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Hydrogel Based Nano composition System: Characterization and Application for Drug Delivery System

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Abstract

One of the main topics of study in the realm of pharmaceutical science is the targeted delivery of drugs to particular organs and tissues. By regulating the drug's release qualities, targeted drug delivery systems reduce toxicity and adverse effects while increasing the bioavailability of drug molecules at the delivery site. Although hydrogel is frequently utilized for controlled medication delivery, it has several limitations. Hydrogels nanocomposition system (HYGs-NC) was created in order to address the shortcomings of conventional hydrogels. Due to their porous and hydrated molecular structure, HYGs-NC are composed of many types of nanoparticles or nanostructures in the hydrogel network and may hold high amounts of therapeutic substance. In comparison to conventional hydrogel, HYGs-NC seeks to improve hydrogel's mechanical, electrical, and biological capabilities. For tissue replacement, contact lenses, biosensors, actuators, wound dressings, and cancer treatment delivery, nanocomposition hydrogel is employed. The most current developments in nanocomposition hydrogels, various types of nanocomposit hydrogels, methods of synthesis, characterization, and their use in biology or pharmacology as innovative drug delivery systems are covered in this chapter. The ideal qualities for targeted drug delivery applications are enhanced by the interaction between the hydrogel polymer and nanoparticles, which is improved by the unique properties of each type of nanocomposit hydrogel.

Key words: Hydrogel, drug delivery, tissue replacement, polymers, biosensor.

Introduction

Currently, one of the most important initiatives is the delivery of drugs to specified or specific organs. Many scientific activities are engaged in to increase the therapeutic index and bioavailability in order to develop newer drug delivery techniques [1]. In order to lessen toxicity and adverse effects, newer drug delivery strategies are intended to minimize the solubility problem, block photodegradation, prevent pH fluctuations, and increase control over the release profile of drug molecules [2]. The entire delivery system should be flexible, biodegradable, and biocompatible [4]. Because of its small size, complex surface structure, and large surface area, nanomedicine showed various physicochemical features. As a result, nanoparticles overcome the drawbacks of conventional formulations and aid in the uptake of specific cellular targets within the cell. Numerous biological uses of nanomedicines have been documented, including the therapy of cancer, safeguarding of medication molecules, proteins, peptides, and DNA, analyzing environmental risks, delivering proteins and genes, self-regulated releasing devices, biorecognizable systems, and stimulus-controlled vectors [5]. Thus, nanotechnology has been applied to a variety of industries, including imaging, diagnostics, and the delivery of drugs and genes [6, 7]. Oral, nasal, transdermal, parenteral, pulmonary and ocular methods are used to give Nano medicines. The drug molecules are delivered to the site of action using this nonmetric, which results in powerful biological activity. Drug compounds with limited solubility or a brief half-life and a hazardous character are transported via nano-vectors.

Hydrophilic polymer networks that are insoluble in water and capable of holding a lot of water (20 to 40 times their dry weight) are known as hydrogels. The inclusion of -NH₂, -COOH, -OH, -CONH₂, -CONH -, and -SO₃H groups contributes to the hydrophilic nature of hydrogel. By cross-linking polymer chains through physical interactions such as covalent bonds, hydrogen bonds, and van der Waals interactions between these functional groups, hydrogels are created. The size and shape of hydrogels can vary [8]. The steps in the hydrogel swelling process are as follows: Firstly polar hydrophilic groups of the hydrogel are hydrated with water, this bounded water is known as primary bounded water.

1. Hydrophobic interactions between water molecules are also referred to as secondary bound water.
2. Primary bound water and secondary bound water are used to compute total bounded water.
3. This dilution relies on osmotic force, which is resisted by cross-linking that is either physical or chemical.

All of the hydrogel's pores are filled with this absorbed water, also known as bulk or free water. The temperature and the particular way that water molecules interact with polymer chains affect how much water is absorbed [10].

