Supramolecular Hydrogel : A Review

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ABSTRACT

One of the most promising soft material platforms for contemporary biomedical applications is the formation of supramolecular hydrogels, which are kept together by non-covalent interactions like electrostatics, hydrogen bonds, and hydrophobic forces. They respond well to environmental signals and physiological cues due to their inherent reversibility and dynamism, and they can efficiently dissipate mechanical energy. The permanent cross-linking of covalent hydrogels makes it difficult to achieve these crucial characteristics, which are well suited for cell culture, tissue engineering, on-demand controlled release of therapeutics, tissue adhesion, molecular sensing, and artificial gel replacements in organs (such as vitreous humour and synovial fluids). As a result, supramolecular hydrogels have recently experienced rapid growth for biomedical applications, increasing in popularity. Through the varied uses and innovative developments over the past five years discussed.

Key words: ***Supramolecule ,Hydrogel,Tissue adhesion ,peptide ,synovial***

INTRODUCTION

With physical properties resembling soft biological tissues, hydrogels are cross-linked 3D hydrophilic polymer networks that can contain a lot of water through surface tension or capillary action, making them crucial for several applications in both academic and industrial domains. 1-9 Based on the types of forces that induce crosslinking ,hydrogels can be categorised into two main groups.: synthetic hydrogels and supramolecular hydrogels. In general, non-reversible covalent connections that produce permanent chemical crosslinks between the polymer chains are used to construct synthetic hydrogels.[1] Since Wichterle and Lim published the first example of synthetic hydrogels in 196010, there has been a lot of interest in these materials because of their hydrophilic engineering, When the cross-linked network is destroyed, these hydrogels cannot repair themselves. they are frequently brittle, and occasionally opaque, which severely restricts their use in a variety of biological applications. For instance, it could take a while for drugs to take effect while offering little benefit. Additionally, the cross-linking process can attach medications to the hydrogel or otherwise jeopardise their integrity, and the hydrogel itself might acquire a murky makeup and stop degrading. It is therefore highly desirable to develop a better delivery formulation that permits gelation and drug loading to occur simultaneously in aqueous medium without covalent cross-linking.[1-3]

A novel family of noncovalently crosslinked polymer materials known as supramolecular hydrogels fully combines the benefits of synthetic hydrogels with those of supramolecular polymers . Supramolecular cross-linking brought on by a number of non-covalent interactions, such as hydrogen bonds, metal-ligand coordination, host-guest recognition, and electrostatic interaction, results in the creation of 3D cross-linked networks.[1] These interactions have a big Contrarily, Due to the inherent processability of the supramolecular cross-linking units, these noncovalent hydrogels exhibit reversible gel-sol transition behaviour in response to a number of bio-related stimuli, including pH, redox agents, enzymes, and bioactive compounds. As a result, they can be used as intelligent carriers for delivering a variety of therapeutic agents, such as drugs or gene therapies. In recent years, there has been a documented increase in the quantity of articles on supramolecular hydrogels. . In light of recent advancements in this emerging field ,It is vitally necessary to conduct a thorough analysis of the synthesis, characteristics, and bioapplications of supramolecular hydrogels. diminish structural flexibility and alter performance at the macro level.[5]

In this paper, we evaluated the most recent advances in supramolecular hydrogel design and production as well as their therapeutic delivery, tissue engineering, and bioimaging applications in the diagnosis and treatment of diseases. . Based on our evaluation of recent noteworthy achievements in this field, we forecast that the significance and bright future of supramolecular hydrogels as biomaterial scaffolds for clinical diagnostics and therapy will be thoroughly established.[6]

