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Potential Role Of Hydrogel And Its Future Applications In Bioprinting And *In-Vitro* Organ Development

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Abstract: Recent studies on hydrogels have shown them as promising biomaterials for numerous applications involving tissue-engineering, drug-screening, drug-delivery, and 3-D bioprinting because they show unique physicochemical properties. The ability of these structures to hold large amounts of water is because of their hydrophilic nature that provides a soft and hydrated environment like natural tissues. This makes them ideal for mimicking the extracellular matrix and supporting cell growth and proliferation. In tissue engineering, hydrogels might be used to create scaffolds that promote cell growth and facilitate tissue regeneration. Hydrogels can also be engineered in such a way that they intimate the mechanical and biochemical in-vivocharacteristics making them a versatile tool for applications in tissue engineering. Hydrogels are being used in drug screening, as they can be functionalized with different biochemicals in order to match the microenvironment of specific tissues. This allows researchers to study how drugs interact with cells and tissues in-vitro conditions, which can lead to more efficient strategies for drug development. For applications in drug delivery hydrogels are designed to release drugs in a sustainable and controlled way, improving the drug efficacy and reducing the toxicity of drugs. Designing can also be done in a way that they can target specific tissues and cells making them a promising tool for personalized medicine. Hydrogels are being used in 3-D bioprinting, where they serve as bio-inks that can be fabricated into complex structures with high precision. In comparison to conventional technologies, this is a promising technique that allows the construction of complex three-dimensional structures in a sequential manner by a computer-aided system. One major challenge in bioprinting is finding such material that is suitable for printing and also satisfies the mechanical strength requisite for tissue engineering applications. That is where hydrogels serve as the most appropriate model and have encouraging or favorable operation potential as cell-affable materials. This technique has revolutionized tissue engineering by allowing researchers to create functional tissues and organoids and spheroids. Overall, hydrogel-based tissue engineering, drug screening, drug delivery, and 3D bioprinting are exciting areas of research with great potential to significantly impact different areas of medicine and biology.

Keywords: Hydrogels, Tissue Engineering, scaffolds, 3-D Bioprinting, Drug Screening, organoids, spheroids.

Introduction

Hydrogels are defined as 3-Dimensional networks which contain polymers in them and havethe ability tostore a large amount of water as result of their hydrophilic nature. (Naahidi et.al 2017). These biomaterials have a large quantum of biological fluids in it due to which they become swell up and become squashy or rubber like and can assemble live cells or tissues with them and show admirable biocompatibility (Chamkouri et.al 2021). Now a days Due to its vast properties they are proven to be a great tool in biomedical engineering as well as in areas of pharmaceuticals for drug delivery systems, Drug screening,screening of wounds, T.E (Tissue Engineering), formation of contact lenses (Li et.al 2018). Presence of high amounts of water in hydrogels leads to its application in T.E because live cells (tissues) need a moist surface for the development and adheration of cells (Naahidi et.al 2017). Most of the cells are dependent upon solid surface or need anchorage dependent cell culture. Most widely used in T.E and regenerative medicine (Chamkouri et.al 2021). Hydrogels are also used as the most common T.E scaffolds (These are support structures designed to facilitate cellular growth and augmentation upon inculcating into the patient) over the past two decennary due to their ability of maintaining 3-D structures of tissue, providing mechanical support for engineered cells etc. (Mantha et.al)

Bioprinting is a major tool for producing cell-laden hydrogels for stacking of cells in spatial patterns with the help of a computer assembler that generates layer-by-layer orderly patterns to printlive tissues and organs (Guillemot et.al 2010). Bioprinting shows high degree of precision in the patterning of cells, genes, drugs, proteins, and other biologically active particles in a spatial

