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# Next-Generation Hydrogels for Precision Drug Delivery: Current Status and Future Prospects

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**Abstract:** Hydrogels have developed as flexible drug delivery systems due to their distinct features, including high water content, biocompatibility, and variable mechanical properties. The developments uses, and future viewpoints of hydrogels in drug delivery are investigated in this study. We addressed the design ideas of hydrogels, including the use of biodegradable and stimuli-responsive materials, to accomplish focused and regulated drug release. The subject of study is applications across several distribution routes-- oral, transdermal, and injectable, stressing their part in improving therapeutic efficacy while minimizing unwanted effects. Furthermore, it covered integrating smart hydrogels for individualized medicine and nanotechnology into combination medicines. While using hydrogels to transform biomedical uses, future directions concentrate on conquering obstacles including scalability and regulatory approval. This study provides information on the present situation and possible future improvements of hydrogels, highlighting their transforming power in improving drug distribution methods.

**Keywords:** Hydrogels, Drug delivery, Biocompatibility, Stimuli-responsive, Nanotechnology

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## Introduction

Hydrogels are a class of soft materials distinguished by their remarkable property to undergo large volume expansion while still remaining as true solid bodies. These gels, made up of hydrophilic polymer networks are capable to expand in aqueous conditions without getting dissolved which has great importance towards numerous biomedical and pharmaceutical applications. Hydrogels are a type of biocompatible polymer that contain between 50-99.5% water (by weight) (Sanchez-Cid *et al.*, 2022, Ho *et al.*, 2022), and their use has been extensively researched earlier. This extensive research highlights their superior mechanical properties compared to many other biomaterials, such as silicones or PDMS, commonly used in microfluidic lab-on-a-chip applications. Furthermore, these materials exhibit tunable viscoelastic behavior upon the application of external forces, exemplified by redox-responsive gels (Saroia *et al*., 2018; Cao *et al*., 2021).

These polymer chains are either made from synthetic sources or derived from natural polymers and be crosslinked to form the hydrogel. This cross-linking is mediated by chemical bonding, physical interactions or a compination of both (Nielsen, 1969; Maitra and Shukla, 2014). The resulting three-dimensional network is capable of absorbing and retaining water, which contributes to the gel's soft and elastic properties (Haraguchi, 2011). The composition of hydrogels can be tailored to suit specific applications by selecting appropriate polymers and cross-linking methods.

*Historical development*:

The origin of using hydrogels can be traced to the 1960s when they were firstly used for biomedical purposes. A milestone in the hydrogel research is represented by early work of Wichterle and Lim (1959) which resulted in poly(2-hydroxyethyl methacrylate) PHEMA for contact lenses. These results led to the recognition of potential utility in medical applications for hydrogels and sparked further investigation. Hydrogels were first recognized for their potential in wound care and soft tissue implants (Haraguchi, 2011; Oliva *et al*., 2017; Islam *et al*., 2022) during the 1970s and throughout the early to mid-1980s. Both synthetic polymers such as PVA and polyacrylic acid (PAA) and natural polymers including alginate, chitosan, and collagen have been studied (Islam *et al.*, 2022). These early studies led to many of the diverse uses for hydrogels seen today.

Nowadays hydrogels have been extremely explored in several biomedical applications such as drug delivery systems. Due to their drug-loading and controlled release potential, these have dramatically changed the way therapeutics are delivered. For example, hydrogels have been designed to sense pH (Oliva *et al.*, 2017), temperature (Mazidi *et al*., 2022) and enzymes that can be used for controlled or on-demand drug release (Lavrador *et al*., 2021). The ability to do this could be a crucial asset in the treatment of chronic diseases, such as diabetes and cancer where controlled drug delivery is essential for optimal patient outcomes. Hydrogel dressings have gained popularity in wound care because of their capability to create a moist healing environment that supports tissue repair while managing pain. Inclusion of antimicrobial agents in the hydrogel dressings also contribute to their therapeutic presence as these prevent infections.