Pharmaceuticals, biomedical applications, tissue engineering and regenerative medicines, diagnostics, wound dressing, separation of biomolecules or cells, barrier materials to regulate biological adhesions, and biosensor may all use hydrogel drug delivery methods [11].

1. Hydrogel Classification

Hydrogels are classified based on their physical properties, nature of swelling, method of preparation, origin, ionic charges, sources, rate of biodegradation and observed nature of crosslinking [12].

- A.** Physical properties: Amorphous, semicrystalline, Smart and Conventional.
- B.** Method of preparation: Copolymeric, Homopolymeric and Interpenetrating network.
- C.** Response
 - a.** Biochemical response: Antigen, Enzyme and Ligand
 - b.** Chemically response: pH, Glucose and Oxidant.
 - c.** Physical: Temperature, Light, Pressure, Magnetic field and Electric field.
- D.** Cross linking: Physical and chemical cross linking.
- E.** Degradability: Biodegradable and non-biodegradable.
- F.** Sources: Natural, synthetic and hybrid.
- G.** Ionic Charges: Cationic, Anionic, Non-ionic and Ampholytic.

One type of hydrophilic monomer makes up "homopolymer hydrogel," two types of monomers make up "copolymer hydrogel," three or more types of monomers make up "multipolymer hydrogel" or "interpenetrating polymer networks," and so on. An anionic hydrogel is a thermosensitive carboxymethyl pullulan with a negative charge. Cationic hydrogels carry positive charges and are a new type of thermosensitive hydrogel made of (3-acrylamidopropyl)trimethylammonium chloride and N-isopropylacrylamide (NIPAAm). While ampholytic hydrogels are based on acrylamide polymers, neutral hydrogels have no charge and are made of miscible mixtures of water-insoluble polymers such poly (2,4,4-trimethylhexamethylene terephthalamide) [11].

Chains are randomly organized in amorphous hydrogel [5]. Semicrystalline hydrogels can shift from a solid to a liquid state quickly [6]; similarly, "hydrogen-bonded" structures are three-dimensional networks connected by hydrogen bonds [13]. Through rapid changes in the network's physical makeup, smart hydrogels are polymer networks that can react to outside

stimuli [14].

2. Hydrogel Characterization

The size, strength, orientation, composition, network mesh size distribution, amount of bound and free water, chemical bond strength, and chain crosslinking of polymer chains all affect the hydrogel's properties [15]. It's crucial to assess the static and dynamic behavior of hydrogels at various pH levels, ionic strengths, concentrations, temperatures, and environments. Hydrogels' swelling, viscosity, elasticity, rigidity, and mechanical strength qualities all affect how functional they are.

Hydrogel properties can be determined using a variety of characterisation techniques, including rheology, scattering, composition determination, strength, and microscopy. All of these techniques, meanwhile, have some drawbacks, including sample preparation, resolution, data statistics, and data quality.

The main characteristics of hydrogels are as follows: First, weigh the hydrated hydrogel or the freeze-dried hydrogel; the weights of the two differ. Hydrogels differ due to these structural differences.

Mechanical Properties

Fiber type, composition, organization, cross-linking, and water content all affect mechanical properties [16]. Tissue engineering, drug delivery, and super absorbents are used to test the mechanical strength and viscoelastic characteristics of hydrogels [17].

Hydrogel's viscoelastic properties are assessed using rheological data [18]. By applying a shear and measuring the strain, or vice versa, rheologists can determine the kinetics of gelation and the stiffness of gels. Shear strain or stress applied to the hydrogels in a sinusoidal oscillation causes deformation. Measurements of shear stress or strain are made in relation to the phase shift in the sine wave caused by the applied angular frequency. Rheology is the best method for detecting changes in gel structures during the phase change from sol to gel (assembly formation) and the reverse (assembly breaking) [19].