arrangement as a helpful guide in tissue regeneration and formation. Bioprinting should not be mistaken or interchangeably used for printing of inert materials that are devoid of biological entities. (Ozbolat et.al 2015). The use of hydrogel solution for encapsulation of cells thereby acting as carriers of cells has great scope for researchers in different areas of TE (Tissue Engineering), and as cancer cells and stem cell targeted delivery vehicles and in research due to recent advances in 3-D bioprinting (Burdick et.al 2012). Recent popularity of this technique is due to disburdening the load of researchers during the assembly processes in regenerative or reconstructive medicine (Thomas et.al 2016). The development of layer-by-layer 3D tissue epitaxy has shown powerful approaches to treat diverse diseases such as cancer and organ failure (Hasan et.al 2009). Through numerous research, it has been evidently shown that for the fabrication and seeding of cells, biomolecules, and biomaterials by utilizing different types of hydrogels and 3D bioprinting techniques is a safe and efficacious process. This review aims to explore the recent advancements in application of hydrogel based bioprinting, achievements of hydrogel as bioinks to be used in 3D bioprinting.

Recent Trends in Hydrogel-based Bioink and Bioprinting

Bioink are basic cell carriers that aid the delivery of cells during the process of bioprinting (Levato et.al 2017) (Fatimi et.al 2022) (Levato et.al 2014). In recent years researchers have most widely used hydrogels as material for bioprinting of cells but now not just the solution of hydrogel precursors also new advancements including microcarriers (Levato et.al 2014).and nanoparticles that greatly serve as drug releasing platforms and provide an improved design for bioactive TE. (Baumann et.al 2017) (Loukelis et.al 2023), nanofibers with better rheological and mechanical properties, microgels containing cell or microsphere involved in drug delivery utilized as bioink materials for three dimensional bioprinting (Loukelis et.al 2023). Current studies evidently shown that hydrogel shown greater achievements to be utilizedas bioink for fabrication of organoids, tissues, and spheroids for TE applications due to properties such as enhanced crosslink ability, higher printability, greater biocompatibility, high mechanical strength, biodegradation, better rheological properties, elegant design tunability (Asim et.al 2023) (Levato et.al 2014) (Fatimi et.al 2022).

Through 3d bioprinting we can create complex structures using living cells, biomaterials, and growth factors. It involves 3D printers to deposit biological materials in a precise sequence to produce functionally active tissues and organs. The process begins with a digitalized model of the structure to be printed, which is then converted into a series of printing instructions that are executed by the 3D bioprinter. There isbasic three categories of bioprinting in which the generate various printed products using bioink namely the droplet based bioprinting which includes inkjet-bioprinting technique, the extrusion-based bioprinting and the energy-based bioprinting technique which includes the stereolithography. Broad classification of 3d bioprinting is shown in figure 1.