*Future prospects*:

The future of hydrogels in biomedical realm seems bright where more investigations take place to improve their properties and broaden the scope of its application. One area of enormous advancement is the development of personalized medicine. These hydrogels can be tailored to the patient, for much better and customized treatment. Combining 3D printing technology with hydrogel fabrication will dramatically transform the manufacturing of custom implants and drug delivery devices (Jacob *et al.*, 2020; Wang *et al*., 2021).

Another promising trend is the progress in developing stimuli-responsive hydrogels. Currently, researchers are investigating ways of increasing sensitivity and specificity to external stimuli. More complex products would allow for monitoring and using hydrogels further as drug transport systems that are sensitive to particular biological signals. Moreover, sustainability and environmental issues are addressed.

*Nano hydrogels and their impact*:

Further Nanotechnology pushed the hydrogel beyond its potential, Nano-hydrogels. This is hydrogel in a particle size at nanometer size with benefits derived from hydrogels that combined with special qualities in nanomaterials that will include improved surface area, better bioavailability and targeted capacity towards some of the cells or tissues – all that nano hydrogels provide (Vashist *et al*., 2018; Elkhoury *et al.*, 2019; Ayoubi-Joshaghani *et al.*, 2020) depend on nano hydrogels do hold huge promise for targeted drug delivery, and they also assist in reducing the side effects and enhancing the therapeutic effectiveness. Their ability to trap a wide range of drugs, protect them from degradation, and release them under control makes treating complex disorders like cancer (Chowdhury *et al.*, 2017).

## Historical Perspective

Hydrogels have an fascinating history with achievements, along the way that have turned them into crucial elements, in today's biomedical and pharmaceutical realms shedding light on how the technology has evolved and influenced diverse sectors over time.

### *Past developments*:

The exploration of hydrogels started in the twentieth century with a focus, on their possible applications in the field of medicine and healthcare technology. Many breakthroughs have been achieved over the years due to the innovation of polymers and cross linkage methods as well as a better comprehension of the physical and chemical features of hydrogels.

### *Early research (1960s-1980s)*:

### *The Birth of Hydrogels*:

In the 1960s Czech chemists Otto Wichterle and Drahoslav Lím introduced the idea of hydrogels to the community for the first time. Their innovative exploration, into 2 hydroxyethyl methacrylate)(PHEMA) which is known for developing the contact lenses based on hydrogels (Kopecek, 2009) showcased the immense potential of hydrogels in various biomedical applications directly impacting fields, like ophthalmology. PHEMA hydrogels have gained attention for their attributes in contact lenses, like biocompatibility and transparency and their capacity to maintain water content effectively.

### *Expansion of hydrogel research*:

After the favourable outcome of the PHEMA gel, more studies were carried out to other hydrophilic polymers that could be utilised in the formation of hydrogels. The 1970 and 1980 witnessed a growing interest in the preparation of both synthetic and natural hydrogels.

## Biomedical Applications

The preliminary studies on hydrogels provided a basis for several applications of hydrogels in Biomedical sciences. By the 1980s, hydrogels were being explored for their potential in various fields:

### *Drug Delivery*:

Hydrogels were awarded for its characteristics of encapsulation of drugs and controlled release of the same in the body. Hydrogels are good drug delivery systems because they could extend the drug release; protect the drug from degradation; and deliver the drug to the target tissue (Narayanaswamy and Torchilin, 2019).

### *Wound Care*:

Hydrogel dressings offered a moist environment needed for tissue repair and activation as they helped in freeing the wound from pain. These were effective in maintaining the right level of moisture needed for treatment of such wounds. The addition of antimicrobial agents into the hydrogel dressings increased the therapeutic effectiveness of these dressings due to the ability of the incorporated antimicrobial agents to inhibit germs.

### *Tissue Engineering*:

Scaffolds that help tissue regeneration were found in hydrogels, which creates the appropriate platform for cell division and differentiation. Because of the biocompatibility and adjustability of hydrogels, it can be employed in cartilage repair, bone tissue engineering, and creation of organs (Xue *et al.*, 2021; Isaac *et al.*, 2024).