The shear storage modulus (G' ; energy stored in deformation), shear loss modulus (G'' ; energy released in deformation), and loss factor ($\tan \Delta = G''/G'$) are all evaluated in the study of hydrogel rheology. Regarding measurement duration, frequency, and strain, these factors explain the hydrogels' viscoelastic properties. While $G'' > G'$ ($\tan \Delta > 1$) indicates a hydrogel driven by a viscous liquid, $G' > G''$ ($\tan \Delta < 1$) denotes a hydrogel controlled by its elastic solid nature. Atomic Force Microscope (AFM)-based nanoindentation and tensile testing are additional methods used to assess the mechanical properties of hydrogels [20].

2.1. Hydrogel Swelling and Cross-Linking Density

The hydrogel swelling ratio (SR) gauges the water content. Hydrogel's higher water content makes its ability to swell a significant parameter. The hydrogel's network structure and mechanical strength are considerably altered by water diffusion and the subsequent swelling [21]. The SR value of a hydrogel depends on its structure and is influenced by factors such as pH, ionic strength, and hydrophobicity [22]. The SR value is calculated by contrasting the hydrogel's dry and wet masses [23].

$$\text{Swelling ratio (SR)} = \frac{M_{\text{wet}} - M_{\text{dry}}}{M_{\text{dry}}}$$

Where,

M_{wet} : The wet mass of hydrogel

M_{dry} : The dry mass of the hydrogel.

The hydrogel structures before absorption of water (non-swollen) and after water absorption (swollen) are shown in **Figure 1**.

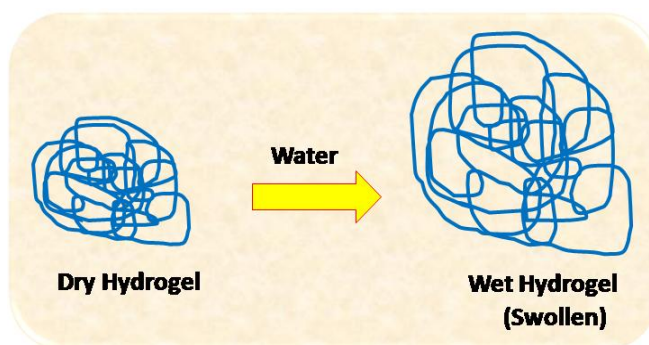


Figure 1: Schematic of hydrogel in dry state and swollen hydrogel after absorption of water

In order to create a local 3-dimensional structure, the hydrogel's polymer chains are crosslinked to one another using physical or chemical linkages. The number of polymer chains that are interconnected with one another per unit volume to produce the local hydrogel structure is indicated by the cross-linking density (CLD in mol/m³) of polymer chains [24]. CLD alters the shear modulus, swelling ratio, and diffusion coefficient of molecules trapped in hydrogels, including proteins, enzymes, medicines, and nanoparticles [25].

2.2. Local Hydrogel Structure

One of the most important factors in the characterization of local hydrogels is the determination of their structure and shape. The hydrogel structure created by bonding, fiber orientation, and pore spacing determines several hydrogel properties. The hydrogel structure and morphology

are revealed using direct imaging and indirect scattering techniques.

Indirect methods that directly produce real-space images of the hydrogel structure include optical, scanning electron microscopy (SEM), and transmission electron microscopy (TEM) [26, 27].

Direct probing of the original hydrogels is challenging because of the high water content in hydrogels [28]. The hydrogel must be dried using a cryo/freeze drying process or in the air since high resolution microscopy (SEM/TEM) requires samples to be in a low-pressure chamber. The local hydrogel structure can be studied over a greater volume of the original sample using indirect X-ray or neutron scattering methods, which are significantly more powerful [29]. The hydrogel structure can be resolved using scattering techniques on length scales between 1 and 1000 nm.

Hydrogels can be imaged using optical microscopy [30], but there are restrictions on the thickness of the gels through which light can pass, resulting in limited resolution and the loss of information for thick samples.

