

## Stimuli-responsive supramolecules for bone tissue engineering

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## ABSTRACT

In the recent scenario Stimuli responsive supramolecules are used for bone tissue engineering. Stimuli responsive Supramolecules are responding towards the desired stimuli. This has a property to change their dynamics and undergo impulsive and continual assembly or disassembly processes under specific conditions. These supramolecules respond towards chemical and physical stimuli which include: pH, temperature, light, ionic strength, magnetic and electric field sensitive. Stimuli responsive supramolecules are used to various preparations such as hydrogels, scaffolds, hydrogel scaffolds, 3D bioprinting, 4D bioprinting, nanogels and microgels used for the bone tissue repair and regenerative medicine. Manuscript deals with various approaches used to prepare stimuli responsive supramolecules for bone engineering applications.

**Keywords:** Stimuli; engineering; supramolecules; hydrogels; scaffolds; hydrogel scaffolds; bone tissue engineering.

## 1. INTRODUCTION

Recently the stimuli-responsive supramolecular assemblies received attention because their structures can be modified by applying a stimulus. They can be reverting back towards their original structures by applying another stimulus. The assemblies of supramolecular are prepared by at least two molecules through various noncovalent bonding modes like cationic-anionic electrostatic interactions, hydrogen bonding, aromatic interactions, hydrophobic-hydrophilic interactions, metal-ligand bonding and charge transfer interactions [1,2]. In biomolecules, the stimuli responsive features are used for function control in response to desired stimuli [3]. Supramolecular materials are dynamic in nature and defined as the materials those components are bridged with reversible connections and undergo continuous and spontaneous assembly or disassembly processes under specific conditions. Supramolecular polymers are reversible and dynamic in nature due to noncovalent interactions. They can have the potential to adapt their environment which possesses a wide range of engrossing properties includes shape memory, degradability and self-healing [4]. Many stimuli-responsive systems have been developed dealing with polymeric gels, solutions, interfaces, surfaces and polymeric solids. These states of matter impose a different degree of restrictions on the mobility of polymer chains or segments, making dimensional responsiveness easy to achieve for systems with higher solvent content and low energy inputs. The responses are classified into chemical and physical categories where multiple responses result in one or more responses or one stimulus results in more than one response. The modified polymer has been used in the application of bone tissue engineering [5].

Stimuli responsive polymers are those polymers that responses with property changes to small changes in their environment. These can be classified according to stimuli they respond to as: pH, temperature, light, ionic strength, magnetic and electric field sensitive. Few polymers response to a combination of two or more stimuli. These polymers classify according to their physical forms deals with the chains grafted on a surface, free chains in solutions,

physical or reversible gel and covalently cross-linked gels [6]. Tissue engineering is the application of chemical, biological and engineering principles towards the repair, regeneration or restoration of living tissue by using the cells, biomaterials and factors individually or in combination [7]. Bone is a tissue that can respond to external stimuli. The structural development of bone and mechanical forces on the mass has been accepted. This is a very complex process that involves multidisciplinary concepts [8]. The ability of bone cells to undergo proliferation, cell spreading, adhesion, differentiation and migration are necessary for the regeneration of bone tissue. Recent formulations for bone tissue engineering have beneficial properties because of their high porosity, low cytotoxicity, high mechanical strength, biocompatibility and cost-effectiveness [9]. Bone tissue engineering is beneficially used to create implants for bone regeneration. This can be used as the bone substitute for defects in skeletal that cannot heal by itself. These types of defects are common in craniofacial and orthopedics surgery for the treatment for loss of bone because of infection, trauma and tumor resection [10]. Bone has mechanical properties because of its extraordinary extracellular matrix organization and composition. To gain these mechanical properties inorganic and organic matrix components are highly organized at multiple hierarchical levels and continuously remolded by osteoblasts (bone forming cells), osteoclasts (bone resorbing cells) and osteocytes (regulating cells). Recently the bone engineering method is used to mimic the bone. Bone tissue engineering tailored for the growth of grafts for patients with large osseous defects, progenitor cells, scaffolds preparation, mechanical stimuli and soluble factors. For bone regeneration, this approach is used to achieve constructs with osteoconductive, osteoinductive and osteogenic properties [11].