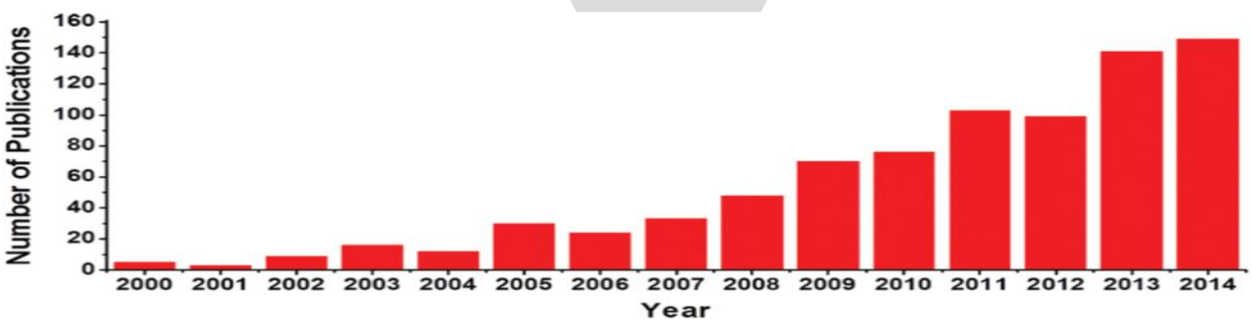

FIG: Histogram of "SUPRAMOLECULAR HYDROGELS" publications by years in the web of sciences[1]

supramolecular hydrogels for stem cell delivery :

An optimal hydrogel for tissue engineering should encourage cell delivery to target cells and encourage infiltration and encapsulation of cells. Additionally, it need to repeatedly, swiftly, and autonomously self-heal in place under physiological circumstances. But the higher compatibility with cells is the basis of the aforementioned features. New discoveries in supramolecular hydrogels are reported in this article that are used in three-dimensional stem cell culture but not in cartilage tissue engineering, in accordance with their supramolecular interactions this paragraph.[7-8]

Hydrophobic Interactions:

Hydrophobicity gives non-polar aqueous solutions remarkable properties and is crucial for a number of chemical and biophysical processesinvolving protein folding and the formation of micelles and membranes by amphiphilic compounds (Whitesides and Grzybowski, 2002).Non-covalent interactions known as hydrophobic interactions are distinct in that they don't involve intermolecular attraction directly. They are motivated by water molecules' propensity to maintain their H-bond network around non-polar solutes [8-9].Amphiphilic molecules can behave incomplicatedlycolloidally in aqueous solution as a result of the subsequent chemical rearrangements. A polymer-based hydrogel with hydrophobic interactions is produced by including a hydrophobic sequence at the conclusion or inside the hydrophilic polymer chain. The concentration of the polymer affects the transient networks produced by the interchain interactions.[9]

Peptide Amphiphiles:

Peptide is a fantastic option for a supramolecular hydrogel building component due to its inherent biocompatibility.Peptide amphiphiles (PA), which are created by covalently bonding one or more peptides to a cleverly created hydrophobic synthetic polymer, are commonly employed in the manufacture of self-assembled, bioactive supramolecular hydrogels .[10] In 3D cell culture applications, PA hydrogels have drawn a lot of research attention because of their biodegradable and non-toxic properties described a dynamic system created by peptide amphiphiles' conformational alteration of elastin-like proteins (ELP). This technique created a sturdy membrane with highly spatiotemporal controlled creation of tubular structures ,self-healing, sealing, and adjustable assembly and disassembly abilities to surfaces.It was successful to develop mouse adipose primary stem cells (mADSC) for 21 days using the ELP/PA tube material.[10]
The cells developed in numerous layers and shown strong adherence and diffusivity on the test tube's exterior during the cultivation procedure. Additionally, they constantly had strong metabolic activity,they had the same level of vitality as cells plated on tissue culture plastic. In order to research the use of amyloid-based hydrogels as scaffolds for stem cell development in neuronal cell lines, developed a series of peptides based on the Ab42 high aggregation tendency C-terminus of the Alzheimer's disease. These Fmoc-protected peptides generated thermally reversible, non-toxic, thixotropic hydrogels by self-assembling into b-sheet-rich nanofibrils.[11]

Amphiphilic Block Copolymers:

