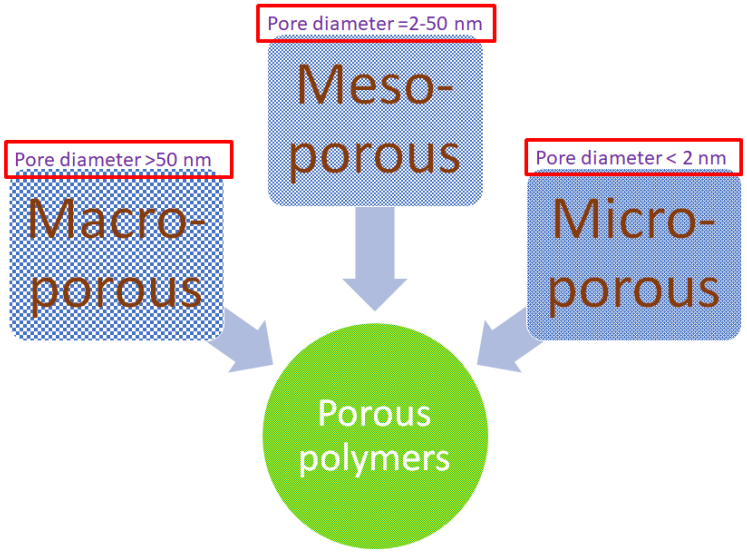

Figure 2 Types of porous polymers

2.1 Microporous polymers

There are various approaches to preparing microporous polymers. In general, polymers have a wide range of flexibility and rotation that enables them to maximize intermolecular and intramolecular interactions as well as to pack space in a solid state. As a result, the free volume inside the polymer, which is the space within the non-polymer molecule content, can vary significantly due to certain factors. As a result, contact will occur if the material is free and large enough, and microporosity will be significantly introduced [29, 30]. The hyper crosslinking method is based on significantly high cross-linking of polymer networks in a solvent. Subsequently, when the solvent is removed from the system, a microporous polymer is formed [30]. Polystyrene and its derivatives are the most widely exploited systems to develop microporous materials via the hyper cross-linking method [29]. Another interesting method to prepare microporous polymers is based on the concept of intrinsic porosity. Polymers with stiff backbones and sites of contortion fail to pack efficiently, yielding a huge free volume [30]. A nice fusion of these approaches leads to the development of conjugated microporous polymers.

2.2 Mesoporous polymers

Mesoporous polymers are prepared by a variety of methods. In the smooth-templating method, suitable surfactant molecules are used as templates (e.g., block copolymers or surfactant micelles). In the hard templating method, the inorganic templates (e.g., mesoporous silica or silica nanoparticles) are used [30]. Attention should be paid to ensuring appropriate rigidity of the monomer unit and resultant network structure to avoid the collapse of inter-network pores during drying [31]. Apart from this, radical polymerization and polycondensation methods are also widely exploited to develop mesoporous polymer composites.

2.3 Macroporous polymers

According to the International Union of Pure and Applied Chemistry (IUPAC), macroporous polymers have pores ranging from 50 nm to 1 μm. In general, macroporous copolymers are materials synthesized in the presence of a pore-forming agent (diluent) and characterized by a lower network density due to voids than the matrix polymer [32, 33]. A monovinyl monomer, a divinyl monomer (crosslinker), an initiator, and an inert diluent are used in the free-radical crosslinking copolymerization (FCC) process for the manufacture of microporous polymers. Free radicals are created when the initiator decomposes, and they start the polymerization and crosslinking reactions. After a certain reaction time, a three-dimensional network of infinitely large size may start to form. Suspension polymerization has also been widely used for the development of microporous polymers. A mono-vinyl-divinyl monomer mixture containing a free-radical initiator is blended with an inert diluent in this approach. In most cases, the inert diluent must be soluble in the monomer mixture but insoluble in the continuous phase of the suspension polymerization. The reaction mixture is then agitated and introduced to the continuous phase, where it spreads as droplets within the continuous phase. The copolymerization and crosslinking events that occur in monomer-diluent droplets result in the creation of beads. After that, the beads are extracted with a suitable solvent to remove the soluble polymers and diluent from the network [33].