## Natural PolymersUsed in Hydrogel Formulation

### *Alginate*:

Alginate is a water soluble natural biopolymer derived from brown by-products of seaweed. A polymer containing β-D-mannuronic acid (M) and α-L-guluronic acid (G) linked together in a random manner. It is non–cytotoxic and has low interactivity with biological organisms so it can be used in medical and drug related products. An example of this type of polymer is calcium ions ($Ca^{2+}$). The gelation is rapid, recoil-free, and is amenable to low temperature and pH. Good water absorbency, it keeps wound moist- ideal for healing process.

### *Chitosan*:

Chitosan is produced through the deacetylation of chitin a polymer that is abundant in marine animals such as shrimp and crabs. It is polycondensation product of N-acetyl-D-glucosamine and D-glucosamine units. This product is made from natural materials that decompose into non-hazardous substances. It has inherent antibacterial qualities, which makes it suitable in the therapeutic management of wounds and prevention of infections or infection spread (Zhong *et al.*, 2020). It provides stable immobilization to mucosal areas allowing targeted drug penetration across mucosal barriers.

### *Collagen*:

Collagen as a polypeptide is the most abundant protein in the human body and is richest in the connective tissues like skins, bones and tendons etc. It is proteinaceous, complex, made of three polypeptide chains coiled around each other in the form of a triple helix. It is bio-compatible, bio-active, and promotes the cell's attachment to the surface and the growth of cells. It is self-degradable, and consisting of a scaffold with a short-life span which is slowly replaced by tissue in the body (Zhang and King, 2020). It provides good mechanical properties that improve the lack of structural rigidity that is characteristic of hydrogels.

## Synthetic Polymers Used in Hydrogel Formulation

### *Poly*(*vinyl alcohol*) (*PVA*):

A man made synthetic material derived from poly (vinyl acetate)by hydrolytic cleavage. It is made from the execution of vinyl alcohol monomers. It is biocompatible and non-toxic so has the potential for use in surgery. It possesses good mechanical characteristics such as tensile strength and flexibility and is very soluble in warm water, forming colourless spongy masses.

### *Poly*(*acrylic acid*) (*PAA*):

A generic name for a group of synthetic polymers created from the polymerization of acrylic acid monomers. It is recycled from a number of acrylic acid units and displays inverse phase transition in alkaline solutions, the gel swells and in acidic solutions the gel contracts. It is harmless and compatible with biological systems, hence can be used in biomedical products. It forms crosslinked hydrogels whereby water absorption is at maximum, it can swell to 1000 times its own weight.

### *Poly*(*ethylene glycol*) (*PEG*):

Polymer reproduced by the polymerization of ethylene oxide whereby it becomes a synthetic polymer. This polymer is made up of ethylene glycol repeating units. Ecologically friendly and chemistries do not evoke immune responses in the body, fits well in various medical procedures. Very soluble in water, to form hydrogels which swell with the uptake of large volumes of water. Can be easily adjusted, to incorporate functional groups to be used for specific purposes.

## Present Applications of Hydrogels in Drug Delivery

Hydrogels are considered as an essential component of contemporary drug delivery since they possess properties like, high water component, biocompatibility, capability of encapsulating and releasing the drugs at specific rates. Some of these attributes have helped in creating different drug delivery systems to enhance organizational compliance and treatment (Fig. 1).