The adherence between the cell and the hydrogel contact can be seen using total internal reflection microscopy (TIRF) [31]. The resolution offered by TIRF, which ranges from 100 to 200 nm, is insufficient to resolve the essential scale of a few nanometers present at the cell-hydrogel interface contact zone. Reflection interference contrast microscopy (RICM) [32] has arisen as a substitute technique to circumvent TIRF's limitations, but it has encountered difficulties since the interferometric patterns at the hydrogel-liquid interface are not well contrasted.

2.3. Mesh Size

Proteins, nanoparticles, and pharmaceuticals diffuse into hydrogels through pores that are created when polymer chains are crosslinked. The correlation length or network mesh size, which is the linear separation between two nearby entangled chains, is used to define the hydrogel network's pores ξ (**Figure 2**) [33]. The distribution of mesh size can range from a few nanometers to the microscale range.

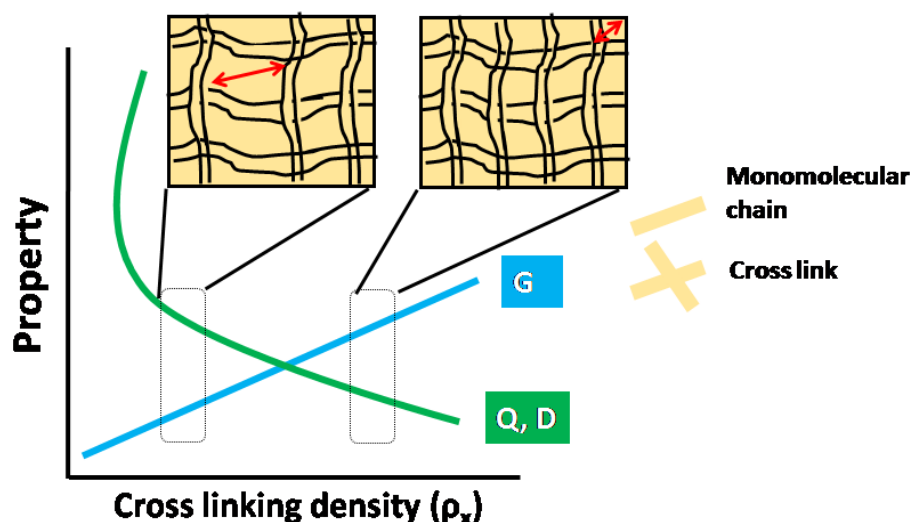


Figure 2: Hydrogel properties relationship with the cross-linking density (CLD). Low and high cross-linking densities have different mesh sizes (ζ) which have relationship with the hydrogel properties of shear modulus (G), equilibrium swelling ratio (Q) and diffusivity (D) [34]

Smaller mesh sizes prevent diffusion while larger mesh sizes enable rapid diffusion of entities in the hydrogel network. Due to an increase in protonation, the creation of hydrogen bonds, and charge screening, pH and ionic strength have a significant impact on the hydrogel mesh size [35].

The following equation can be used to determine the mesh size for the highly swollen hydrogels:

$$\xi = Q^{1/3} (C_n N L^2)^{1/2}$$

Where, ξ is the mesh size, C_n is the Flory characteristic ratio of the polymer, L stands for the bond's length along the polymer's backbone. Q is the hydrogel's volumetric swelling ratio, and N is the number of bonds connecting two cross-links. The value of Q and N is determined by the volume of hydrogels before and after equilibrium.

Since swollen hydrogels contain a lot of water, it is challenging to gauge their mesh size directly. On prepared samples, however, indirect scattering techniques can be used to determine the correlation length (mesh size) between cross-linked fibers through study of scattering curves [36]. A potent and non-destructive contrast-based method to identify the hydrogel network nanoscale structures in the region of 1 nm - 1000 nm is small angle scattering (SAS) using X-ray (SAXS) or neutrons (SANS) [37].