3. Biomedical applications

Porous polymers are now widely used in a variety of biomedical and microbiological applications. Porous polymers are fabricated in such a way that they have extensive applications in the biomedical field, such as drug delivery systems, tissue engineering, and wound healing [34]. Porous polymers are a popular candidate in the biomedical field due to their mechanical, biodegradable, and biocompatible properties. Apart from these properties, they also have porous nature, which is very much essential in tissue engineering, especially for fabricating scaffolds [20, 35, 36]. The porous nature of these polymers also permits cell filtration and increases the permeability of nutrients and oxygen. As a result, porous polymers are widely accepted for designing wound-healing formulations [37]. These polymers also have some unique structural properties, such as uniform porous structure, increased surface area, surface properties, stable nature, etc. These properties generate interest for researchers to develop drug delivery systems using this porous polymer [38]. Apart from biomedical applications, porous polymers have a wide range of microbiological applications, including the encapsulation of microorganisms for water purification, biomolecule production, the incorporation of antimicrobial agents as a preservative in food materials, and so on [39].

3.1 Tissue engineering

The concept of tissue engineering is a combination of principles from life science and engineering. Robert Langer in 1993 defined tissue engineering as ‘‘an interdisciplinary field that applies the principles of biology and engineering to the development of functional substitutes for damaged tissue’’. The tissue engineering approach is widely used to fabricate tissues that can repair as well as replace damaged tissues [14]. The tissues which are defective or lost their functions due to various pathological conditions can also be restored, or improved their functions by tissue engineering. In this aspect, porous scaffolds can play a crucial role. Tissue engineering architects artificial scaffolds which can mimic the human extracellular cell matrix and provide support to living cells’ growth. It also stimulates the endogenous cells responsible for tissue formation as well as regeneration.

In the human body, tissues may be damaged due to different disease conditions, injury, or any other reason that requires specific treatment to repair, replace, or regenerate those damaged tissues. Specific treatment includes the transplantation of tissues from one site to another site or from one person to another. The transplantation of tissues during the operation is extremely painful and expensive. Another issue of this transplantation is the rejection of tissues due to the acceptor’s immune system and infection risk factors. These tissue transplantation problems can be overcome by a tissue engineering approach without replacing the damaged tissues [14, 40]. In this approach, porous scaffold biomaterials are designed and attached to body cells which helps in tissue regeneration. Scaffold biomaterials provide adequate cellular interactions for the generation of new tissues. They are three-dimensional porous solid biomaterials [6] with numerous applications such as cell attachment and migration, allowing sufficient transport of gases and nutrients for cell survival, supporting cell adhesion, promoting cell proliferation and migration, retaining cells, and maintaining the function for regeneration of new tissue and organs [41, 42]. After forming the new tissues, the scaffolds will be degraded by the cells in that environment. To fulfill the above purposes the scaffolds should have the following properties, (i) They should have a highly porous three-dimensional interconnected network structure to promote cell migration, reproduction, and transport of nutrients [43]; (ii) They should be biocompatible as well as biodegradable in nature, and the degradation rate must be controlled in a manner to match with the cell growth [44]; (iii) They should have a proper surface chemistry that must be suitable for cell adhesion, cell migration, and proliferation [45]; (iv) They should have sufficient mechanical strength so that they maintain the proper structure and function of newly developed tissues and organs [46]; (v) Their fabrication should be flexible enough to allow them to be available in a variety of sizes and shapes to accommodate themselves in the implantation site and maintain their shape for an extended period of time.

Along with their biocompatibility and biodegradability, the scaffolds' porosity and interconnectivity are critical. Because the porous structure significantly influences cell growth, ensures cellular penetration, and helps to remove waste products from the scaffold. The pore size and porosity of the system can be optimized by altering the process parameters of the manufacturing method and ingredient composition of the scaffold system. The seeding cells are accommodating themselves in the middle inner part of the scaffold matrix. The pore size of the scaffold is very important and must be controlled. If the pore size is very small, then it restricts the accommodation of seeding cells. whereas large pores allow more space for seeding cells and increase the stability of the scaffold system [47]. For example, for cardiac cells, a 50 mm to 70 mm pore size is suitable, whereas, for human osteoblast cells, a 200 mm pore size is essential [48]. Porous scaffolds are made from synthetic biodegradable polymers such as polyglycolide (PGA), polybutylene terephthalate (PBT) [49], poly(L-lactic acid) (PLLA), poly(lactic-co-glycolic) acid (PLGA) [50], and others.

