Review Article

Polymeric hydrogel nanoparticles in drug delivery and bioprinting technologies: a review

Prasanta Kumar Ghosh

Ex-Adviser, Department of Biotechnology, Ministry of Science and Technology, Government of India, New Delhi, Delhi, India

Abstract

Multiple kinds of hydrogel polymers, natural and synthetic, are known. Self-assembly and aggregation are their inherent properties. The diverse applications of hydrogel polymers, encompassing natural and synthetic varieties known for their water-swelling capabilities and biocompatibility, have been explored and summarized. Hydrogels are pivotal in medicine, particularly in drug delivery systems, and emerging three-dimensional (3D) bioprinting technologies. Integrating nanoparticles into hydrogels enhances their functionality for targeted drug release and as components of bioinks used in bioprinting aimed at priming and replicating tissue and organ structures. Natural hydrogel polymers are favored for their biocompatibility characteristics in bioinks, while synthetic polymers and nanoparticles contribute to stronger mechanical properties and increased versatility. This study highlights the importance of the nanoparticle-based hydrogel polymer-entrapped drug substances for efficient use in tissue-specific delivery systems. It emphasizes the critical role of bioink development in advancing synthetic organ fabrication via the 3D bioprinting technology.

Keywords: Bioinks, bioprinted organs, hydrogels, nanoparticles, 3D bioprinting

Address for correspondence: Dr. Prasanta Kumar Ghosh, Ex-Adviser, Department of Biotechnology, Ministry of Science and Technology, Government of India, New Delhi 110058, Delhi, India.
E-mail: gprasanta2008@gmail.com

INTRODUCTION

Hydrogels are three-dimensional (3D) cross-linked polymers capable of holding large quantities of water. These materials unveil their special properties of thermodynamic compatibility in aqueous media and can hold and retain water or biological fluids 10–20 times their dry weight in an aqueous environment. The fluid intake capacity arises from the presence of different kinds of hydrophilic groups in such substances as hydroxyl, carboxyl, carboxylic acid, carboxamide etc., and often due to the presence of multiple cross-linking within the polymers. Hydrogels include natural polymers, synthetic polymers, polymers obtained from polymerization of polymerizable synthetic monomers, and a combination of 3D cross-linked natural and synthetic polymers. Examples of natural hydrogel forming substances are alginates, agarose, collagens, cellulose, chitosan, fibrin, gelatin, hyaluronic acid and some others. Synthetic hydrogel forming materials are made from polymerizable synthetic monomers. Such synthetic polymers include poly (vinyl alcohol) (PVA); poly (ethylene glycol) (PEG); poly (ethylene oxide) (PEO); poly (2-hydroxyethyl methacrylate (PHEMA); polyacrylic acid (PAA) gels; poly lactic acid (PLA) gels; and others.[1-3]

Received: 07-Nov-2024
Accepted: 09-Nov-2024
Published: 20-Dec-2024

Access this article online	
Quick Response Code:	Website: https://journals.lww.com/mgmj
	DOI: 10.4103/mgmj.mgmj_340_24

How to cite this article: Ghosh PK. Polymeric hydrogel nanoparticles in drug delivery and bioprinting technologies: a review. MGM J Med Sci 2024;11:755-62.

There have been extensive scientific and industrial applications of hydrogels since their invention over 60 years ago.[4,5] Multiple kinds of hydrogel polymers have been developed by changing the chemical components of the matrix structure, thereby evolving hydrogel materials responsive to pH, temperature, and light, many of which have found applications in drug delivery. All hydrophilic polymers are water-swellable but all are not water soluble. Self-assembly and aggregation are inherent properties[6] of most hydrophilic polymers and the nanoparticles prepared therefrom.

A wide range of synthetic polymers,[7] including the hydrogel polymers manufactured from a multiple number of monomers, are selected for use in medicine, having acceptable toxicity, biocompatibility, and biodegradation capabilities as also polymer-responsive properties of many such polymers linked to drug release at target sites and tissues. The clinical functions of smart hydrogels are being understood more appropriately with time, and various groups are making intensive efforts. In this context, smart hydrogels have been prepared with nano-sized hydrogels. Our abilities to create nano-sized materials with precise measurements of nano-sized dimensions gave rise to the advent of nanotechnology, and their application in biology expanded their use in nanobiotechnology research and use.[8] Nanoparticle technologies have been introduced and integrated into hydrogels to expand the utilities of hydrogels in drug delivery applications.[9] Hydrogels converted into nanoparticles enable the resolution of several hurdles that restrict drug delivery to the target tissues.[10] The application-driven approach for more precise functional hydrogel design is being researched vigorously, and different groups continue such investigations to develop and impart more precision in preparation of hydrogel-based nanoparticles.[11,12]