2.4. Composition and Molecular Interactions

Properties of hydrogels are influenced by their chemical makeup, interactions between fibers, and interactions between fibers and their environment [38]. Nuclear Magnetic Resonance

(NMR) and Fourier Transform Infrared (FTIR) are efficient methods for calculating chemical composition and chemical structure [39]. The hydrogel network's physical and chemical crosslinking was effectively determined using FTIR. Solid samples can be measured in transmission mode when using FTIR. Since liquid, powder, and coated film materials cannot be evaluated in transmission mode, attenuated transmission reflectance (ATR-FTIR) is employed for these samples [40].

2.5. Thermal Stability

Thermal Gravimetric Analysis (TGA) is used to gauge the hydrogel's thermal stability. Hydrogel is heated at a steady rate (1–10 °C/min) and its mass change is monitored. The water removal process in TGA begins at a temperature of 127 °C, or roughly 27 °C above the boiling point of water. The transition temperature is raised because bound water in polymer chains is present. High heat energy is required to remove interstitial and binding water that is connected inside the hydrogel network [41].

Another thermal analytical method, differential scanning calorimetry (DSC), can measure the thermal phase changes of water molecules, such as melting, crystallization, and glass transition (T_g) [42].

3. Application hydrogel

Hydrogels are a significant group of materials with amazing applications in engineering, biology, and pharmaceutical sciences. Due to their numerous uses in drug delivery, protein, peptide, pesticide, nutrient, hormone, agriculture, horticulture, biotechnology, cell construction, pharmaceutical, and biomedical applications, polyelectrolyte hydrogels are particularly advantageous because they either carry or develop charges on the chain. They also bind with opposite-charged species to form complexes.

Drug delivery systems that can provide controlled dosages for extended periods of time in the affected area have been actively developed worldwide in recent years. Three essential structural components—a area for drug storage, a controlled release rate, and a release drive—are necessary for a successful drug delivery system. These three characteristics are present in hydrogels. Hydrogels can also cover up the unpleasant smell and taste of medications. Therefore, hydrogels offer a great deal of promise for use in a variety of administration methods, including oral, nasal, buccal, rectal, vaginal, ocular, and injectable. The hydrogel can sustain the efficient and regulated release of an embedded medicine into body fluids when it is injected or transplanted into an organism [43]. A number of issues, such as poor solubility, poor dispersion, lack of homogeneity, poor dissolution, low bioavailability, and lack of in vivo stability, restrict

the therapeutic effects of many lipophilic medications. However, the aforementioned flaws can be somewhat corrected when these pharmaceuticals are uploaded to a hydrogel system, leading to solubilization, prolonged release or controlled release effects, and better stability and bioactivity. However, these characteristics are incompatible with effects of prolonged drug administration. In contrast, small molecule medicines that are highly soluble show additional benefits, such as enhanced absorption and high bioavailability. The modification of silicone elastomers with a poly(2-hydroxyethyl methacrylate) (PHEMA)-based hydrogel, which is characterized by a surface-connected hydrophilic carrier network inside the silicone, was done to create a novel interpenetrating polymer network in order to take advantage of these more desirable properties [44]. These structures were subsequently loaded with the antibiotic ciprofloxacin, and the resulting drug release prevented the growth of bacteria when placed on agar, indicating that these hydrogels may someday be used in medical devices that release drugs [44].

3.1. Hydrogel based anti-aging formulation

External variables including pollutants, chemicals, and ultraviolet (UV) radiation as well as internal factors like cellular metabolism, hormone changes, and genetic mutation all contribute to skin aging [45, 46]. Pro-inflammatory mediators generated by inflammatory cells have been shown to accelerate the activation of collagenases, which in turn causes collagen degradation [47, 48] and lowers the level of collagen and elastin in skin. Dermis and epidermis wrinkle and thicken due to a decrease in collagen and elastin levels. Numerous peptides and growth factors (VEGF, EGF, keratinocyte, etc.) promote collagen production and exhibit promise anti-aging properties.