When a single linear molecule has two or A type of copolymer that can be manufactured to specifications and has a specific chemical more unique structural segments, that is one approach to recognise it. In a solution, the amphiphilic block copolymers self-assemble to form micelles, vesicles, or fibres, among other supramolecularorganised aggregates. When the amphiphilic block copolymer is dissolved in water, it spontaneously forms a polymer micelle with a lipophilic core and a hydrophilic shell claim that an amphiphilic branching PEG-PPS block copolymer-based degradable self-assembled hydrogel has been created.Human induced pluripotent stem neural progenitor cells (iPS-NPC) were successfully delivered and promoted using PEG-PPS hydrogels as an injectable biomaterial. Additionally, PEG-PPS permits angiogenesis while also specifically inhibiting astrocyte invasion. Numerous applications for tissue engineering regeneration can also employ this hydrogel technology.By including the essential signals, such as proteins, growth factors, and RNA, additional 1 potential abilities can be attained.[12]

Host–Guest Interactions:

Specific non-covalent interactions known as host-guest interactions have been extensively used in the creation of supramolecular hydrogels.These interactions depend on the careful complexation of macrocyclic hosts like cucurbiturils (CB), cyclodextrin (CD), crown ethers, and calix[n]arenes with smaller guest molecules. Beyond the basic concept of a hole-fitting, the solvent, different binding sites, or secondary interactions may have an impact on the host selectivity for the visitor[13].By copolymerizing readymade host-guest inclusion complexation with co-monomers or mixing polymers with the host and guest, self-healing supramolecular hydrogels can be generated from inclusion complexation . Although all macrocycles have the potential to produce self-healing hydrogels, CB and CD have mostly been used to produce supramolecular hydrogels for cell transportation. This study examines CB and CD as a result.[14]

Cyclodextrin (CD):

A type of cyclic oligosaccharides known as cyclodextrin is composed of glucopyranose subunits connected by an a- (1,4). A-CD, b-CD, and g-CD,the subunits are composed of six, seven, and eight glucose molecules, respectively. CD acts as a host molecule by

forming an inclusion complex with a specific guest through its hydrophobic cavity . In a recent study, developed a thermosensitivepoly(organophosphazene) including b-CD (b-CD PPZ, host) and adamantane elongated with Arg-Gly-Asp (Ad-RGD, guest). The guest molecules AD and RGD were attached to biocompatible PEG in order to avoid steric hindrance between MSCs and the b-CD PPZ.Based on the application of Ad-RGD controlled concentration in vitro and in vivo, regulated MSCs behaviour were induced. As the concentration of Ad-RGD in the b-CD PPZ hydrogel rose, the survival rate of MSCs and the expression of osteogenic factors also rose. Contrarily, lowering the Ad- RGD caused the MSCs' viability and adipogenic potential to decline. This demonstrated that the survival and development of MSCs may be controlled by altering guest molecules in a host-guest interaction system using a 3D hydrogel that is thermosensitive .Injectable 3D hydrogels composed of b-CD PPZ and two guest molecules were reported to work similarly (Ad-TGF and Ad-HAV). (Figure 1). They retained their gelling qualities at body temperature. By using stoichiometrically exact regulation of Ad-peptides based on host-guest interaction, the injection of MSCs included in this finely tailored hydrogel induced multiple chondrogenic differentiation phases 3 weeks after the injection.By simply altering the adamantane-bearing peptide and its stoichiometry, the changeable and injectable 3D hydrogel can be used as a platform technology for on-demand stem cell niche.[15]

Cucurbiturils (CB):

The CD cavity size and the CB cavity size are identical. However, unlike CD, it has two identical cavity openings with carbonyl borders. In order to generate binary 1:1 or ternary 1:1:1 host-guest complexes, cucurbiturils, macrocyclic compounds made up of glycoluril units (CB[n], n = 5-8, 10; n = 14 the most abundant), can join with numerous guest molecules.The cavity of CB can comfortably accommodate two guests .But chemical functionalization of CB is tough, and the manageable complexity leads to a number of multi-arm functionalized CB mixtures. Because of the aforementioned complicated properties, the appropriately functionalizing CB has multiple biological applications functions.The cytotoxicity of several CBs on HaCaT keratinocytes and erythrocytes was recently studied . Incubation with CB at a low dose (3.75 mg/ml) led to apoptosis, but CB and CB were noncytotoxic at high concentrations (30 mg/mL). None of the CBs under examination caused erythrocytes to hemolyze.These results suggest that CB is a promising host complex choice for cell delivery applications. also exploited the selectivity and powerful host-guest interactions between CB and polyamines to produce a supramolecular HA hydrogel with regulated crosslink density and excellent physical properties.[16]
They employed hyaluronic acids that could withstand the body for more than 11 days, such as those that were conjugated to cucurbit uril and diaminohexane . By changing the guest molecules. This supramolecular HA hydrogel, which is biocompatible, has controllable physical and chemical characteristics. Furthermore, mice may endure hydrogel-encased engineered mesenchymal stem cells (eMSCs) for longer than 60 days.The findings above show that supramolecular HA hydrogel has a lot of potential for application as a 3D synthetic ECM in cartilage engineering and cell transport.[17]