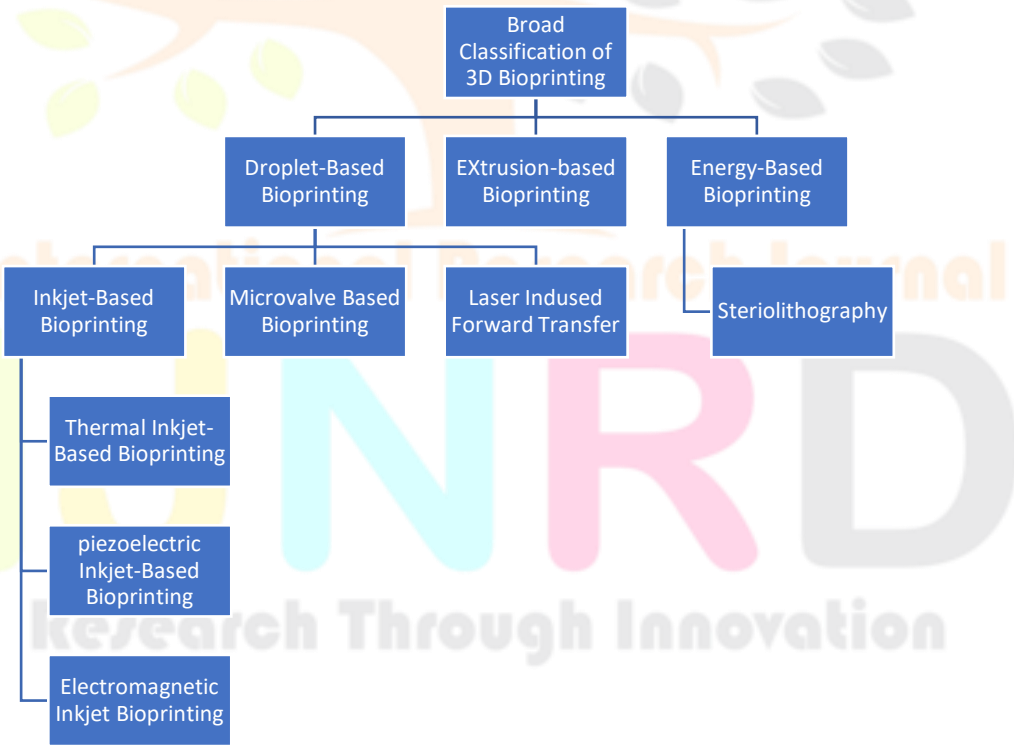

Figure 1: Classification of 3-D Bioprinting

Extrusion-Based bioprinting is quite similar to conventional 3D printing which involves the forcing of controlled and continuous filament streams of bioink via a nozzle on a surface to create a 3D structure. Steam of bioink can either be generated by pneumatic pressure or can be mechanically derived with the help of pistons or screws. Extrusion-based bioprinting involves the generation of constant beads of biomaterials stored in a syringe and in accordance with computer aided design (CAD). The bioink (cells mixed with various biopolymer) is arranged layer by layer ejecting through a nozzle tip of the desired diameter and each layer serves as foundation of the following layers (Zhang and Zhang, 2015) (Hermanova et.al2022) (Ooi et.al 2018).In contrast to extrusion bioprinting **droplet-based bioprinting** deposits a discrete number of droplets of biomaterial onto a surface. **Inkjet bioprinting** is a drop on demand techniquewhich includes a continuous inkjet bioprinter utilizes fluids with lower viscosities and high dropping velocities and uses a pulse of pressure to eject a droplet of bioink (Vaezi and Yang, 2014). Inkjet bioprinting provides greater

printing speed due to the advantage of allowing parallel workflow, a property of its printer nozzle, providing higher cell viability (Zhang and Zhang 2015). Pulse pressure or drop on demand can be generated in one of the following ways Thermally, piezoelectrically, using electromagnetic force and laser source (Daly et.al 2015) (Skardal et.al 2015).In **thermal-inkjet bioprinting** the thermally heated printhead of these printers heats and vaporizes a small surface of the bioink to create a bubble, the bubble has a larger surface area the fluid bioink had thereby creating a pressure that allows droplet of bioink to eject through the nozzle over a surface, once a bubble collapses a bit of biomaterial is sucked from the reservoir in order to refill the tank (Angelopoulos et.al 2020 39).in the printer as the process of printing continues, heating of the ink drops for asmall period of time about 2 μs at 4 to 10^{o} C (Guillotin et.al 2010) (Mohebi and Evans 2002 40) (Gao et.al 2015). Temperature requirement for the process is usually between 200 to 300^{o} C for a short duration of 2 μs and as small heat interval,a very smaller deviation is observed that lies between 4 to 10^{0} C of the whole system and is important as safer and no harmful effects are observed on biological entities (Cui et al., 2010). In a piezoelectric system with the help of electric current, a piezoelectric actuator changes its form in such a way that it changes the shape of the chamber and applies force to the droplet of the bioink to eject it out of the nozzle. Basically, a piezoelectric actuator is a device that response to the change in applied voltage by mechanical deformation of polycrystalline piezoelectric ceramic by stretching and bending (Chameetachal et al., 2018) (Khalil et al., 2005). **Electromagnetic inkjet 3D bioprinting** uses an electromagnetic source that allows the bioink to eject in such a way generate different 3D shapes and insignificant effect on the viability of cells (Loukelis et al., 2023) (Li et al., 2020) (Gudapati et al., 2020). **Laser assisted bioprinter**contains aribbon, a laser, a focuslens, and a substrate. There is a clear quartz in the ribbon with a coating of inert metal such as gold coated with bioink. When the laser hits the gold, it heats and expands ejecting a very small quantity of bioink to the surface which will have been coated with suitable hydrogel. These bioprinters usually contain multilayer ribbons as support. Like inkjet bioprinters these bioprinters also produce droplets of bioinks but just that heating is done by laser guided in a sequential manner which ultimately helps in fabrication of different structures (Keriquel et al., 2017) (Yang et al, 2021). The Wavelength of the directed laser and also the optical property ensurswhether the laser will be able to induce the ejection of bioink from the printer nozzle (Gullimot et al., 2010). The **Energy-based bioprinting** uses different energy sources, usually a laser that selectively helps in the solidification and stabilization of bioink; it is different from extrusion bioprinting as bioink is already in place. The most widely used method of energy-based bioprinting is stereolithography. In this method of 3D bioprinting laser is used as a source to selectively solidify a small concentration of bioink which also contain a light-sensitive type hydrogel this layer lies on a stage that moves away from the laser by doing so the platform is immersed in bioink and then a fresh coat of bioink is permitted to flow on top of solidified layer of bioink repeating these steps will form a 3d structure (Kumar et al., 2020). It provides high resolution,smooth surface quality, and removes the uncured resin from the printed product. (Mobaraki et al., 2020) (Mukhtarkhanov et al., 2020).