Due to their large molecular size, which limits their capacity to permeate the tight stratum corneum [49] and the solitary action of collagen production, without an anti-inflammatory effect, topically administered growth factors and peptides have not been very beneficial as anti-aging agents. The material must be given to the deep layers of the skin for the best anti-aging effects. A substance's anti-aging properties should be enhanced by greater skin absorption, collagen formation, and anti-inflammatory effects.

Hydrogel of peptide-based Substance P (SP gel) was created by Da Jung Kim et al. in 2019 to improve the stability, keratinocyte, and fibroblast proliferation of Substance P [50]. Through the activation of collagen synthesis and an anti-inflammatory action, this SP-based hydrogel demonstrated strong wound healing characteristics [51, 52]. SP gel stimulated higher collagen formation than SP alone and improved skin absorption properties without producing skin

pigmentation. Even at high doses, SP gel is non-irritating and safe for extended usage. As a novel element in anti-aging cosmetics, SP gel has potential cosmetic benefits.

3.2. Hydrogel in cosmetics and skin diseases

In skin, oral, hair, and mucous membrane cosmetology care, hydrogel formulations made from natural, semi-synthetic, or synthetic polymeric materials are utilized (Figure 3).

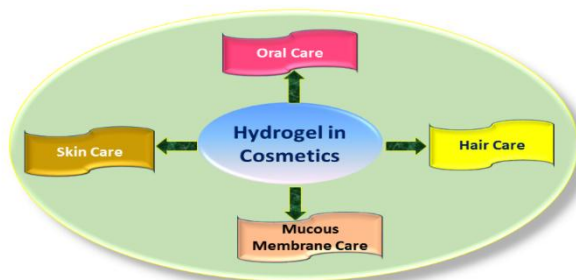


Figure 3: Hydrogel in Cosmetics

Hydrogels' ease of use and significantly reduced adverse effects are two of their key benefits when used topically to treat skin conditions.

In general, hydrogel formulations are used to treat psoriasis, mycosis, and acne vulgaris (Table 1). Due to their prolonged residence period at the application site and low frequency of application of a particular product to the skin surface, bioadhesive hydrogels play a significant role in dermatology and cosmetology. For the treatment of cellulite, Parenete et al., 2018 created a bioadhesive hydrogel containing caffeine by combining carbomer homopolymer type C with xanthan. Self-adhesive hydrogel patches with Triclosan were reported to comprise sodium polyacrylate and carboxymethyl cellulose by Lee T.W. et colleagues in 2003 [54]. Peel-off hydrogel masks with a cooling and calming effect that are suitable for sensitive skin are based on carboxymethyl cellulose [55]. By mixing silk sericin and carboxymethylcellulose, Aramwit, P. et al. (2014) created hydrogel-based masks [56]. To improve diclofenac sodium's permeability through the skin, Huang et al. 2019 created microcapsule-embedded hydrogel patches [57]. By crosslinking polysaccharide with polyethylene glycol diglycidyl ether, Monticelli, D. et al. 2019 created a hydrogel that is resistant to hyaluronidase and will be employed as a filler in cosmetic procedures [58].

Table 1: Hydrogel in Skin disease

Hydrogel	Skin Disorder	Remark	Ref.
Carbomer homopolymer type C or carbomer copolymer type B +	Treatment of cellulite	Bioadhesive hydrogel of Caffeine	53

xanthan gum or guar gum + Caffeine			
sodium polyacrylate + carboxymethyl cellulose + Triclosan	Acne therapy	Triclosan adhesive hydrogel patches	54
Carboxymethyl cellulose	For sensitive skin	Produced soothing and cooling effects	55
Carboxymethyl cellulose	For sensitive skin	silk sericin active substance	56
polysaccharide cross-linked by polyethylene glycol diglycidyl ether	Filler in aesthetic procedures	resistance to hyaluronidase present in the skin	58
Combination of clindamycin (1%) + tretinoin (0.025%)	Acne vulgaris	Greater reduction in the number of inflammatory and non-inflammatory lesions	59
Bifonazole	Mycosis	Sustained release	60
Amphotericin B+ Dextran	Mycosis	quick killing of fungi	61
Gemcitabine hydrochloride, methotrexate sodium salt, tacrolimus, betamethasone 17-valerate, triamcinolone acetonide	Psoriasis	supramolecular bis-imidazolium based amphiphile hydrogels	62
Methotrexate	Psoriasis	Carbomer hydrogel Bearing nanostructured lipid carriers	63