MATERIALS AND METHODS

This review was inspired by the research and development (R&D) of polymeric hydrogel nanoparticles for use in tissue-targeted drug delivery, initiated in the mid-1990s through multiple understanding and advancements, including our work on the development of polymeric hydrophilic nanoparticles using hydrogel polymers developed from vinylpyrrolidone (VP) and acrylic acid (AA) monomers. The scientific work carried out by various investigators in these areas using different kinds of hydrogels, from the beginning to the present time, in biology and medicine, extending toward tissue engineering and organ development *in vitro* with efforts to make these useable in tissue repair and organ development is considered in this study. Hydrogels have made fast inroads into the 3D bioprinting and biomanufacturing area for creating functional multicellular tissues or organs in a 3D environment during the last three decades, serving as one critical component of bioinks. Bioinks are complex mixtures containing living cells, materials required for the survival and proliferation of the cells, and other materials, including suitable hydrogel polymers. The progress made in these areas has been documented and compiled from the published literature of academic institutions' websites of prominent commercial companies available from the Google search engine, vibrant in 3D bioprinting research and applications. The area is complex and requires sound understanding and expertise in hydrogel polymers, polymeric nanoparticles, cell science, and cell-biology among others.

HYDROGEL NANOPARTICLES

The term "nanotechnology" was introduced in 1974 by Prof Norio Taniguchi of Tokyo University of Science, who was working on ultra-precision material processing technologies to describe semiconductor processes, and he predicted that by the late 1980s, dimensional accuracies of better than 100 nm would be achievable.[13,14] Substances less than a micrometer in dimension are measured and expressed in a nanometer-scale; therefore, the numeric scale extends from 1 to 1000 nm. Nanotechnology involves the layout and configuration of atoms and molecules, including polymers, in a systematic manner in nanometer dimensions because of which the evolved substances acquire and manifest novel properties that are much different from their non-nano counterparts. Nanoparticles with size ranging from 1 to 100 nm of precisely narrow size distribution are important cellular particles in molecular biology.

For making inroads into nanotechnology, skills in multiple measuring techniques are required, which enable detailed profiling of the size, shape, charge density (for charged nanoparticles), and chemical properties of the developed substances. Knowledge and training in handling dynamic light scattering (DLS), laser Doppler electrophoresis (LDE), atomic force microscopy (AFM), and electron microscopy (EM), including scanning electron microscopy (SEM) and transmission electron microscopy (TEM), are extremely useful and valuable.

Nanoparticle chemistry gradually evolved into a rigorous academic research field at the end of the twentieth century, when accurate dimensional measurement and analysis of such particles were done using electron microscopy and other particle characterization tools and techniques. However, such particles were utilized much earlier

in manufacture of pigments, stained glass wells, and construction.[15] The history of development and progress of nanoparticle technology has been documented.[16]

POLYMERIC NANOPARTICLES

There is no recorded history of manufacturing and using polymeric hydrophilic nanoparticles in biology. We, from the University of Delhi, under the leadership of Professor Amar Nath Maitra,[17] were among the pioneers in inventing and utilizing hydrophilic polymeric nanoparticles in the mid-1990s. We investigated hydrophilic polymeric nanoparticles from 1995 onward. Our techniques involved creating micelles of various sizes in pure water utilizing appropriate amphiphilic surface-active agents and suitable monomers, incorporating water-insoluble substances inside the core of the amphiphilic surface-active area, which were hydrophobic in characteristics and which would aggregate naturally because of hydrophobic interactions and attractions among one another. Reporter molecules could be incorporated inside the core, and thereafter, the monomers captured within the micelles are triggered with radical initiators, initiating polymerization. The particles cannot increase in size much larger than the diameter of the inner core of the micelles and keep the reporter molecules entrapped there. The entrapment and concentration of the reporter molecules within the core can be tracked later by studying their quantitative presence through release kinetics from the core under preset conditions. Once polymerized, the reporter molecules remain entrapped inside the polymeric shell and can be preserved under solvent-free conditions. We used fluorescein isothiocyanate-dextran (FITC-dextran, mol. wt. 19.3 kD) as our reporter molecule. We also produced micelles in non-polar solvents like hexane (called reverse micelles) by dissolving pure water in it, where the dissolution was facilitated by using appropriate amphiphilic surface active substances like 1-butyl-3-methylimidazolium 1, 4-bis-2-ethylhexylsulfosuccinate (bmim-AOT). Appropriate monomers and water-soluble "reporter molecules" were then dissolved in the water droplets, followed by polymerization of the monomers. We used VP and AA cross-linked with NN′ methylene bis acrylamide to prepare our nanoparticles of the precise size range of around 50 nm. We also used other monomers. Our process resulted in the formation of tiny but precise nanoparticles of a narrow size range. It could be isolated by evaporating hexane and removing the amphiphilic substances using appropriate chemical methods. Several publications emerged from our research work on hydrophilic polymeric nanoparticles.[18-21] Our work on nanoparticles has been widely cited and applied.