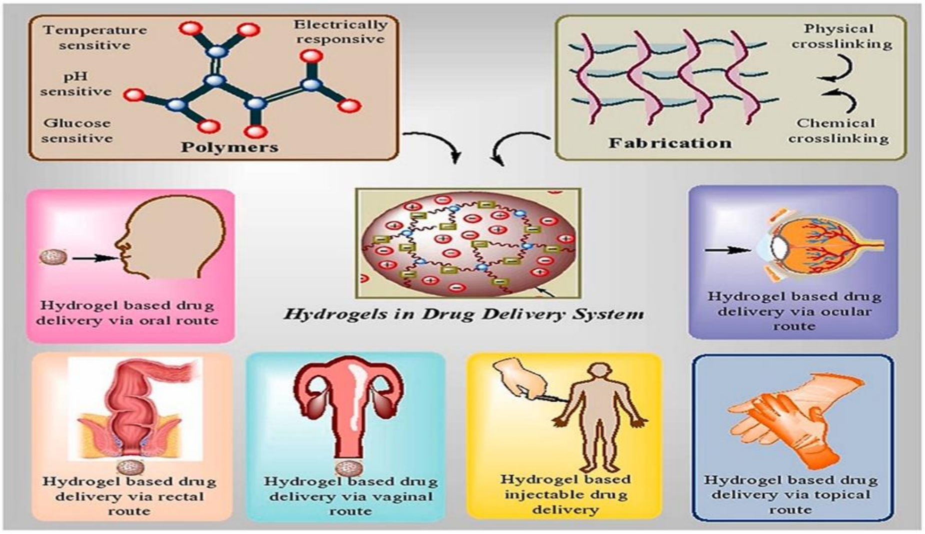


Fig. 1: Different use of hydrogels (Kesharwani *et al.,* 2021).

## Controlled Drug Release

### *Oral drug delivery*:

In oral drug delivery systems, hydrogels can protect drugs from the degradation by the low pH of the stomach and release the drug in the intestine. This is made possible through the development of hydrogels that respond to certain pH conditions in a manner such that they swell or degrade. Sustained release formulations lengthens the time that the drug remains active in the body, and therefore, produces the need for repeated administration and better patient compliance.

### *Transdermal drug delivery*:

They are comfortable to use since they are applied over the skin and they are a transdermal hydrogel patches. The drug lies in the hydrogel matrix and when the formulation is applied on the skin, the drug diffuses through the skin into the blood stream. Compared with other administration routes, transdermal systems reduce the risks associated with first-pass metabolism in the liver thus improving bioavailability. It is routine to have a constant release of the drug and this reduces fluctuations of concentration which would affect the side effects and the cure.

### *Injectable drug delivery*:

To achieve the controlled drug release at specific site in the body, injectable hydrogels are employed. Such hydrogels can be delivered in a liquid form and then solidify *in situ* to create a depot for the drug that may release the drug slowly over time (Fakhari and Subramony, 2015). Local delivery reduces the degree of toxicity to a system as well as other effects while on the other hand, controlled release ensures that the level of the drug required to treat persists in the body. The injectable hydrogels are particularly useful in cancer and for delivering bioactive macromolecules, including proteins and peptides that are unstable in the GI tract.

## Smart Hydrogels

### *Responsive to environmental stimuli*:

The other type of hydrogels are referred to as “smart”, “intelligent” or “responsive hydrogels” characterised by the ability to respond to particular stimuli present in the surrounding environment (Mahinroosta *et al*., 2018). This makes drug release to be in demand and aspire to the physiological conditions of a certain patient.

### *pH-responsive hydrogels*:

These hydrogels change their size when

accompany by changes in pH levels. They are most valuable in delivering drugs to certain regions of the gastrointestinal tract, where the pH is quite different.

*Temperature-responsive hydrogels*:

Some of the ability of these hydrogels is that they can readily undergo sol-gel transition at certain temperatures. While the temperature is below the transition temperature, the hydrogel state remains in the liquid phase; if the temperature is beyond the mentioned value, then the state of the hydrogel changes into the gel phase.

*Glucose-responsive hydrogels*:

These hydrogels consist of glucose-sensing moieties that cause the release of drugs when glucose level fluctuates.

### On-Demand Drug Release for Chronic Diseases

The detailed control of drug release makes smart hydrogels a promising solution for chronic illnesses, such as diabetes and cancer.

*Diabetes:*

Responsive hydrogels based on glucose may release insulin when the blood glucose level is high; this results in better control of diabetes than the conventional injectable insulin. On-demand work minimizes the occurrence of hypoglycaemic episodes and also improves patient's quality of life.

*Cancer*:

Intelligent hydrogels can release chemotherapeutic agents at the tumour site such as by changing pH or temperature. This narrowed targeting reduces the probability of system toxicity, as well as the general effectiveness of cancer treatment. The drug delivery capacity from smart hydrogels can be programmed to release the same drug in different time intervals, or different drugs altogether and this feature is particularly advantageous in situations where the growth of drug resistance is possible and warranted.