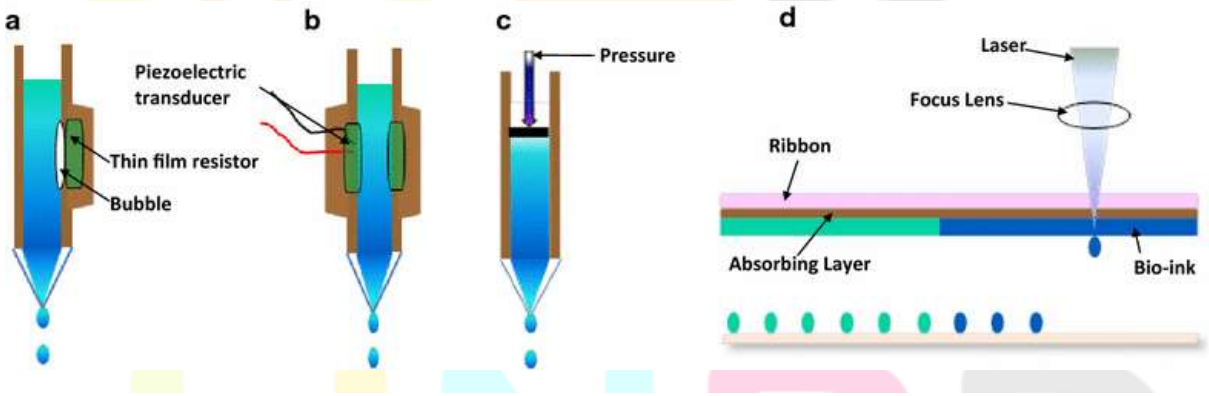

Figure2: Types of Bioprinting

Different types of bioprinting techniques. **a** Thermal inkjet-based bioprinting dispenses droplets of bioink on a substrate via a non-contact process generating pressure pulse and forming bubbles to eject bioink from the nozzle.**b**.Piezoelectric transducer produces a pulse to create temporary pressure .that leads to the ejection of droplets. **c**.Pressure-assisted bioprinting dispenses bioinks due to pressure generated in a continuous filament form through a microscale printer nozzle. **d** Laser-associated bioprinter contains multilayer ribbon and a laser that vaporises the liquid biological particle that reaches the platform in droplet form. (Li, J., Chen, M., Fan, X., & Zhou, H. (2016) *Journal of translational medicine*.)

Key Properties of Hydrogel as Bioink for Advanced 3D Bioprinting

Printing-fidelity indicates the level of accuracy to which a printed product is obtained according to the designed CAD plan that is characterized by various measures of printed strand including its diameter, angle, and uniformity in area. Challenges of hydrogels to 3D bioprinting include the weak mechanical properties providing poor geometry that result in shrinkage and swelling and other structural deformities and the inherent flow nature of the hydrogel that is due to its limited structural shape fidelity (Ning et al., 2020). Various modifications including nanoparticles and other biopolymers showed enhanced electrostatic interaction between nanoparticle and polymer and show an effective reduction in shrinkage and swelling during the process of crosslinking providing greater printing fidelity (lee et al., 2018) (Montalbano et al., 2023).