Hydrophilic polymers have gained importance because of their advantageous characteristics such as biocompatibility, degradability, and minimal toxicity in biological systems. Such polymers find application in multiple areas of medicine, such as ophthalmic applications, implants, vascular grafts, and drug delivery systems. Various investigators have converted such polymers into nanoparticles for use in medicines for drug delivery.[22,23] Nanoparticle-based drug delivery systems have been deployed since the mid-1990s, and a couple of such medicines have been approved in therapy.[24] Several others, especially the hollow ones loaded with drugs, are being experimented upon for use in applications and research in different kinds of intricate biological systems.[25-27]

Depending upon the choice of hydrogels, the nano-polymer-based hydrogels can be used to entrap both hydrophilic and hydrophobic active pharmaceutical substances within their core. The evolved products would exhibit added value in targeted drug delivery. These particles enable ease of internalization by various cells and tissues, especially the macrophages, which recognize and internalize nanoparticles with hydrophobic ligands on their outer surface. The nano-polymer-based hydrogels have larger surface areas. By choosing appropriate monomers and their combinations for making the hydrogels, a large range of ligands can be generated on the outer surface of such nanoparticles, and the tissue internalizing particles loaded with appropriate active pharmaceutical ingredients can be made to respond to change in physiological stimuli such as change in temperature, ionic strength and pH. Multiple such strategies have been thought of for exploring development of nano-polymer-based hydrogel nanoparticles.[28-31]

Along with the diverse deployment of hydrophilic polymers in various technologies, these substances are also finding applications in 3D bioprinting technology. The potential use of hydrophilic polymers and the nanoparticles prepared therefrom in developing the emerging 3D bioprinting technologies is briefly described herein.

3D BIOPRINTING TECHNOLOGIES

In the early 1980s, Charles Hull, an American engineer, proposed the 1st 3D printing technique, known as stereolithography, using an acrylic-based photopolymer following a computer-aided design (CAD), and made the print 3D by simultaneously cross-linking the print using ultraviolet light. The technology was extended later to develop 3D bioprints by others, using bioinks containing living cells. In 1999, Odde and Renn[32] prepared the first

3D bioprinted particles (100–10,000 nm in diameter) using living cells in a laser-assisted bioprinting machine. The technology then made rapid progress, especially in the bioprinting process with multiple printing principles[33] utilized in various commercial bioprinters and inventing various bioinks.[34]

By utilizing the bioprinting technology, 3D structures are fabricated using living and nonliving materials and substances; the prime aim is to manufacture parts imitating real tissues and organ functionalities. Multiple additive technologies, such as stereo lithographic printing using CAD, are integrated, producing bioengineered structures. Such structures are known to have multiple applications in many areas of cell-biology research, including tissue and organ development, with potential for use in human medicine.

The main components of the 3D bioprinting technologies are 3D bioprinters and bioinks. In 3D bioprinters, three different principles are mainly used: extrusion-based, droplet-based, and photocuring-based. In extrusion-based printers, bioprinting extrudes bioinks to form continuous filaments, thereby building printed constructs. In droplet-based bioprinting, also known as inkjet bioprinting, droplets are produced by pushing bioinks through the nozzle of the printer which enables precise control over droplet size and volume; the bioinks used in such printing contain cells, growth factors, other biological components and/or hydrogels. The droplets are stacked in precise positions to form structures by thermal and 'piezoelectric-drop-on-demand' techniques. The photocuring-based printed constructs uses photo-curing materials, which solidify and stack layer-by-layer by exposing the printed constructs to ultraviolet light to achieve 3D-printed structures. Bioinks contain hydrogels, scaffolds of hydrogels, additives, growth factors, and living cells.

