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Hydrogel Based Nanocomposition System: Characterization and Application for Drug Delivery System

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Abstract
The targeted drug delivery is one of the key areas of research in the field of pharmaceutical science for delivery of drug molecules to specific organ and tissue. The main aim of targeted drug delivery system is to improve bioavailability of drug molecules to delivery site and minimized the toxicity and side effects of by controlling the release properties of drug. Hydrogel is widely used for controlled drug delivery, but traditional hydrogel has some drawback. In order to overcome the drawbacks of traditional hydrogels, hydrogels nanocomposition system (HYGs-NC) were developed. HYGs-NCis composed of different types of nanoparticles or nanostructures in the hydrogel network, due to their porous and hydrated molecular structurethey entrap large amount of therapeutic agent. The aim of HYGs-NC is to enhance the mechanical, electrical, and biological properties of hydrogel compared to traditional hydrogel. Nanocomposition hydrogel are used for wound dressings, biosensors, actuators, contact lenses, tissue replacement, and cancer drug delivery.In this chapter we discuss about the recent advancement in naocomposition hydrogel, different type of nanocomposit hydrogels, method of synthesis, characterization and their biological or pharmaceutical application as novel drug delivery system. Each type of nanocomposit hydrogels has specific properties to improve interaction between the hydrogel polymer and nanoparticles to enhance the desirable properties for targeted drug delivery applications.

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

1. Introduction

Currently drug delivery to particular or specific organs is one of the critical endeavors. For the development of newer drug-delivery approaches many scientific programs are involved with aimed to improve the therapeutic index and bioavailability [1]. Newer drug delivery approaches are planned to minimized the solubility issue, inhibit the photo degradation, pH changes, and improve control the release profile of drug molecules [2] to reduce toxicity and side effects [3]. These entire delivery devices should be biocompatible, versatility and biodegradable [4]. Nanomedicine showed different physicochemical properties because of their small size, surface structure, and high surface area. Therefore, nanoparticles conquer the limitations of conventional formulations and they facilitate the intracellular uptake to specific cellular targets. Nanomedicines have reported various biological applications: cancer treatment, protection of drug molecules, proteins, peptides, and DNA; analysis of environmental hazards; protein and gene delivery; self-regulated releasing devices; biorecognizable systems; and stimulus-controlled vectors [5]. Thus, nanotechnology has beenadopted in several fields such as drug/gene delivery, imaging, and diagnostics [6,7]. Nanomedicines are administered by oral, nasal, transdermal, parenteral, pulmonary, and ocular routes. This nano-metric delivers the drug molecules the site of action and produce potent biological activity. Nano-vectors are used to transport drug molecules that have poor solubility or a short half-life and toxic in nature.

Hydrogels are water-insoluble, three-dimensional networks of hydrophilic polymers that can swell in water and hold large amounts of water (20- to 40-fold their dry weight). Hydrophilic nature of hydrogel is due to presence of $-NH_2$, -COOH, -OH, $-CONH_2$, - CONH -, and $-SO_3H$ groups. Hydrogel are formed by cross-linking of polymer chains via physical interaction like covalent bonding, hydrogen bonding, and van der Waals interactions between these functional groups. Hydrogels are available in various sizes and shapes [8]. Hydrogel swelling process comprising of following steps:

1. Firstly polar hydrophilic groups of the hydrogel are hydrated with water, this bounded water is known as primary bounded water.
2. Water molecules are also interacts with the hydrophobic groups, which is known as secondary bound water.
3. Total bounded water is calculated by primary bound water and the secondary bound water.
4. This dilution is based on osmotic force, which is resist by the physical or chemical cross-linking.

   This absorbed water is called the bulk/free water, which fills all the pores of hydrogel. This absorbed water is very with the temperature and the specific interaction between the water molecules and the polymer chains [10].

Hydrogel approaches of drug delivery may be applied in hygienic products, agriculture, sealing, coal dewatering, artificial snow, food additives, pharmaceuticals, biomedical applications, tissue engineering and regenerative medicines, diagnostics, wound dressing, separation of biomolecules or cells and barrier materials to regulate biological adhesions, and Biosensor [11].