*Wound care*:

*Hydrogel dressings*:

*Moist environment for healing*:

Hydrogel dressings create a moist wound healing environment, which is optimal for the wound healing process (Nuutila *et al.*, 2021). High water content in hydrogels brings several advantages. Water continues to promote the movement of epithelial cells across the injured area, which helps to restore the layers of skin more quickly, and also reduces inflammation. Hydrogels have been seen to warm the affected areas thereby giving the patient a soothing feeling which eradicates pain and discomfort (Edwards *et al.*, 2010). The warm wet climate is conducive to autolytic debridement of tissues; to help the body remove dead tissues, also cover the wound from invasion by pathogenic agents and thus minimizes chances of infection.

*Incorporation of antimicrobial agents*:

- *Silver nanoparticles*: Silver is a known antimicrobial agent that is used in many hydrogel dressings. Silver nanoparticles liberate chemically active silver ions and exhibit bactericidal, fungicidal and virucidal properties.
- *Antibiotics*: Gentamicin, vancomycin and ciprofloxacin are among the antibiotics that can be incorporated in hydrogel for wound infection intervention by releasing the antibiotic directly where it is needed most, at the wound site.
- *Natural antimicrobials*: Food contact friendly antimicrobial agents include honey, chitosan, and essential oils. Such agents can be incorporated into hydrogels in the spirit of providing natural routes of managing infection.

### Tissue Engineering

*Bone regeneration*:

When hydrogels are altered, they become osteoconductive, this means they promote the adhesion, proliferation and differentiation of

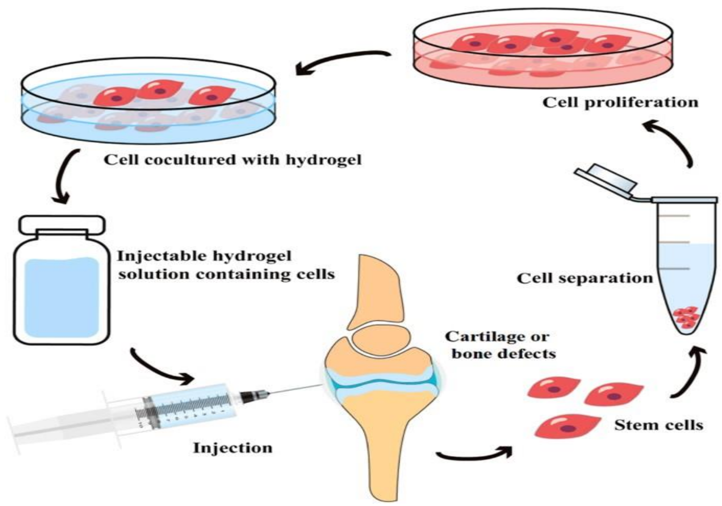


Fig. 2: Schematic representation of injectable hydrogel for bone regeneration (Liu *et al*., 2017).

osteoblasts. Nanotechnology can fill hydrogels with growth factors such as the bone morphogenetic proteins that elicit bone formation. Such factors are brought in controlled manner into the body in order to induce the formation of new bone tissue (Fig. 2).

*Scaffolds for cell growth and tissue regeneration*:

A large number of hydrogels have been employed as scaffolds in tissue engineering in view of their ability to support cell adhesion, proliferation and tissue formation. Their biocompatibility, high water content, and tunable properties make them ideal for various applications. Hydrogels are a close imitation of the ECM in terms of the supplying platform, allowing cell adhesion and division. Scaffold sturdiness can be designed to mimic that of the target tissue in which hydrogels are used to offer structural support during tissue development.

*Applications in tissue engineering*

Hydrogels can have the ability to facilitate the growth and differentiation of chondrocytes or cartilage cells, (Vega *et al.*, 2017). It also explains why these scaffolds offer the information that leads to the formation of cartilage-specific ECM components by cells.

## Artificial Organs

*Organogenesis*: These hydrogels are useful in developing constructs which represent the biological structure of living tissues. These scaffolds are to which cells are cultured and then develop tissue architectures resembling to target organ.

*Vascularization*: Propagation of the tissue has been cited as a major problem in tissue engineering especially in the aspect of blood supply to the engineered tissue. They can be developed to encourage the process such as angiogenesis, which is the formation of blood vessels, essential especially for the functioning of organs such as a heart.