Another property includes resistance of fluid hydrogel (here as bioink) to change its shape or movement of neighboring portions with respect to one another it is called viscosity. Precursors of hydrogels are non-Newtonian in nature and thus show nonlinear and concave curves when plotted between shear stress-shear rate representing low viscosity. Rheological study shows that the viscosity at low shear stress provides better maintenance to form stable structure but also greater viscosity may reduce cell

survival and function (Dorishetty et al., 2020) many mathematical equations are there to obtain shear thinning behavior.The most used mathematical equations involve the Ostwald-de Waele power-law equation.

$$\eta = K\gamma^{(n-1)}$$

Where the symbol η representsviscosity (mPa.s).
K represents the flow consistency index, (mPa.s) (viscosity when shear-rate is $1s^{-1)}$.*n* represents the power law constant (unitless) or (shear thinning index).

n<1 indicates the shear-thinning material

n>1 indicates the shear-thickening material

n=1 indicates the Newtonian fluid character

This model is relatively simple and helps in printability detection (Chimene et al., 2020) (Paxton et al., 2017). The Assumptions made during this model that at medium shear the fluid is steady and linear it also neglecting the reduce this causative near the needle walls (wall slipping) sir as a limitation and other is that is only applies to a limited share rate between 10 to 10^4 s^{-1} (Paxton et al., 2017) (Schwab et al., 2020).

The Herchel-Bulkely gave as a more useful model that not just considers the wall slipping but also includes shear response and yield stress and thus can be applied for effective printability (Sarker et al., 2017) (Chimene et al., 2018) (Pakutsah et al., 2020).

$$\tau = \tau_o + k\gamma^n$$

Where, shear-stress is represented by $\tau$and,$\tau_o$represents the yield-stress

And (K, n) are shear-thinner parameters of the power law.

Swelling is one of the characteristics of hydrogels that enables them to become soft and spongy like rubber which helps in the fabrication or patterning of the tissue or cells. This can be expressed mathematically (1), (2)

$$Swelling=Ws-Wd/Wd \quad (1)$$

Were,

The Weight of hydrogel in a swollen state is represented by Ws.

The weight of hydrogel obtained after dryingis represented by Wd.

$$Swelling=C/B*100Swelling=C/B*100 \quad (2).$$

C represents the weight of dry hydrogel.

B represents the weight of the insoluble part after separation with water (Malpure et.al 2018) (Chaudhary and Charkraborty, 2022)

With relatively lower cost the 3D structures bio printed through hydrogel usually show biocompatibility and biodegradation and in order to improve the nature of hydrogel to mimic biological system some modifications are done by adding cells, growth factors, cytokines, fibrin, polyethylene glycol as per desired application (Xie et.al 2023).Someresearchers also showed the use of various growth factorslike bone-morphogenetic factor, transforming-growth factor and differentiation-factor to increase biocompatibility (Bashir et.al 2023) (Caldera-Villalobos et al., 2023). The addition to these bioactive factors to enhance cell viability, proliferation, high metabolic activity, synthesis of new ECM enhanced compatibility, mentioned physical function at high level (Xie et al.,2023) (Yoon et al., 2018) (Azadmanesh et al., 2021). Different bioprinting techniquesmight also hinder the cell viability due to various mechanical disturbances (Nair et al., 2009).The degradability, another important measure, is based on the type of hydrogel, the process of crosslinking, the amount of hydrogel used, Temperature and physiological condition and using other added constituents. The rate at which the cell-laden hydrogel degrades should match the required biomedical application and importantly the material of hydrogel must be replaced by the constituents of the cell as degradation occurs to develop ECM components thus providing enhanced tissue remodeling (Zidarič et al., 2020). Some Other properties that affect the quality of bio printed products include the printing speed, printing pressure and feeding rate.