2. Hydrogel Classification

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

A. Physical properties: Amorphous, semi crystalline, 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.

“Homopolymer hydrogel,” is composed of one type of hydrophilic monomer; “copolymer hydrogel,” is composed of two types of monomers; and “multipolymer hydrogel”/ “interpenetrating polymer networks,” is made of three or more types of monomers. Anionic hydrogel has negative charge and it is thermos associative carboxymethyl pullulan. Cationic hydrogel have positive charge and it is new thermo sensitive hydrogel of N-isopropyl acrylamide (NIPAAm) and (3-acrylamidopropyl)trimethyl ammonium chloride. Neutral hydrogel has no charge and it is composed of miscible blends of water-insoluble polymers like poly (2,4,4-trimethylhexamethylene terephthalamide), while ampholytic hydrogel are based on acrylamide polymers [11].

Amorphous hydrogel is randomly arranged chains [5]. Semi crystalline hydrogel are rapidly change from solid state to liquid state [6]; and "hydrogen-bonded" structures, is a three-dimensional network linked by hydrogen bonds [13]. Smart hydrogel are the polymer network able to respond to external stimuli through abrupt changes in the physical nature of the network [14].

3. Hydrogel Characterization

Hydrogel properties are depended on the polymer chain dimension, strength, fibres orientation, composition, network mesh size distribution, level of bound and free water content, strength of chemical bonds, chains cross linking [15]. Evaluating the static and dynamic behavior of hydrogels at different pH, concentrations, temperatures, and ionic strength is also important. Functionality of hydrogel is depending on swelling, viscosity, elasticity, rigidness and mechanical strength properties of hydrogels.

Property of hydrogel and measured by various characterization methods such as rheology, scattering, composition identification, strength, and microscopy. However, all these methods have some limitations like sample preparation, resolution, and data statistic and data quality.

Mainly hydrogels are characterized by: Firstly measure the weight of hydrated hydrogel or freezed dried hydrogel, there is a difference between weight of hydrated and dried hydrogel. Because of these structures of hydrogels differ.

Mechanical Properties

Mechanical properties are depended on fiber material, composition, fiber arrangements, fiber cross linking, and water content [16]. Hydrogel mechanical strength and viscoelastic properties are measured by tissue engineering, drug deliveries, and super absorbents [17].

Viscoelastic of hydrogel are measured by rheology study [18]. In rheology, the gelation kinetics and gel stiffness are revealed by applying a shear and measuring the strain or vice- versa. Deformation is introduced as shear strain or stress on the hydrogels in a sinusoidal oscillation. The shear stress or strain is measured with respect to the sine wave phase shift due to applied angular frequency. Rheology is ideal to measure change in gel structures during phase transition from sol to gel (formation of assembly) and vice versa (breaking of assemblies) [19]. In rheology of hydrogels, the shear storage modulus (G'; energy stored in deformation), shear loss modulus (G"; energy release in deformation) and the loss factor (tan Δ = G"/G') are measured. These parameters describe the viscoelastic properties of hydrogels with respect to the measurement time, frequency and strain. G">G' (tan Δ >1) reveals a viscous – liquid driven hydrogel, while G" <G' (tan Δ<1) indicates hydrogel governed by its elastic solid behavior. Mechanical properties of hydrogels are also characterized by tensile testing and Atomic Force Microscope (AFM) based nano indentation [20].

3.1. Hydrogel Swelling and Cross-Linking Density

In hydrogel swelling ratio (SR) determines the amount of water present. Due to higher water content in hydrogel swelling property is an important parameter. Water diffusion and its subsequent swelling significantly change the hydrogels network structure and its mechanical strength [21]. The SR value of hydrogel is depending on structure of hydrogel and it is affected by pH, ionic strength and hydrophobic property [22]. SR value is determined by comparing the dry mass of hydrogel to the wet mass of hydrogel [23].