*Functional Integration*: Hydrogels subsequently serve as a scaffold that supports multiple cell types and various signals needed to create functional tissue constructs that may serve as substitutes for compromised organs.

## Future Prospects

The current and potential biomedical application of hydrogels seems to be good in the future as there is research that goes on to improve hydrogels functions and uses.

Several exciting prospects are on the horizon:

*Personalized medicine*:

*Customized hydrogels*:

Actualizations in inkjet printing and tissue engineering techniques in facilitating the fabrication of hydrogel grafts that will fit patient's needs. Hydrogels can mirror the exact individual need for a given patient in regards to anatomy and physiology delivering better treatment responses (Raman and Langer, 2020; Facklam *et al*., 2020).

*Patient-specific drug delivery*:

It means that in near future hydrogels can be designed to deliver drugs according to the features of patient's body to provide effective therapy.

### Advanced Smart Hydrogels

*Multi-responsive systems*:

The next-generation smart hydrogels are predicted to undergo changes in swelling and/or sol behaviour due to more than one stimulus including pH, temperature, light, and/or biochemical signals (Lim *et al.*, 2014). These multi-responsive systems could offer a higher degree of regulatory over drug distribution and the general tissue interface.

*Real-time monitoring*:

Hydrogels containing sensors and diagnostic components can also feedback physiological statuses in real time and respond to drug delivery autonomously (Tan *et al*., 2022). This capability is most useful for treating chronic diseases and in choreographing the best course of treatment with the patient, client, or consumer.

### Sustainability and Environmental Impact

*Biodegradable hydrogels*:

The synthesis of hydrogels that obtain the ability to degrade into innocuous materials after they perform their assigned task is a major goal. These hydrogels conform well with this trend towards sustainability in medical and pharmaceutical sectors.

*Green manufacturing*:

Current and future research reveal that environmentally sustainable processes for synthesis of hydrogels with fewer hazardous chemicals and less energy are also under the process of development.

### Regenerative Medicine and Organ Transplantation

*Complex tissue engineering*:

The agenda for tissue engineering is to build even further developed tissue and organs. In the context of regenerative medicine, the hydrogels will contribute significantly to the creation of biomimetic multi-tissue constructs of whole organs.

*Immune modulation:*

Current advances in hydrogel technology have made it possible to cue immune response, thus minimizing rejection and improving compatibility of engineered tissue with the host tissue (Li Xiaoting *et al.*, 2021).

### Future Prospects in Personalized Medicine and Advanced Stimuli-Responsive Hydrogels

*Personalized medicine*:

*Development of patient-specific hydrogels*:

Personalized medicine targets developing specific medical treatment for specific characteristics of the patient. Ideally suited to the development of patient access therapies, due to the obvious and well teach characteristics of hydrogels, they offer the potential for a correctly tailored solution as per the individual needs of the patient.

*Customization for individual needs*:

*Patient-specific conditions*:

Hydrogels can therefore be designed to qualify to the medical requirement of a particular patient. For instance, one patient suffering from chronic wound would need a hydrogel with certain anti-bacterial functionality while another patient in need of a bone defect, would need a hydrogel that

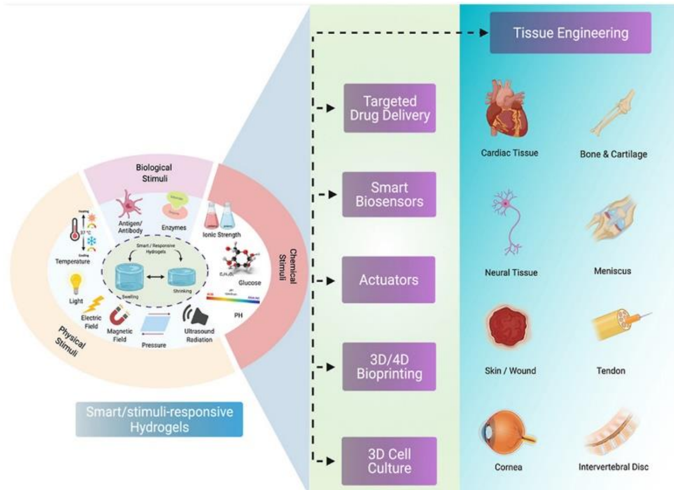


Fig. 3: Schematic representation of smart responsive hydrogel (El-Husseiny *et al.*, 2022)**.**

has osteoinductive function.