3.2 Drug delivery applications

Innovative drug delivery platforms have exploited diverse types of polymeric materials as an integral part of formulation or processing adjuvants [15-25, 35, 51-55]. Porous polymers are the multifunctional materials used to deliver drugs and work on the principle of host-guest systems [56, 57]. They are promising materials having potential features for fabricating drug delivery systems,

such as excellent biocompatibility, programmability as well as predesigned porous structures, easy surface modification properties, a large effective surface area, flexible pore sizes, the ability to accommodate guest molecules, a stable nature, etc. [58, 59]. These polymers have huge numbers of pores, through which the drug gets inserted into these porous systems [60]. These pores are also responsible for releasing the drug in a more predictable and as reproducible manner [15, 22].

Porous polymers are widely used to improve the bioavailability of various poorly soluble drugs. Porous materials such as Flourite (porous calcium silicate), Neusilin (magnesium aluminometa silicate), Sylysia (porous silicon dioxide), etc. are used to enhance the bioavailability of poorly soluble drugs such as aspirin, griseofulvin, indomethacin, furosemide, etc. [19, 22, 35, 61].

Porous polymers are also used for designing sustained or controlled-release drug delivery systems. Porous minerals such as porous hydroxyapatite, silica xerogel materials, composites of porous silica-calcium phosphate, zeolite, porous calcium carbonate, porous ceramics, etc. are widely used by researchers to fabricate various sustained or controlled release devices [62, 63]. Volodkin et al., encapsulated protein in porous $CaCO_3$ microparticles [64], Kim et al., developed hydroxyapatite/poly(epsilon-caprolactone) composite coatings on hydroxyapatite porous bone scaffold for drug delivery [65], Suzuki et al., prepared porous silica-poly (N-isopropylacrylamide) hybrid gels for thermo-responsive drug delivery system [66], Kortesuo et al., designed alkyl-substituted silica gel as a carrier for controlled release of dexmedetomidine [67], Moes, developed floating drug delivery system using microporous Accurel MP 1000 [68], Singh & Kim developed low-density microparticles as floating drug delivery system using porous carrier material [69], etc. Porous polymers are also useful to fabricate pH-responsive drug delivery systems where the drug gets released selectively in a unique chemical environment. pH-responsive drug delivery systems are extensively used for various biomedical applications. These drug delivery systems can deliver the drug in a controlled manner at the targeted site, which increases therapeutic efficiency [[37, 70]. In some cases, it is very much essential to deliver the drugs in slightly acidic environments, such as inflammation, basal cell carcinoma, melanoma, squamous cell carcinoma, tumor tissue, skin cancers, etc. [71]. pH-sensitive micelles, acid-sensitive liposomes, and hydrogels are extensively used in such cases. pH-sensitive micelles release the encapsulated drug when they come into contact with an acidic environment. These micelles show prolonged residence time, improved half-life, and an excellent effect on tumors [72]. Xu et al., designed a porous organic polymer with a pH-sensitive link to deliver quercetin in a sustained manner to treat cancer cells [73]. Huang et al., also reported a controlled release of triclosan using a pH-responsive PS-b-P4VP block copolymer [74]. Porous gelatin nanofibers were reported to deliver hydrophobic drug substances [75]. The investigations to explore the surface morphology of the gelatin nanofibers using Field Emission Scanning Electron Microscopy (FESEM) have clearly shown the porous nature of the material. Porous polymers are also used for developing optical fibers for delivering drugs. These porous polymers' optical fibers are capable of transmitting light, which is essential for the activation of drugs and very much useful for photodynamic therapy. Yu et al. developed optical fibers using porous polymer i.e. polycarbonate and poly(methyl methacrylate to deliver the drug locally for treating cancer [76].

3.3 Wound healing

Wounds disrupt normal anatomical structure as well as the function of the skin. This may be due to thermal or physical injuries, which abnormally break the skin. This break also further affects underlining tissues such as subcutaneous tissue, muscles, tendons, nerves, and vessels [77], etc. Depending on the healing process, wounds are of two types, i.e., acute wounds and chronic wounds. Acute wounds heal completely within 8 to 12 weeks, whereas chronic wounds tend to reoccur and take more than 12 weeks to heal. Furthermore, wounds can be graded based on the skin layers and affected areas. When the epidermal skin surface is only injured, then it is termed a 'superficial wound'. When the epidermis, deeper dermal layers, blood vessels, sweat glands, and hair follicles are affected then it is termed a 'partial thickness wound'. And when the epidermis, dermal layers, subcutaneous fat, and deeper tissue are injured then it is called a 'full-thickness wound' [78]. The physiological process of wound healing involves the hemostasis phase, the inflammation phase, the proliferation phase, and the remodeling phase [79].