The potential benefits of using the 3D bioprinting technology in various main areas of usage, including the nature and types of 3D bioprinters and the bioinks, along with the rapid industrialization efforts through the setting up of startups and other companies all over the world, have been highlighted and reviewed recently.[35,36]

HYDROGELS AND BIOINKS

The supply of human organs is limited and cannot mitigate the requirements, especially in organ transplantations, as the demands of the needy are continuously increasing globally; the rise in the aging populations worldwide is contributing to a rise in the demand for the replacement of damaged and diseased organs. This situation can be effectively managed if 3D bioprinted allogenic organs are available for clinical use. At present, such technologies are in the developmental stage.

Besides the choice of the right kinds of 3D bioprinters, the right kind of bioprinting method, and appropriate hydrogel materials, the composition of bioinks and the choice of the right kinds of living cells therein become the major technological components of the evolving 3D bioprinting technologies. Different bioinks would be required to work on different tissues and organs, such as the liver, heart, bones, kidney, skin, lungs, brain, and cartilage. Research suggests the potential for bioprinting whole organs, revolutionizing medical procedures. Ideal hydrogel materials should have excellent mechanical properties, a controllable degradation rate with high biodegradability, and produce nontoxic degradation products.

Natural hydrogel polymers satisfy the latter two properties, but these substances often do not have the desired mechanical properties. Several natural hydrogel polymers have been used to produce bioinks, which include alginate, collagen, chitosan, fibrin, gelatin, hyaluronic acid, silk, and a few others. These materials are useful in developmental processes but do not have the desired mechanical properties. The differentiation, proliferation, and maintenance of desirable mechanical properties in printed structures prepared from natural hydrogel polymers—such as protein- and peptide-based hydrogels such as collagen, collagen derivatives (including hydrolyzed proteins and collagen peptides), silk, and fibrin, as well as natural carbohydrate hydrogels such as agarose, alginate, and cellulose—have been found to offer more optimal properties for the cells used in bioprinting with these bioinks.[37] Different kinds of protein and peptide-based hydrogels are described in the literature.[38]

Bioinks manufactured from natural hydrogel polymers have better compatibility with cell stability, cell proliferation, and factors involved in maintaining near-natural rheological properties. However, it is surmised that a bioink based on a single natural polymer would not be able to mimic all the extracellular environments needed to support and maintain the correct tune and pitch of the natural system of tissue and organ formation. Using a judicious combination of natural hydrogel polymers is a better option in developing better bioinks.

Bioinks manufactured from natural hydrogel biopolymers have usually mechanically weak properties, as mentioned earlier, and cannot adequately maintain the 3D scaffold to imitate or resemble the anatomical size, tissue architecture,

and natural tissue-specific functions, probably due to their heterogeneously cross-linked network, resulting in faulty energy dissipation manifestations.[39]

The design of advanced bioinks necessitates incorporating the ability to dissipate mechanical energy during printing and the capacity to maintain anatomical dimensions and tissue-specific functions. This involves creating a biocompatible microenvironment that preserves or enhances the mechanical properties of the printed structures.

In a study by Gillispie *et al.*,[40] the printability characteristics of a bioink consisting of gelatin methacrylate/ gelan gum (GelMA/GG) composite bioink with and without cells were carefully deliberated. GelMA is a semi-synthetic hydrogel where gelatin is derivatized with methacrylamide and methacrylate ligand groups. GG is a gellan gum, an anionic extracellular bacterial polysaccharide, usually obtained from the fermentation of *Sphingomonas elodea*, a Gram-negative bacteria. GelMA/GG composite bioinks can be easily and quickly photo-crosslinked at physiological temperatures, and this property can be utilized to impart shape fidelity and stability of the printed objects obtained by 3D bioprinting using this bioink.

It was observed from the study that printing outcomes were dominantly linked with the speed ratio. The speed ratio is the flow rate-to-feed rate ratio and hypothetically represents the printed filaments' cross-sectional area. The results indicated that feed rate, flow rate, and cell density (in the working range of over 10^6 cells/mL) had little impact on printing outcomes. However, maintenance of the desired rheology of the printing objects at printing conditions was more sensitive, requiring closer attention to desired printing outcomes. The hydrogel components of the bioink required strengthening.

In another study, certain amphiphilic supramolecular tripeptides were attached to gelatin methacryloyl via intra-/intermolecular interactions, and the resulting co-assembly resulted in 10-fold or more compressive strength improvement of the structure emanating from the use of the material. This strategy enabled the development of more efficient cartilage regenerative biomaterials.[41] Appropriately modifying natural protein-based hydrogels is a promising approach for creating more effective materials for enhanced bioink compositions.