Applicationsof Hydrogel as bioink in 3D bioprinting

Hydrogels are found to be the best-suited models for bioinks materials in 3D bioprinting due to their mechanical and dynamic functional property and their ability to intimate the native space of ECM (Peppas et al., 1994) (lutolf et al., 2005). Natural biopolymers as hydrogels have been used as hydrogels since they already contain numerous biochemical signals, cell adhesive domains, and show greater maintenance and higher cell viability and proliferating rate when printed for TE (like collagen, fibrin, thrombin, hyaluronic acid etc.) (pati et al. 2014) (Yi et al., 2019) (Jang et al.,2016) (Jakab et al., 2010). Many applications of hydrogel based bioink for bioprinting include.

Clinical applications of hydrogel in *in-vitro* tissue engineering:

The complexity of biologic tissues cannot be exactly replicated by the microenvironment of hydrogel as biological tissue is usually heterogeneous in nature. Thus, there is a need for the development of innovative fabrication techniques that will help in dynamically modulating a hydrogel which could be used to alter its shapes in the predetermined path and also in controlling heterogeneity, localized behaviors and cell material (Seliktar et al., 2017) (Zhang et al., 2017) (Burdick et al. 2012) (Khetan et al., 2009). Improvement in hydrogel polymer with different biopolymeric agents. Bioink formulation including fibroblast along with nanocellulose-alginate based hydrogel ensured uniform cell distribution while also mentioning cell viability of skin and cartilage tissue (Thayer et al., 2018). Success of fibrin encapsulated hydrogel was observed in 3-D bioprinting of nervous tissue (Abelseth et al., 2019). Chemical modification of human kidney cells with photo-crosslinking dECM by methacrylate evidently showed that the bio printed cells fromhuman-kidney were highly viable and show maturation with time moreover they were also able to mimic the structural propertiesas well as the functionalproperties of native renal tissue (Ali et al., 2019). A new study over development of **DNA-basedhydrogel** in the improvement of current strategy to as an advantage in resistance to enzymatic degradation, controlled structure tunability, improved mechanical characteristics and efficient programmability. The study also shows promising development in fabrication of regeneration scaffolds for the treatment of bone defects by using light based 3D bioprinting using DNA hydrogel for bone organoids (Loi et al 2023).

Fabricated tissue	Hydrogel polymer	Cellular material	3D bioprinting technique	references
Epithelial	gelatin and chitosan	UMR-106 cells	Extrusion-based 3-D bioprinter	Loi et al. 2023
Nervous tissue	gelatin methacrylate (GelMA)	Human neural progenitor cell	Extrusion-based 3-D bioprinter	Curz et al.,2023
Heart valve	Alginate gelatin	Human cardiac-derived cardiomyocyte progenitor cells Aortic valve leaflet interstitial cells	Extrusion-based bioprinting	Duan et al., 2013
Neural tissue	Polyacrylamide	Neural stem cell	Inkjet bioprinting	Likhanizadeh et al., 2007
Nervous tissue	Fibrin, thrombin utilizing Hyaluronic acid (HA) and polyvinyl alcohol (PVA)	Schwann cells	----------	England et al 2017.

Table 1: Hydrogel as bioink for fabrication of different tissue for TE.

Modernized Hydrogel based *in-vitro* organ development and its future:

Recent studies have evidently shown that the development of hydrogel-based organoids and spheroids has a high success rate. In the popular Wetering et al; authors explained that characterization of patient drives colorectal cancer (CRC) organoids show a success rate of approximately 90% (Luo et.al 2021) (Koliaraki et.al 2017) Also other studies over different tumor types breast, ovarian, brain, and neck organoids described that the model are well studied for in *in-vitro* screening and discovery of drugs (Koliaraki et.al 2017) (Hoffmann et.al 2015) (Prestwich et.al 2011) (Ng et.al 2019) (Calon et.al 2014). The table 2 below show the bioprinting of numerous organoids using different hydrogel polymers.