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

Where,
M_{wet}: The wet mass of hydrogel
M_{dry}: The dry mass of the hydrogel.
The hydrogel structure before absorption of water (non- swollen) and after water absorption (swollen) is shown in **Figure 1.**

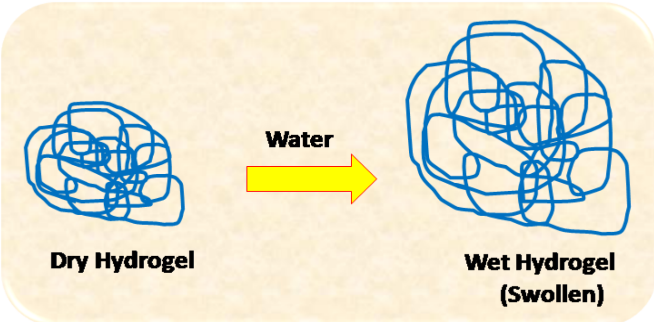

Figure 1: Schematic of hydrogel in dry state and swollen hydrogel after absorption of water

The polymer chains of hydrogel are cross linked to each other via physical or chemical bonds into a local 3-dimensional structure. The cross- linking density (CLD in mol/m^3) of polymer chains shown the number of polymer chains inter- connected with each other per unit volume to form the local hydrogel structure [24]. CLD affects many properties of hydrogels such as shear modulus, swelling ratio, and diffusion coefficient of entrapped molecules entities such as proteins, enzymes, drugs, nanoparticles [25].

3.2. Local Hydrogel Structure

Identification of structure and morphology of local hydrogel is one of the most vital parameters for hydrogel characterization. Many properties of hydrogel depend on the hydrogel structure formed by bonding, orientation of fibers, and pores between the fibers. Direct imaging and indirect scattering methods are used to reveal the hydrogel structure and morphology.
Optical, scanning electron microscopy (SEM) and transmission electron microscopy (TEM) are direct method which provides real space images of the hydrogel structure [26, 27].
Due to high water content in hydrogel, it is difficult to directly probe the original hydrogels [28]. High resolution microscopy (SEM/TEM) requires samples to be in a low - pressure chamber; this necessitates to dry the hydrogel either by cryo/freeze drying method or in air. Indirect X- ray or neutron scattering methods are much more powerful to study the local hydrogel structure over a larger volume of the original sample [29]. The scattering methods

can resolve the hydrogel structure in the length scale ranging from 1 nm - 1000 nm.

Optical microscopy allows imaging hydrogels [30]; however, there are limitations in the thickness the light can penetrate the gels, leading to restricted resolution and the loss of information for thick samples.

Total internal reflection microscopy (TIRF) can be used to visualize the adhesion between the cell and the hydrogel interface [31]. TIRF provides a resolution of 100- 200 nm which is not sufficient to resolve the cell - hydrogel interface contact region with a critical scale of a few nanometers. Reflection interference contrast microscopy (RICM) [32] has emerged as an alternative method to overcome the capabilities of TIRF but has had challenges due to poor contrast of interferometric patterns at the hydrogel - liquid interface.

3.3. Mesh Size

The diffusion process of active entities, such as proteins, nanoparticles, or drugs, in the hydrogels depends on the pores formed due to cross linking of polymer chains. The pores between the hydrogel network are the linear distance between two neighboring entangled chains which is defined as the correlation length or the network mesh size ξ (**Figure 2**) [33]. The distribution of mesh size can range from a few nanometers to the microscale range.