*Biocompatibility and Biodegradability*:

Designing hydrogels by altering their composition and architecture allows for acquiring materials with appropriate biological and mechanical characteristics of the target tissues; this increases biocompatibility and biodegradability.

*Integration with 3D printing technology*:

*Custom implants*: Hydrogels make it possible to develop implants using 3D printing with the exact measure of the client's body in area. Such implants can offer improved conformity, performance and tissue incorporation than the standardized ones.

*Drug delivery devices*: It is also possible to use 3D printing technology for fabricating drug delivery hydrogel devices with intricate outer and inner shapes. One of these can be made to deliver drugs in a systemic way that is controlled and this will suit the needs of a patient as far as dosage and timing is concerned.

*Personalized scaffolds*: Applications of tissue engineering techniques now includes using hydrogel scaffolds constructed by a 3D printer to aid the growth and development of living tissues from patients' samples. These scaffolds can have growth factors, cells and any other kinds of mol Achilles Tendinopathy with focus on the Mechanobiology of Tendons ecular bioactivity to support tissue build up and integration.

Advanced Stimuli-Responsive Hydrogels

*Enhanced sensitivity and specificity to external stimuli*:

Smart or stimuli-responsive hydrogels are capable of altering properties in response to external stimulus like pH, temperature, light, etc. or in response to biochemical signals (Kasinski *et al.*, 2020) (Fig. 3).

*pH-responsive hydrogels*:

These hydrogels have ionizable groups which are capable of undergoing reversible changes in volume depending on the pH of the surrounding environment. This property can then be exploited to deliver drugs in specific regions of the gastrointestinal tract or in the acidic milieu of a tumour mass.

*Temperature-responsive hydrogels*:

Temperature sensitive hydrogels aggregate in a change of phase, termed sol-gel transition at certain temperatures. For instance, they can be a liquid at room temperature and become a gel type substance at body temperature.

*Light-responsive hydrogels*:

Smart hydrogels include photoresponsive moieties which undergo reversible changes undergoing radiation with certain wavelength. This make it possible to manage drug release mechanisms by use of external light sources.

*Smart drug delivery systems*:

Physiological signals can be incorporated into hydrogels and controlled by electronic devices to control the delivery of the drug (Tan *et al.*, 2022). For instance, hydrogel can release insulin through the response of glucose sensor at high blood glucose levels.

*Wearable health monitors*:

Smart textiles incorporating stimuli-responsive hydrogels in the wearable devices can detect some of the body's parameters including temperature, pH, and some chemicals (Barhoum *et al.*, 2023). Wearable devices can constantly track a patient's conditions, offer timely interventions for heart diseases, udder infections and diabetes and other life-threatening metabolic diseases.

*Implantable biosensors*:

Smart hydrogels may also be used in implantable biosensors which are able to detect environmental changes inside the body and when these occur release drugs. Hydrogels can work synergistically together with implantable biosensors for the localized delivery of drugs used in treating cancer.

## Conclusion

It is concluded that the advancement of nano hydrogels in the field of drug delivery can be considered valuable path of treatment in contemporary medicine for developing the personalized treatment corresponding to the patient's individual needs. In the future, researchers can bring positive change to a wide aspect of health care delivery and treatment systems to improve patient outcomes. The nano hydrogels improve the delivery of therapeutic agent; by directly targeting cells or tissues thus minimizing the necessary dose and its side-effects. The hydrogels can be adapted to patient's requirement and augmented with 3D printing for creation of unique implants for delivery devices of drugs. With growing demand in nano hydrogel research, these hydrogels will be a great solution to change the direction of clinical treatment, providing novel approaches to dealing with both treatment and diagnosis.

## Ethical Statement

This is a review article hence no Ethical Approval needed.

## Author Contributions

Each author has contributed equally to the study's planning, analysis, writing, and editing. All authors have read and agreed to the published version of the manuscript.

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## Conflict of Interest

The authors declare no conflicts of interest.

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