An ideal wound dressing material should properly cover the wound area, retain the body fluid, permeate oxygen for tissue cell growth, and prevent bacterial infection by achieving the desired sealing of the wound [80]. These materials must be biocompatible and permanently non-adherent to the cell. For the treatment of chronic wounds, scaffolding materials, as well as temporary dressings, are used. Scaffolding materials help to host the endogenous cells and assist cell growth, whereas temporary dressings help to cover the affected area and support the healing process.

An ideal wound dressing material should have the following properties: (i) be non-toxic and non-irritant; (ii) increase cellular interactions and promote tissue regeneration; (iii) maintain a moist environment in the affected area; (iv) produce a protective mechanical barrier and prevent secondary infections; (v) allow efficient oxygen permeability in the affected area; (vi) properly absorb the exudate, and (vii) be non-allergic and biocompatible.

The wound dressing bioactive materials help to control the water passage rate, release the by-products, increase the diffusion of the active ingredient, and promote tissue regeneration [81]. The water uptake phenomenon is very crucial for wound dressing materials. This phenomenon depends on the pore size of the materials through which the water gets absorbed by capillary movement. The absorption of water through capillaries also depends on the effective porosity of the materials and pore tortuosity [82].

A number of natural bioactive materials are used as wound healing materials, such as chitin and chitosan, cellulose, collagen, gelatin, dextran, elastin, hyaluronic acid, alginate, etc. Chitin and chitosan are well-known materials used in wound healing. They promote cell adhesion, and proliferation and improve the fibroblasts as well as the functions of inflammatory cells. Both materials also have excellent antibacterial and antifungal activities, which make them suitable for wound healing. They also help in the quick regeneration of bones as well as increase the granulation of wounds [83]. Cellulose helps in tissue formation and vascularization by activating different growth factors such as platelet-derived growth factor, epidermal growth factor, fibroblast growth factor, etc. [84]. Collagen can bind to the extracellular integrin receptors and promote cell adhesion. This binding takes place at glycine, arginine, or aspartate binding sites [85]. It also helps to develop extracellular matrix structures. Gelatin participates in cell adhesion and proliferation, elastin helps in protease synthesis and cell migration, and hyaluronic acid increases keratinocyte and fibroblast proliferation as well as activating the deposition of collagen [86]. Dry wounds can be treated with alginate, which has excellent swelling properties and helps to grab exudate in wounds. Alginate helps to hydrate the wounds by absorbing water, accelerates tissue formation, and increases the concentration of cytokines by stimulating the monocytes [87].

Different synthetic polymers are also used as wound-healing materials. These polymers are superior as to natural polymers in terms of physicochemical properties and stability issues. Synthetic polymers are biologically as well as therapeutically inert, free from any impurities, and their degradation can be controlled. Commonly used synthetic polymers for wound healing are polyethylene oxide,

poly(lactic-co-glycolic) acid, polydimethylsiloxane, polyurethane, polyvinyl alcohol, polyethylene glycol, poly(caprolactone), poly(glycolic acid), polyvinyl pyrrolidone, etc. Sometimes these synthetic polymers are coupled with natural polymers to increase their hydrophilicity, biodegradability, and cell adhesion properties. When natural and synthetic polymers are mixed together, they can be used to make scaffolds like sponges, membranes, nanofibers, nanogels, hydrogels, etc., that can be used to treat wounds.

These scaffolds used for wound healing should have some characteristic features i.e., adequate cell adhesion, biocompatibility, proper mechanical properties, high porosity, inter-linked geometry, maintain the moist environment of the wound, and flexibility to accommodate the shape of the wound. When the scaffold is applied for wound healing, it should maintain the normal tissue temperature, which allows proper blood flow to the wound and boosts epidermal migration. To get optimal cellular function, the temperature should be maintained at the same level as the body temperature. In the wound-healing process, oxygen plays a very crucial role. If the oxygen supply is less, it directly affects the healing process by reducing granulation and epithelization processes. So, for the selection of a wound-healing polymer, sufficient porosity, and proper morphology are very important features. Porous polymers are the ideal candidates, consisting of desirable porosity to maintain a moist environment at the wound site as well as supply oxygen to promote granulation and epithelization processes as well as improve wound healing [88]. In recent times, extensive research has been conducted on the application of porous polymers as wound-healing materials. For example, Rethinam et al., [89] developed porous scaffolds using collage, aloe vera, and graphene oxide. They showed that fabricated porous scaffolds have excellent antibacterial activity against E.coli and S. aureus, good mechanical properties, and biocompatibility. They also suggested that prepared scaffolds showed excellent wound-healing properties. Martínez-Ibarra et al., [90] designed a porous hydrogel using polysaccharides derived from vegetable origin and reported the hydrogels had promising wound dressing applications.