Organoids	Hydrogel material	Cellular material	Approaches	Reference
Brain organoids	Gelatin methacrylate (GelMA)	Induced pluripotent stem cells	application for drug toxicity testing and Quantifying drug effect.	Tomaskovic-Crook et.al 2023
Retinal organoids	Polyethylene glycol (PEG)	Mouse Embryonic Stem Cells (mESC)	Development of such organoid culture systems that show scalability and single-organoid traceability.	Decembrini et.al 2020
Breast cancer organoids	Polyethylene glycol-derived hydrogels and Gelatin derived hydrogel	(Patient-derived) breast cancer cells	Advantages of thesematrices involveefficient preclinical tools for therapy and *in-vitro* drug screening platform.	Bock et.al 2023
Salivary gland organoids	Polyisocynopeptide hydrogel (PIC)	salivary gland (SG)-derived stem cells	Development of PIC hydrogel as an Alternatives to Matrigel as model hydrogel that show effective clinical translation of organoids.	Schaafsma et.al 2023
Lung cancer organoids	alginate and hyaluronic acid HA) and arginine-glycine-aspartic acid peptide.	Human pulmonary carcinoma cell line (A549)	Anticancer drug evaluation, personalized and drug screening.	Dong et.al 2023
Hepatic organoids	Gelatin-methacrylate (GelMA), lithium phenyl-2,4,6-trimethylbenzoylphosphinate (LAP)	adult stem cells	Applications in personalized drug testing and o build liver-like metabolic bio factories for liver-specific ammonia detoxification.	Bernal et.al 2022
Cardiac organoids	collagen	human-induced pluripotent stem cells (hiPSCs) and human embryonic stem cells (hESCs).	Applications in biology of heart development, in drug screening, and regenerative medicine.	Zhu et.al 2022

Table 2: Development of different organoids using suitable hydrogel materials.

Development of Hydrogel-based Spheroid and Organoid forDrug screening:

Hydrogels have a quantum of biological fluids in it due to which they swell up and become soft and spongy or rubber like and are able to assemble like tissues with them and show excellent biocompatibility (Chamkouri et.al). Drug delivery system mainly includes polysaccharides-based hydrogels for deliveringanti-cancer drugs(Datillo et.al 2023). Recently, Joseph Biden signed legislation certified by the FDA (Food and Drug Administration) authorizing new drugs. According to this new regulation, animals used in testing of a drug before its clinical research is no longer performed by the FDA. Instead, they can rely on alternatives such as organ-on-a-chip, computer modeling, and organdevelopment. (Yang et.al 2023) (Wadmen et.al 2023).

Since the formation of an organoid mainly relies on the capacity of the self-assembling of cells, the creation of microenvironment niche factors is mandatory (yang et.al 2023). Tumor models which use spheroids and organoids have the potential to improve specific precision medicine(Wang et.al 2022).The field of vascular biology is being transformed by the remarkable advancements in angiogenesis (the formation of blood vessels). This progress has led to significant achievements in drug screening and other areas. (Kim et.al 2014) (Sorbino et.al 2016). For example, Ali and colleagues developed a model for non-alcoholic fatty liver disease using a GelMA substrate. They were able to demonstrate the reversibility of steatosis with the use of an antisteatotic drug. In this example the metformin and pioglitazone and steatiotic drugs are screened by the change in the level of intracellular lipids.

Biomedical applications of hydrogel-based scaffolds

Many known applications of the copolymers of ethylene dimethacrylate and 2- (HEMA) include the development of contact lenses, urinary catheters, dressing of wounds and gloves of surgery etc. (J.C wheeler et.al,1996). For breast implantation, plastic surgeons have been extensively studying Hydrogels. The radio translucency of hydrogel implants made up ofCarboxy methyl – cellulose (CMC) is more than silicone gel andthe probity of the device was proven clinically (Brunner et.al,2006). Most of the hydrogels which are temperature sensitive exist in sol- state at room temperature but on increasing the temperature they transform into a gel (commonly body temperature) (Al-Sabah et.al, 2019).