Hydrogen Bonding :

Another way to develop a self-healing reversible network is to incorporate complementary hydrogen bond donor and acceptor motifs into dynamic supramolecular polymer building blocks. Since hydrogen bonding naturally aids in the nucleobase pairing and protein synthesis processes for DNA and RNA, it is acknowledged as a crucial self-assembly mechanism.The strength of a single hydrogen bond is lower than that of several other non-covalent and covalent bonds. However, the degree of connection within supramolecular structures is greatly increased and the bonding strength is increased by multivalent bonds. Additionally, through a process known as synergy .The creation of some hard covalent polymers, like silk, depends on hydrogen bonds .[18]

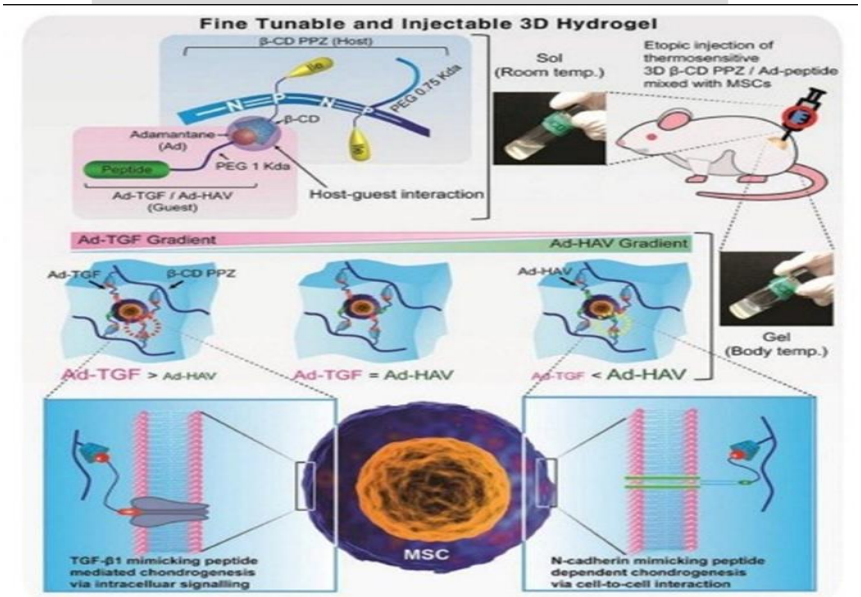

FIGURE 1 Schematic of 3D b-cyclodextrinpoly(organophosphazene), adamantane-TGF, and HAV (AdTGF and Ad-HAV)-encapsulated mesenchymal stem cells (MSCs). A 3D thermosensitive hydrogel was created by combining the aforementioned chemicals and cells. It was feasible to change the liquid into a gel condition at body temperature after its injection. By adjusting the stoichiometric ratio of the various chemicals, the fate of the MSCs can be managed. Adapted from Hong et al. with their permission (2019).

Properties and functions :

The ability to retain water, load drugs, be biodegradable and biocompatible, be biostable, and have mechanical properties are just a few of the fundamental physicochemical traits that supramolecular hydrogels share with covalent polymeric hydrogels. Additionally, they display the natural stimuli responsiveness and processability of noncovalent cross-linking, a range of functional components can be easily added to supramolecular hydrogels to produce desired activities including optoelectronic and bioactive properties. The intrinsic molecular structures of foreign materials are mostly responsible for these abilities.