A summary of the porous biomaterials for biomedical applications, discussed in recent literature, is presented in Table 1.

Table 1 Summary of a few recent porous biomaterials deployed in biomedical applications.

Type of porous biomaterial	Biomedical application	References
Gelatin methacrylate (GelMA) and poly(ethylene glycol) dimethacrylate (PEGDA)	Alveolar bone tissue engineering	[91]
Composite hydrogels (Modified alginate, Gelatin, and Bioactive Glass)	Bone tissue engineering	[92]
Collagen hydrogel	Muscle tissue engineering	[93]
Poly-epsilon-caprolactone and hydroxyapatite	Tissue engineering	[94]
Poly-epsilon-caprolactone and polysaccharides	Tissue engineering	[95]
Poly(vinyl alcohol) and hydroxyapatite	Tissue engineering	[96]
Polylactic Acid/Hydroxyapatite	Bone tissue engineering	[97]
Gelatine-Hydroxyapatite-Tricalcium Phosphate	Bone tissue engineering	[98]
Chitosan hydrogel	Wound healing	[99]
Alginate-fibrinogen composite hydrogel	Wound healing	[100]
Parylene (poly-p-xylylene) incorporating keratin	Wound healing	[101]
Lignin-agarose-SF-ZnCr2O4	Wound healing	[102]
Lignin-poly(ethylene glycol)-poly(methyl vinyl ether-co-maleic acid)	Drug delivery	[103]
Cellulose–Lignin	Drug delivery	[104]
Porous silicon	Drug delivery	[105]
Porous silicon	Drug delivery	[106]
keratin	Drug delivery and tissue engineering	[107]

4. Future directions

The vast work done on the fabrication of porous polymeric materials for possible application in biomedicine is evident from the recent literature review. The research has been directed toward exploring novel methods to fabricate porous materials. The newer strategies for such fabrication include electrospinning, three-dimensional bioprinting, and microfluidics-based technologies [91-108]. Electrospinning is an electrohydrodynamic method for the fabrication of fibers, where the fiber diameter may range from macro to nanoscale [52, 54]. Porous nanofibers have been successfully exploited for the delivery of many therapeutic agents [52]. In the electrospinning method, a charged liquid droplet (dispersion of a suitable polymer in solvent) is stretched or elongated to form fibers under an electrostatic force using a high-voltage power supply that may vary from 6- 60kV [52]. Three-dimensional (3D) printing has also gained a lot of momentum for the development of porous polymers for biomedical applications. Bioprinting is the process of precisely designing scaffolds for functional tissue engineering using 3D printing technologies [91, 93, 94]. As bio-ink, a variety of polymers can be used to initiate the desired cellular interactions, resulting in increased cell motility, proliferation, and differentiation [97, 108]. Natural and synthetic polymers have both been considered for various bioprinting applications, each with its own set of benefits and drawbacks. Bioprinting optimization remains a challenge because many of these bio-ink materials are based on traditional tissue engineering scaffold design. However, emerging trends in bio-ink development have begun to circumvent these issues, providing bioprinting research with a very promising future in regenerative medicine.

5. Conclusions

Researchers across the world have exploited porous polymers for biomedical applications and the efforts made by the supporting industries are also commendable. The arena of material science has received a lot of momentum following the introduction of porous polymers due to their advantageous high surface area which could be exploited for their versatile applications. Owing to the flexibility in the synthesis of these polymers, a huge range of chemical moieties may be placed on the surface or the interior framework. This functionalization of the porous polymers provides smart properties like stimuli-responsiveness. With a plethora of research directed in this interdisciplinary field led by material scientists, synthetic chemists, physicists, pharmaceutical scientists, and biomedical scientists, new products and applications are anticipated in the future.

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