4D Bioprinting

Despite of various advantages and rapid success in 3d bioprinting some limitation like the assumption that printed object is static and inanimate also can instantly generate tissue by cell adhesion, fusion and cell sorting and will maintain geometrical mechanical properties by synthesis of ECM (Gao et al., 2016l) (Naniz et.al 2022). To overcome these limitations time is added as anotherdimension to 3d bioprinting giving us a new technique to 4d bioprinting (Fatimi et al 2022). It provides tunability in shape and obtains desired functional changes according to required stimulation with time. Here time is not the measure of the duration of printing; instead, it refers to the evolution of bio-printed material with time (Gao et al., 2016). Introducing time has allowed constant monitoring the production of 3-D bio-printed materials and the bioinks allowing the development of bio mimic tissue and achieving more native like results (Ionov et al., 2013) (Inverardi et al 2020). Complex material and its programmability, multimaterial printing, and accuracy in structure design form the major requirement of 4D bioprinting and thus provide more tunability in shape, size, and geometry of the printed constructs (Pourmasoumi et al., 2023).

Future of Hydrogel-Based Bioprinting

The appealing ecological properties and capabilities of hydrogel to behave as the natural tissues are appealing and their vast range of uses in biomedical research. Still, the revelation of the attentive emendation is that there are some alterations that can be developed in these soft – materials. We believe that future studies of 3D bioprinting will be incredibly promising, since technology has the capability to transform many aspects of healthcare and the area of regenerative medicine. In the coming years, 3D bioprinting is expected to achieve several significant advancements that will improve its functionality and effectiveness. 3D bioprinting holds great achievements to create customized implants that perfectly fit an individual's anatomy. With the ability to print patient-specific implants, the risk of rejection can be reduced, and patient outcomes can be improved. Moreover, 3D bioprinter implants can also be designed to stimulate tissue regeneration, making them the best-suited model for tissue engineering. This technology also has the potential to be used in developing new therapies for a wide range of diseases. 3D bioprinting is also expected to play a significant role in drug testing. By creating 3D bioprinter tissues that mimic the human body, researchers can test the effectiveness and safety of new drugs without the need for animal testing or human clinical trials. This will not only minimize the cost and time required for developing the drug but also help to identify potential side effects of drugs early in the development process. Another exciting aspect of 3D bioprinting is its potential for disease modeling. By creating 3D bioprinter tissues that replicate specific diseases, researchers can study the mechanisms of disease and develop new treatments. This technology also has the potential to be used in personalized medicine, where 3D bioprinter tissues can be created that are tailored to an individual's unique needs. The future holds great potential to transform healthcare in many ways through 3D bioprinting. With continued advancements in this field, we can expect to see significant improvements in personalized medicine, tissue engineering, drug testing, and disease modeling, leading to better outcomes for patients and a brighter future for healthcare.

Conclusion

In this review, we manifest or reveal that the hydrogels show immense potential so that they can be used in the field of bioengineering. The arrangement of materials of different scales on various scales can take advantage of harmony and promote the development of new purposes or functions because of the distinctive arrangement between multi components or multi biomaterials new combinations of properties can emerge providing opportunities for further modernisation in hydrogels. Further investigation is needed to optimize the development of different organs through 3D bioprinting and use of hydrogen-based organoids and spheroids for drug screening. The authors believe that the future studies in this field must consider many unexplored properties like mechanical properties under dynamic conditions,Interactions with immune cells,Further studiesare needed todevelop an understanding of the degradation mechanisms of hydrogels, and to know how these mechanisms can affect the release of drugs from the hydrogel to target site,Swelling behaviour in complex environments, hydrogels also exhibit interesting electrical properties, such as electrical conductivity, piezoelectricity, and electrochemical activity. These properties could serve in the development of bioelectronic devices, such as biosensors and neural implants. However, these properties of hydrogels are not well understood, and further research is needed to explore these properties and their potential applications.

Availability of data and materials

Not applicable.

Abbreviations:

TE – Tissue Engineering

3-D – 3 Dimensional

FDA – Food and Drug Administration

GelMa – Gelatin methacrylate

mESC - Mouse Embryonic stem cells

PIC – Polyisocynopeptide

PEG – Poly ethylene glycol

CRC – Colorectal cancer

PVA – Polyvinyl alcohol

DNA – Deoxyribonucleic acid

CAD – Computer aided design

SMC's – Smooth muscle cells

CMC - Carboxy methyl cellulose

ECM - Extra cellular matrix

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