Biodegradability, biocompatibility and biostability :

The body gradually accumulates elements from the environment that are not biodegradable or metabolizable, which is exceedingly detrimental to one's life or even their health. Consequently, biocompatibility and biodegradability play a major role in the adoption of new physiologically friendly biomaterials Because the hydrogel networks contain noncovalent cross-links , In vitro and in vivo, supramolecular hydrogels exhibit stronger biodegradability and biocompatibility than covalent hydrogels. This is because they can spontaneously degrade or be metabolised the human body's varied physiological environment . The programmable breakdown properties of hydrogels may make them useful injectable biomaterials for controlling medication release as well as cellular function as a regenerative cell matrix. Currently supramolecular hydrogels that are biocompatible and biodegradable can be made either by means of self-assembly, naturally occurring amphiphiles that contain biomolecules or through the aqueous multivalent cross-linking of synthetic polymers with both host and guest functionalities. Therefore, a key criterion for supramolecular hydrogels, Biostability is used in the detection and treatment of human malignancies. Supramolecular hydrogels' biostability was enhanced by Xu et al. developed a bioconjugate-based hydrogelators represent a new class.,comprising nucleobases and short peptides that might build supramolecular hydrogels in water by self-assembling in response to an enzymatic or pH trigger. The resulting hydrogels showed strong opposition to the potent protease proteases K, and as a result, they have promise as a novel biomaterial for applications needing long-term biostability. At physiological pH, the DOPA-Fe3+ complexation was also found to produce strong but reversible crosslinking, giving the resultant hydrogels resistance to oxidative breakdown.

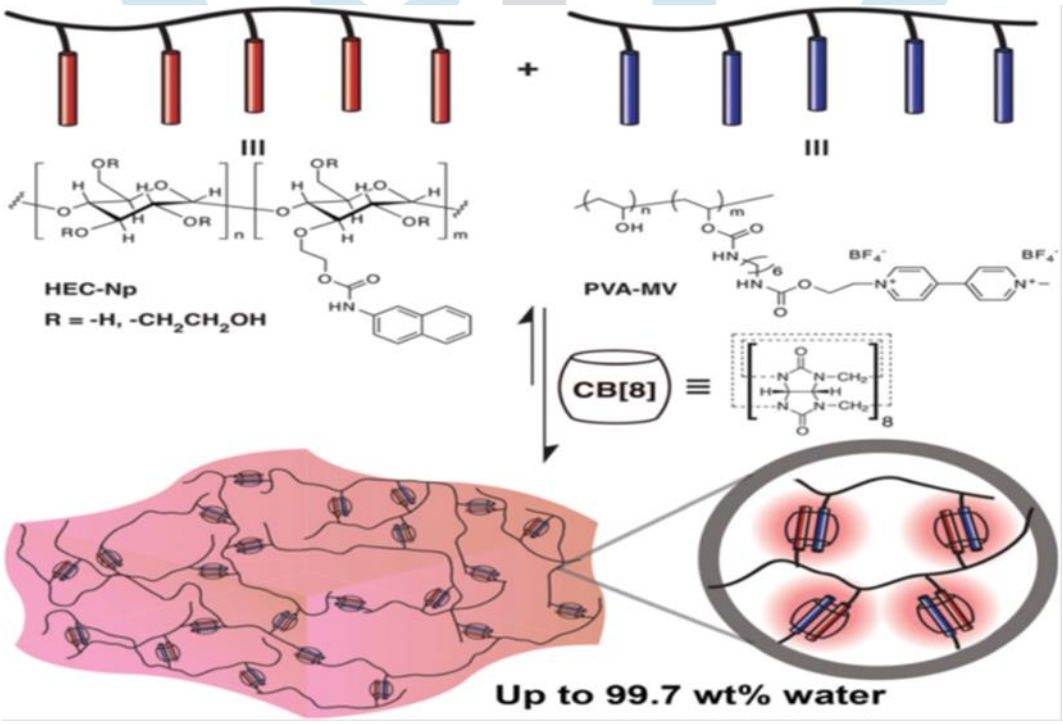

Fig , . A water-soluble naphthyl-functionalized cellulose (HEC-Np) and methyl viologen-functionalized poly-(vinyl alcohol) (PVA-MV) solution was mixed with CB to produce a supramolecular polymeric hydrogel. With permission, taken from ref. 57. American Chemical Society 2012 Copyright[1]

Biomedical applications :

Supramolecular hydrogels are excellent biomaterials for use in a range of biomedical fields because, as was already mentioned, they not only have distinct physical and biological characteristics, as well as special abilities to swell reversibly and transition in reaction to a variety of environmental stressors, from gel to sol. This section primarily focuses on the application of supramolecular hydrogels in disease diagnosis and treatment, including bioimaging, biodetection, drug administration, protein transport, tissue engineering, and gene transfection.