3.3. Wound Healing

In order to improve the wound healing process that occurs in the event of various skin disorders as well as during treatments given as part of therapy as limited adhesion, various hydrogel matrices are used. By establishing a hypoxic environment inside the wound, hydrogel preparation helps to maintain an acceptable wound moisture level, which promotes

cell proliferation and migration and lowers the risk of wound infection [64]. **Table 2** displays a hydrogel preparation for wound healing.

Table 2: Hydrogel in Wound healing

Type of hydrogel	Biological activity	Ref
poly(vinyl alcohol) (PVA)/ β -glucan (β -1,6-branched- β -1,3-glucan)	wound healing quickness, skin regrowth, and capillary vessel development	65
Dextran hydrogel	Dermal rejuvenation with entire skin appendages	66
Self-crosslink able dextran-isocyanatoethyl methacrylate-ethylamine hydrogel (DexIEME)	low pro-inflammatory response, dwindling of scar formation.	67
Injectable silk fibroin hydrogel	inclusive wound closure after 21 days	68

3.4. Applications in Contact Lenses

In addition to requiring particular preparation materials, hydrogel-based contact lenses also need to be cozy, have adequate oxygen permeability, and possibly even be able to help treat eye conditions [69]. The majority of soft contact lenses are made of silicone or poly(2-hydroxyethyl methacrylate) hydrogels that have been cross-linked with these substances [70]. These hydrogels' high water content, chemical and thermal stability, adjustable mechanical characteristics, and oxygen permeability are crucial for everyday wear safety [71].

3.5. Hydrogels in Tissue Engineering

The term "regenerative medicine" has also been used to describe tissue engineering. Hydrogels are a vast class of materials that can serve as tissue engineering scaffolds. Tissue engineering is the construction of a biocompatible and biodegradable cell scaffold [72]. The following characteristics of hydrogels make them a good contender for tissue engineering: (1) Hydrogels are flexible and soft, similar to soft tissues in vivo; (2) they can be injected into the body in a liquid state and quickly fill tissue defects by forming irregular nonflowing semisolids [73]; (3) their three-dimensional network structure resembles that of a natural extracellular matrix and will eventually encourage cell engraftment, adhesion, and growth by modifying the porosity and pore size and increasing the internal environment; (4) Up to 99% of hydrogels' composition is water, which is advantageous for the movement of biological metabolites, nutrients, and oxygen.

For the engineering of neural tissue, filamentous collagen materials are used, hydrogels of poly(lactic-co-glycolic acid) and polylactic acid scaffolds combined with osteoblasts for the engineering of bone tissue, and cellulose acetate scaffolds combined with chondrocytes for the engineering of cartilage [75]. For the transport of mesenchymal stem cells in vitro and in vivo, Vo et al. showed the osteogenic potential of injectable, dual thermally and chemically gelable composite hydrogels [76].

4. Conclusions

Due to their exceptional qualities, engineering flexibility, abundance in nature, and simplicity of manufacture, hydrogels are a specific type of polymer networks that are used in the medical industry. Nanocomposite hydrogels are cutting-edge biomaterials used in pharmacological and biological applications. In cell engineering and drug delivery systems, hydrogel scaffolds are also employed. The physical, chemical, electrical, and biological properties of nanocomposite hydrogel are superior to those of ordinary hydrogel. The interactions between the polymer chains and the nanoparticles are primarily improved in nanocomposite hydrogel.

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