A biologically functional 3D bioprinted structure with optimized characteristics, including biological functionality, physicomechanical characteristics, and rheological properties, is difficult to establish and maintain using only a single-component hydrogel polymer, natural or synthetic. These materials require modifications and the use of multicomponent hydrogels.

In another study, the utility and usefulness of multicomponent bioinks for extrusion-based 3D bioprinting were discussed, and how the limitations of using single-component bioinks can be overcome[42] was elaborated.

Synthetic and natural polymers modified by incorporating synthetic ligands are therefore being experimented upon to assess their desirable mechanical properties.[43] Yet there are issues in developing hydrogel polymers that would enable the cells grown after 3D bioprinting to have the desired vascularized and strong tissue structures for enabling the transplantation of the composites into human bodies and tissues. Each issue is, therefore, to be critically dealt with. Improved mechanical properties of the hydrogels are one important issue that can be tackled through multiple strategies, such as working on controlling the cross-linking mechanism, selection, and incorporation of synthetic hydrogel polymers judiciously into the natural polymers through nontoxic linkers, thereby improving the functionalization of the resultant hydrogels, and adding certain suitable nanoparticles in such bioinks. Such work assembly is complex but doable.

Of all the hydrogel polymers, HA, a natural anionic, nonsulfated glycosaminoglycan, is an excellent choice as a hydrogel precursor for bioinks because of its biocompatibility, hydrophilicity, non-immunogenicity, and complete biodegradability.[44] Various strategies for using this material as a component of bioinks, including printability, modification of their mechanical properties, and printing with loaded cells, have been discussed in a review. It is easy to manufacture HA of tailored molecular size with desired physicochemical characteristics derived from bulk natural material obtained by extracting it from rooster combs.[45] There is a need to intensity R&D on the extensive use of HA to explore if an excellent and versatile bioink can be developed for use in fabrication of organs, organoids, and tissues suitable for medicinal use for treating damages to vital organs such as liver, heart, bones, kidney, skin, lungs, and cartilage.

Hydrogel nanoparticles are available in various sizes, shapes, and surface chemistries. With such diversities, incorporating such particles can impart mechanical reinforcements through physical and chemical interactions. These particles can also bring in and institute newer bio-functionalities to the hydrogels. These can also impart certain smart

functionalities, such as responsiveness to external stimuli, facilitating more maneuverability of the bioprinted structures.[9,46,47] The incorporation of hydroxylapatite nanoparticles in bioinks improves[48] their mechanical properties, resulting in the development of better dental prosthetics. It is anticipated that suitable incorporation of appropriate hydrogel nanoparticles in bioinks would enable the development of more appropriate bioinks for 3D bioprinting of tissue constructs and living organs *in vitro* with more appropriate hierarchical architectures.

Creating tissue constructs and living organs *in vitro* with a hierarchical architecture that maintains the formation of functional vasculatures established in natural tissues and organs in a versatile and reproducible manner are challenging tasks, where global progress is inadequate. Frontline *in vitro* efforts are being made using bioinks containing appropriate living cells and cell aggregates, growth factors, and other biomaterials, including biocompatible scaffolds, and producing a bioprinted structure from an appropriate 3D bioprinting machine and processing the printed structure further to enable use in human medicine. The bioprinted structure can be stabilized or cross-linked immediately after printing or even during printing to generate the desired architecture of the fabricated construct. However, the technology is still in the developmental stage and is far from useful to the human body.[49,50] To scientifically probe into the uncertainties, there is a need to precisely understand and observe the performance of each component of the complex process.

Bioink, in some ways, is similar to the primordial fluid that supports the spontaneous creation of life. Our bioink is manmade; the undetected voids must be understood and complemented. Bioinks are formulations of living cells where the evolved materials are required to mimic the tissue functions, while undergoing manufacturing and processing techniques such as tension, compression, spinning, extrusion, and chipping. The cells would have to bear the stress and divide and rearrange to develop and maintain their vascularized 3D tissue structure, which can happen when the desired biochemical, mechanical, and electrical cues are intact. Therefore, each parameter needs to be precisely understood and maintained. Our knowledge is expanding fast. However, it has not yet reached the required perfection. In every bioink created thus far, hydrogels and precursors must be nontoxic to the cells and the cellular environments. They should be partly or wholly cross-linked materials or fully cross-linkable substances post-fabrication. The bioinks may also contain compatible nanoparticles of hydrogels that may be packed with substances for sustained release into the microenvironment to facilitate cellular growth and differentiation. Various types of bioinks are currently available for experimentation, although none are yet the most perfect and versatile.[51-53]