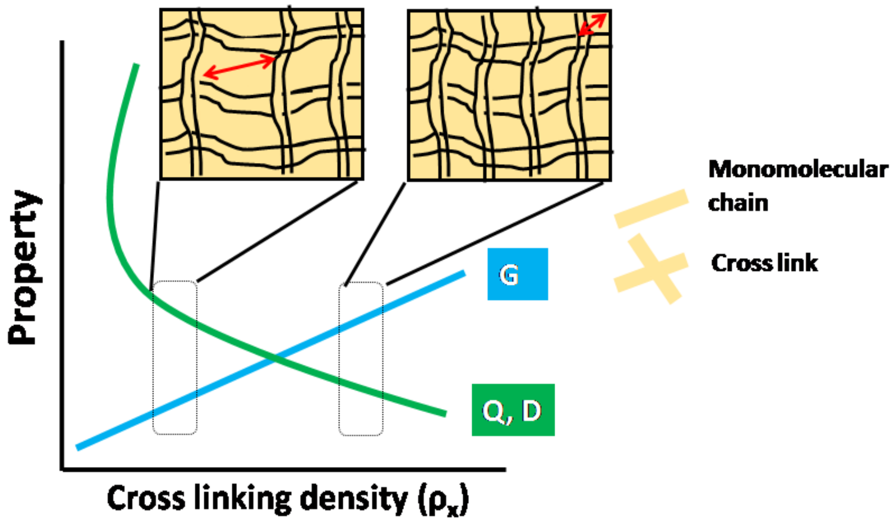

Figure 2: **Hydrogel properties relationship with the cross -linking density (CLD). Low and high cross -linking densities have different mesh size (ζ) which have relationship with the hydrogel properties of shear modulus (G), equilibrium swelling ratio (Q) and diffusivity (D) [34]**

Larger mesh size allows the rapid diffusion of entities in the hydrogel network while the smaller mesh size inhibits the diffusion process. pH and ionic strength strongly affect the hydrogel mesh size due to an increase in the protonation, the formation of hydrogen bonds and charge screening [35].

The mesh size for the highly swollen hydrogels is calculated by the following equation:

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

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

Due to high water content, it is difficult to measure the mesh size of swollen hydrogels by direct methods. However, the indirect scattering methods can be applied on prepared samples, which allow to evaluate the correlation length (mesh size) between the cross-linked fibres from analysis of scattering curves [36]. Small angle Scattering (SAS) with X-ray (SAXS) or neutrons (SANS) is a powerful and non-destructive contrast-based method to determine the hydrogel network nanoscale structures in the range from 1 nm -1000 nm [37].

3.4. Composition and Molecular Interactions

Hydrogels properties are associated to chemical composition, inter-fibers interactions and fibers interaction with surroundings [38]. Fourier Transform Infra-Red (FTIR) and Nuclear Magnetic Resonance (NMR) are effective techniques to quantify chemical composition and chemical structure [39]. FTIR was successfully used to determine the physical and chemical crosslinking of hydrogel network. In FTIR, solid sample can be measure in transmission mode. Attenuated transmission reflectance (ATR-FTIR) is used for liquid, powder and coated film samples, because they cannot be measured in transmission mode [40].

3.5. Thermal Stability

Thermal stability of hydrogel is measured by Thermal Gravimetric Analysis (TGA). Hydrogel are heated at constant temperature (1-10˚C/min) and observed the mass change of hydrogel. In TGA, the water removal starts at 127˚C temperature, about 27˚C above water boiling point. Due to presence of bounded water with polymer chains increase the transition temperature. To remove bounded and interstitial water linked within the hydrogel network need high thermal energy [41].

Differential Scanning Calorimetry (DSC) is another thermal analytical technique able to quantify the water molecules thermal phase transition such as melting, crystallization, and glass transition (Tg) [42].

4. Application hydrogel

Hydrogels are momentous collection of resources with incredible purposes in engineering, biology, and pharmaceutical sciences. Polyelectrolyte hydrogels are especially useful as they either carry or develop charges on the chain, and bind with opposite-charged species to form complexes, which highlight their numerous applications in drug delivery, protein, peptide, pesticides nutrient, hormone, agriculture, horticulture, biotechnology, cell construction, pharmaceutical and biomedical applications.

In recent years, drug delivery systems capable of controlled dosage delivery for extended periods in the affected area have been vigorously developed all over the world. An effective drug delivery system has three critical requirements of the structure: a region for drug storage, a controlled release rate, and a release drive. Hydrogels exhibit these three functions. Moreover, hydrogels can mask the bitter taste and odor of pharmaceuticals. Thus, hydrogels have a great potential for application via oral, nasal, buccal, rectal, vaginal, eye, injection, and other administration routes. When the hydrogel is injected or transplanted into an organism, it can maintain the effective and controlled release of an embedded drug into body fluids [43]. The therapeutic effects of many lipophilic drugs are limited due to a variety of problems including poor solubility, poor dispersion, lack of uniformity, poor dissolution, low bioavailability, and lack of in vivo stability. However, when these drugs are uploaded to a hydrogel system, the above defects can be improved to some extent, resulting in solubilization, sustained release or controlled release effects, and enhanced stability and bioactivity. Conversely, small molecule drugs that are highly soluble exhibit more advantages, including improved absorption and high bioavailability, but these properties are incompatible with sustained drug delivery effects. To exploit these more desirable properties, a novel interpenetrating polymer network was synthesized through the modification of silicone elastomers with a poly(2-hydroxyethyl methacrylate) (PHEMA)-based hydrogel characterized by a surface-connected hydrophilic carrier network inside the silicone [44]. These structures were then loaded with the antibiotic ciprofloxacin, and the resulting drug release inhibited bacterial growth when placed on agar, suggesting that these hydrogels have potential for future applications in drug-releasing medical devices [44].