Bioimaging :

attempts to use sophisticated probes to visualise specific molecular pathways in vivo, especially those that are significant in disease processes. The applications for cancer detection and therapy are expanded since it is also simpler to include complex biological events into the method of rapid imaging at the molecular level. To date, the clinical diagnosis of cancer has made extensive use of a variety of bioimaging techniques, including Radiolabeled probes for nuclear imaging, fluorescent probes for optical imaging, paramagnetic agents for MRI, and acoustically active nanostructures for ultrasound imaging Based on their chemical composition, bioimaging tools can be divided into three types of polymers: ordinary polymers, supramolecular polymers, and small-molecule compounds.. Because of their superior biodegradability and biocompatibility, 3D cross-linked structure, and deft physiological responsiveness bioimaging probes based on supramolecular polymers, particularly those relying on supramolecular hydrogels stand out among them. There is a lot of promise for these probes to be used in the detection of cancer.

Biodetection:

The significance of the biological agent problem cannot be overstated .Numerous biodetection applications have benefited from the development of biosensors using signalling and physiologically based recognition components, demonstrating the benefits of increased speed and simplicity compared to traditional detection methods. Biodetection methods have been developed for illness diagnosis and environmental investigation of conversion elements into a biodetection system. Everyone is aware of the crucial roles that various bioactive chemicals play in a number of biological processes linked to disease. In order to improve basic research and develop diagnostic applications, it is very desirable to develop rapid, useful, and high-throughput sensing techniques for locating these disease-related biomarkers. Supramolecular hydrogels with the thoughtful design of nanostructures offer a great deal of potential for biodetection applications due to their exceptional biocompatibility and quick gel-to-sol transition in response to a variety of bio-related stimuli (e.g., enzymatic processes and biological molecules)

Therapeutic delivery:

Therapeutic agents, such as chemotherapeutic drugs, genes, and proteins, into problematic tissues must be supplied via flexible carriers in order to safely achieve their desired therapeutic effects. Therapeutic delivery is the term used for this. Numerous varieties of supramolecular polymeric systems are used in drug delivery applications. Supramolecular hydrogels are a specific kind of 3D cross-linked supramolecular substance that has a number of advantages, including the simplicity with which functional components can be incorporated for the diffusion of trapped molecules, the high water content the unique mechanical property that is similar to that of human tissues, the simplicity with which a hydrogel can be formed in situ in contact with tissues, and the ease with which a hydrogel can be broken down in vivo. oxidising or reducing substances, enzymes, pH, and other bio-related stimuli, in particular, supramolecular hydrogels can experience reversible swelling and gel-sol transition, allowing for programmable and controlled delivery of loaded therapeutic medicines into tumour locations.
There have been many supramolecular hydrogel-based drug carriers created so far for clinical cancer therapy. Self-assembling peptide hydrogels are especially sensitive to variations in the pH of the environment they have shown promise as pH-controlled drug delivery methods in tumour tissues that are acidic. The aqueous self-assembly of amphiphilic peptide derivatives has generated a variety of supramolecular hydrogels for peptide-based medication delivery. These hydrogels undergo a gel-to-sol phase change when exposed to lower pH levels and enable the regulated release of kanamycin, taxol, anti-inflammatory medicines (such as naproxen, 5-aminosalicylic acid, and anti-HIV medicines). These research demonstrate a novel technique for fabricating useful supramolecular biomaterials for targeted drug delivery.
Particularly Supramolecular hydrogels based on drugs have been touted as novel self-delivery scaffolds for successfully inhibiting tumour growth. A variety of injectable and biodegradable host-guest hydrogels suited for cancer therapy have been made using CDs and their derivatives due to their good biocompatibility, minimal immunogenicity, and capacity for selective inclusion . These supramolecular hydrogels could therefore be employed as an injectable formulation for relatively long-term, sustained, and controlled drug administration. They frequently exhibited a thermo-reversible or thixotropic nature. These supramolecular hydrogels demonstrated a significantly faster release rate while reaching the diseased areas in contrast to traditional polymeric carriers, increasing therapeutic efficacy and reducing drug resistance.