BUSINESS INTEREST IN 3D BIOPRINTING TECHNOLOGIES

There is significant global interest to find appropriate and better solutions to the present bottleneck in 3D bioprinting technologies. This is reflected in the current expanding global 3D bioprinting technologies, emphasizing the development of better bioprinters and more efficient and versatile bioinks. The global market size is estimated and projected by various agencies. One estimate suggests that the global market size in 2024 will be approximately USD 185.6 million, increasing to USD 1.03 billion by 2034, with an annual growth rate of 18.8%.[54] Another estimate places the market value in 2023 at USD 159.5 million, with a compound annual growth rate (CAGR) of 18.1%, projecting it to reach USD 703.1 million by 2032.[55] A third estimate has placed[56] the bioink market value at USD 186.70 million in 2023, increasing at 20.48% CAGR annually from 2024 to reach USD 687.96 million by 2030. All these estimates show high expectations of returns from 3D bioprinting technology. As bioinks are among the most important components of bioprinting technology, there would be increasing global interest in developing more versatile compositions for diverse applications.

DISCUSSION AND CONCLUDING REMARKS

Since their invention over 60 years ago, multiple kinds of hydrogel polymers have been developed, including natural polymers and synthetic cross-linked polymers prepared from polymerizable synthetic monomers. There have been extensive scientific and industrial applications of hydrogels. Hydrophilic polymers are water-swellable, but none are water-soluble. Self-assembly and aggregation are their inherent properties. A wide range of synthetic hydrogel polymers manufactured from a multiple number of monomers has been selected for use in medicine because of their acceptable toxicity, biocompatibility, and biodegradation capabilities, as also the responsive properties of many such polymers linked to drug release at target sites and tissues. Nanoparticle manufacturing technologies have been introduced and integrated into hydrogels to expand the utilities of hydrogels in drug delivery applications. The manufacture of nanoparticles increased with the development of the measuring accuracies of small dimensions, especially through DLS, LDE, AFM, EM, SEM, and TEM techniques, which were extremely useful and valuable.

Hydrogels and nanoparticles made there from have entered into a relatively new field called 3D bioprinting technology where three-dimensional structures are fabricated, using living and non-living materials and substances, utilizing a 3D printer and a bioink; the aim is to build substances imitating real tissues and organ functionalities. Multiple additive technologies, such as stereo lithographic printing using CAD, are integrated to produce bioengineered structures. Hydrogels are one of the most important components for the success of the technology, where these substances would be used as such or along with nano-sized structures for developing ideal bioinks. Hydrogels are infallible components of bioinks.

The cell differentiation, proliferation, and maintenance of desirable mechanical properties of the bioprinted structures developed from the most optimum bioink is from the use of natural hydrogel polymers such as from protein-based hydrogels such as collagen, silk, and fibrin, as also from the use of natural carbohydrate hydrogels such as agarose, alginate, cellulose, and gellan gum. Natural hydrogel polymers are more biocompatible with the cells used in 3D bioprinting technology. Among the natural polymers, HA, a natural anionic, nonsulfated glycosaminoglycan, is an excellent choice for the formulation of bioinks because of its biocompatibility, hydrophilicity, non-immunogenicity, and complete biodegradability, which can be modified for better properties. More advancements in developing optimum bioinks are anticipated by using natural hydrogel biopolymers. For imparting the desired mechanical properties in such bioinks, use of non-toxic synthetic polymers as well as nanoparticles derived from synthetic hydrogel polymers are also anticipated to be more useful into such bioinks. Various types of bioinks from a few commercial companies are currently available for experimentation, although none are yet the most perfect and versatile.

The critical paths for success in 3D bioprinting technology for synthetic organs development are thought to be hiding within the ambit of the most optimum individual bioink development for each individual organ, using a combination of natural and synthetic hydrogel polymers and incorporation there in of suitable nanoparticles (made from appropriate hydrogel polymers and chemical substances) that would impart mechanical strength to the printed articles so as to minimize distortion of the rheological structures of the evolved bioprints.

Acknowledgment

The author thanks Mrs. Deepali Ghosh, Partner at Sompradip Publishers and Consultants, Block: C2B, Flat: 5A, Janakpuri, New Delhi 110058, India, for her encouragement and support.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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