4.1. Hydrogel based anti-aging formulation

Aging of skin occurs due to internal factor like cellular metabolism, hormonal changes, genetic mutation and external factors like toxins, chemicals, and ultraviolet (UV) radiation [45, 46). In aged skin Pro-inflammatory mediators released from inflammatory cells can enhance the activation of collagenases matrix metalloproteinases (MMPs), thus leading to collagen degradation [47, 48] and turn down the collagen and elastin level in skin. Decrease level of collagen and elastin causing wrinkling and thickening of dermis and epidermis. Many growth factors (VEGF, EGF, keratinocyte) and peptides enhance collagen synthesis and show promising anti-aging activity.

Topically applied growth factors and peptides have not been very helpful as anti-aging agents due to their large molecular size, which limits their ability to penetrate the tight stratum corneum [49] and the single effect of collagen synthesis, without anti-inflammatory effect. To get the better anti-aging effects, the substance needs to be delivered into the deep layers of the skin. To get better anti-aging effect, substance should have the dual function of collagen synthesis and anti-inflammatory effects, along with increased skin absorption.

Da Jung Kim *et al.,* 2019 was synthesized Hydrogel of peptide-based Substance P (SP gel) to enhance the stability, keratinocyte and fibroblast proliferation of Substance P [50]. This SP based hydrogel showed potent wound healing properties via induction of collagen synthesis and anti-inflammatory effect [51, 52]. SP gel increased the skin absorption properties without causing skin pigmentation and induced more collagen production then SP alone. SP gel to be safe for long-term use, without causing irritation, even at high concentrations. SP gel has potential cosmetic effects and applicability as a novel ingredient in anti-aging products.

4.2. Hydrogel in cosmetics and skin diseases

Hydrogel formulations from natural, semi synthetic or synthetic polymeric materials are used in skin, oral, hair and mucous membrane cosmetology care (**Figure 3**).

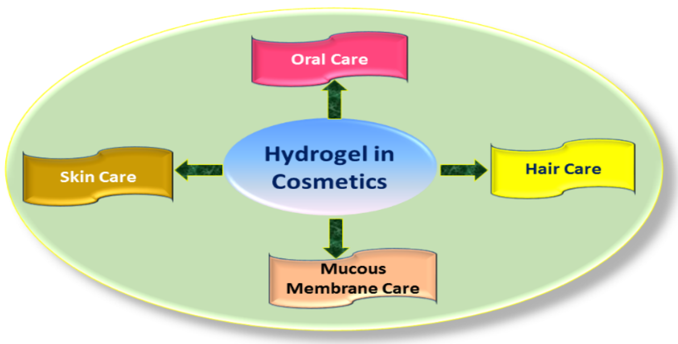

Figure 3: Hydrogel in Cosmetics

One of the main advantages of hydrogels used in the topical treatment of skin diseases is their ease of application and significant minimization of side effects.

Generally hydrogel formulations are used in Acne Vulgaris, Mycosis and Psoriasis treatment **(Table 1)**. Bioadhesive hydrogel have important role in dermatology and cosmetology due to their long residence time at the application site and less frequency of application of a given product to the skin surface. Parenete et al., 2018 was prepared caffeine based bioadhesive hydrogel by mixing carbomer homopolymer type C with xanthan for the treatment of cellulite, [53]. Lee T.W. et al 2003, reported sodium polyacrylate and carboxymethyl cellulose based Triclosan containing self-adhesive hydrogel patches for acne therapy [54]. Peel-off hydrogel masks based on carboxymethyl cellulose showed cooling and soothing effect which are used for sensitive skin [55]. Aramwit, P et al 2014 prepared hydrogel-based masks by combining silk sericin with carboxy methylcellulose [56]. Huang et al. 2019 designed Microcapsule-embedded hydrogel patches of diclofenac sodium to increases its permeability through the skin [57]. Monticelli, D et al 2019 developed hyaluronidase resistance hydrogel by crosslinking of polysaccharide with polyethylene glycol diglycidyl ether, which will be used as a filler in aesthetic procedure [58].