Tissue engineering:

Through tissue engineering, damaged or defective tissues and organs can be locally repaired using the patient's own cells grown on a polymer matrix. How efficiently they function depends on the biological environment and the interactions between implanted biomaterials and cells. Supramolecular hydrogels can efficiently combine tunable mechanical characteristics with management of degradability to offer ideal biological conditions for encapsulating bioactive moieties like growth agents and cells. In tissue

engineering, they also show significant promise as biocompatible scaffolds for guiding, promoting, and supporting tissues' long-term growth. Over the past ten years, numerous supramolecular hydrogel-based biomaterials for tissue engineering have been developed using highly controlled, reversible, non-covalent interactions such hydrogen bonding and host-guest interactions. As dynamic biomaterials for tissue-engineering applications, bioactive peptide-based supramolecular hydrogels are particularly alluring.

Stupp and Zhang made the initial designs and developments of peptide hydrogel-based tissue engineering scaffolds. Stupp developed a variant of the neurite-promoting laminin amphiphilic pentapeptide epitope (IKVAV) that may be used to make supramolecular hydrogels in water. The supramolecular hydrogels that were produced were able to surround neural progenitor cells and promote the cells' selective differentiation into neurons because of the high epitope density in the hydrogels.

Parallel to this, Zhang used -sheet-forming peptides to construct supramolecular hydrogel scaffolds for neural cell entrapment and differentiation. Naphthalene-containing hydrogelators are a novel class that was just developed by Xu132. These hydrogelators swiftly produced a kinase/phosphatase switch to produce supramolecular hydrogels in living organisms.

CONCLUSION

This paper has given an overview of the wide range of biomaterial applications for supramolecular hydrogels, which are preferred to covalently cross-linked gels due to their reversibility.environmental responsiveness, a dynamic environment that allows for stress reduction,and the mechanical properties' flexibility for customizable applications in biomedicine.Within the last five years, significant progress has been made as a result of this special property in well-known and well-liked fields like drug release, cell and tissue encapsulation, tissue adhesives, and cell cultures. The repertoire now includes additional "strange" interactions in the form of aurophilic-cross-linked hydrogels in addition to the standard supramolecular interactions of hydrogen bonding, hydrophobic association, ionic interactions, and host-guest inclusion complexes. It must be kept in mind and stressed that many examples (such as peptide gels) herein do not rely on a single interaction for gelation, but rather frequently multiple interactions working in synergy. This is true even though we have divided the hydrogels into separate non-covalent interactions for ease of discussion.

We anticipate increased focus and advancement in the upcoming years in the following sectors, utilizing the special qualities of supramolecularhydrogels.Improved regulated release of medicines and proteins from hydrogels is desperately needed for therapeutic delivery. Greater therapeutic load optimization is possible by modulating drug release at a pace that directly correlates to illness severity while reducing unneeded waste or overdose concerns. Additionally, hydrogels can be loaded with various medications and their delivery rates can be synchronized such that synergistic therapeutic effects can be achieved as opposed to only delivering one drug at a time.Although some progress has been made in the cited references toward achieving these goals, there is still much room for improvement and novel designs. These will also benefit from a deeper comprehension of the factors influencing release kinetics and supramolecular hydrogel erosion, particularly in vivo.The existing supramolecular hydrogel technology for numerous biomedical applications should be more fully translated into real-world clinical settings. In this regard, the ability to maintain batch-to-batch consistency and quality and the scalability of hydrogel synthesis procedures become crucial for establishing current good manufacturing practice (cGMPs) processes.More methods to make mechanically strong gels may be expected to increase the practical utility of supramolecular hydrogels, whose strength regime now falls below that of covalently crosslinked hydrogels in the great majority of cases.

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