Table 1: Hydrogel in Skin disease

Hydrogel	**Skin Disorder**	**Remark**	**Ref.**
Carbomer homopolymer type C or carbomer copolymer type B + xanthan gum or guar gum + Caffeine	Treatment of cellulite	Bioadhesive hydrogel of Caffeine	53
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,	Psoriasis	supramolecular	62

methotrexate sodium salt, tacrolimus, betamethasone 17-valerate, triamcinolone acetonide		bis-imidazolium based amphiphile hydrogels	
Methotrexate	Psoriasis	Carbomer hydrogel Bearing nanostructured lipid carriers	63

4.3. Wound Healing

Various hydrogel matrices are used to improve the wound healing process occurring both in the case of various skin diseases and during treatments performed as part of therapy as limited adhesion. Hydrogel preparation helps to maintain an adequate wound moisture, which allows cell growth and migration and reduces the risk of wound infection by creating a hypoxic environment within the wound [64]. Hydrogel preparation for wound healing is shown in **Table 2.**

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 acceleration, skin regeneration and formation of capillary vessel	65
Dextran hydrogel	Dermal regeneration with complete skin appendages	66
Self-crosslink able dextran-isocyanatoethyl methacrylate-ethylamine hydrogel (DexIEME	low pro-inflammatory response, attenuation of scar formation.	67
Injectable silk fibroin hydrogel	Complete wound closure after 21 days	68

4.4. Applications in Contact Lenses

Hydrogel based contact lenses need special material for preparation and they must be comfortable, have good oxygen permeability, and potentially have the capacity to assist in the treatment of eye diseases [69]. Mostly soft contact lenses are composed of poly(2-hydroxyethyl methacrylate) hydrogels cross-linked with ethylene glycol dimethacrylate or silicone [70]. These types of hydrogels have high water content, thermal and chemical stability, tunable mechanical properties, and oxygen permeability, which are very important for safe daily, wear [71].

4.5. Hydrogels in Tissue Engineering

Tissue engineering has also been defined as "regenerative medicine." Tissue engineering is the preparation of a biocompatible and biodegradable cell scaffold, and hydrogels represent a large class of materials that can function as tissue engineering scaffolds [72]. Hydrogels have been following properties that make it suitable candidate for tissue engineering: (1) Hydrogels are soft and flexible, similar to soft tissues *in vivo*; (2) In the liquid state hydrogel can be implanted

in the body by injection, where they can quickly fill tissue defects by forming irregular nonflowing semisolids [73]; (3) The three-dimensional network structure of a hydrogel is similar to a natural extracellular matrix, which will eventually promote cell engraftment, adhesion, and growth by adjusting the porosity and pore size and increasing the internal surface area [74]; (4) Hydrogels contains up to 99% of water, which is beneficial for the transportation of oxygen, nutrients, and cellular metabolites.
In bone tissue engineering Hydrogel of poly(lactic-co-glycolic acid) scaffolds and polylactic acid scaffolds combined with osteoblasts in bone tissue engineering and filamentous collagen materials in neural tissue engineering, and cellulose acetate scaffolds combined with chondrocytes in cartilage tissue engineering [75]. Vo et al. reported the osteogenic potential of injectable, dual thermally and chemically gelable composite hydrogels for mesenchymal stem cell delivery *in vitro* and *in vivo* [76].

5. Conclusions
Hydrogels are special class of polymer networks that are used in medical field due to their excellent properties, engineering flexibility, natural abundance, and ease of manufacturing. Nanocomposite hydrogels are advanced biomaterials that are used for biomedical and pharmaceutical applications. Hydrogel scaffolds are also used in cell engineering and drug-delivery systems. Nanocomposite Hydrogel have superior physical, chemical, electrical, and biological properties as compared to conventional hydrogel. Nanocomposite Hydrogel is mainly enhanced the interactions between the polymer chains and the nanoparticles.

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