## 2. APPROACHES TO PREPARING STIMULI RESPONSIVE SUPRAMOLECULES FOR BONE ENGINEERING APPLICATION

Stimuli responsive hydrogels are used in the tissue engineering and drug delivery field. Stimuli responsive hydrogels are have cross linked and hydrophilic polymer networks that can undergo the physicochemical transition to response to the external stimuli changes like as light, pH, analyte concentration and temperature. The response to stimuli often manifests as a change in hydrophobicity or surface charge, breaking of bonds resulted in degradation or gel-sol transition and change in phase volume of the gel [12]. Supramolecular hydrogels self-healing is used as a novel class of biomaterials that combine supramolecule and hydrogels chemistry to develop biomaterials that are functional with benefits such as biocompatibility, native tissue mimicry and injectability. These types of preparation are used as clinically translated tissue engineering therapies [13]. Products that have the ability to change their characteristics in response to the stimuli

## 3. BIOTECHNOLOGY APPROACH

In addition, the ability to modulate biomolecule function, protein immobilization and cell adhesion at the liquid-solid interface are important in a number of medical and biological applications, including biofouling, cell culture, regenerative medicine, chromatography, and tissue engineering. Various materials have been used to induce changes in biological surface properties often based on self-assembled monolayers or polymer films [16]. Stimuli responsive materials are capable of reversibly altering their properties depend on the external stimuli or environmental conditions. External stimuli such as electrical field, thermal, optical, magnetic fields, chemical interactions and mechanical forces. These properties are used in the material science and biotechnology application includes microfluidics, bioanalysis, biosensors and separation systems. All these are an

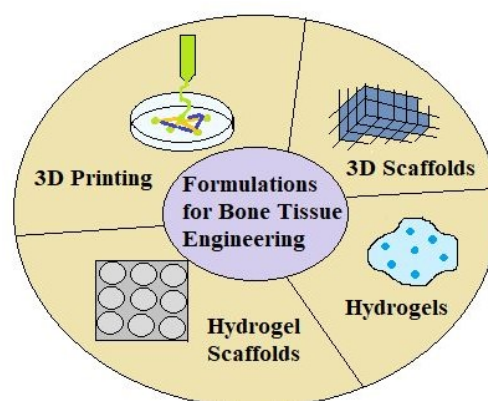
## 4. DIFFERENT STIMULI APPROACH FOR STIMULI RESPONSIVE POLYMER

In the study, new water soluble stimuli responsive polymer poly(N-acryloyl-N-propylpiperazine) was synthesized and characterized. This polymer exhibits lower critical solution temperature in the water at 37° C having application in controlled drug delivery, separation processes and immobilized enzyme reactors. For pH change phase transition temperature was highly sensitive. Theses polymers were soluble in aqueous solutions but undergo transition phase to response stimuli like as temperature, pH, electric field and magnetic field [20]. To modulate the response different types of stimuli can be used mainly for the hydrogels and surfaces, based on biodegradable macromolecules and natural origin. The light responsive and thermosensitive surfaces can modulate the adsorption of protein and cell adhesion. And less conventional smart surfaces such as substrates onto which biomineralization can be triggered. Stimuli response to pH and temperature is a recent development to material that reacts to biochemical stimuli, such as, cells or antibodies, enzymes [21]. Various thermo responsive hydrogels are prepared which have water based homogenous properties to manipulate, encapsulate, and transfer its content to surrounding tissue, in an appropriate manner. This hydrogel is also used in bone tissue engineering. The thermally induced gelation systems are prepared

presented their application in the biomedical arena, which can be allowing the regulation of drug delivery, cell attachments to products and protein adsorption. The thermo-responsive materials utilize changes in temperature as a trigger to switch their properties. Many of these systems are reversible, giving rise to finer control over material properties and biological interactions, which are useful for various therapeutic strategies. Mostly the smart materials intended for biological interaction are based on pH or thermo-responsive materials, although the use of magnetic materials has increased over the past decade, particularly in neural regeneration [14]. The polymers related to stimuli response have the remarkable property to change their chemical or physical state after a change in their environment, their response is dependent on their chemical composition [15].

advancement over static biofunctional surfaces since dynamic surfaces better mimic the microenvironment found in nature. Self-assembled monolayer films are used widely in a variety of stimuli responsive surfaces [17]. The artificial polypeptides like elastin-like polypeptides are found in human tropoelastin that coacervates reversibly above a critical temperature. The genetically encodable elastin-like polypeptides are stimuli responsive biopolymers exhibit an inverse temperature transition, monodisperse and biocompatible which makes them attractive towards drug delivery and tissue engineering. These can also have the potential to self-assemble into nanostructures in response to environmental triggers is another interesting feature of these polypeptides that promises to lead to a host of new applications [18,19].

that have a polymeric chain network that can undergo a phase transition to the gel-sol state because of a change in temperature.



**Figure 1.** Schematic diagram describes the different formulation used in bone tissue engineering.

The elastin based thermo responsive polymers have existed in solvate form below to their transition temperature and above its lower critical solution temperature at 30° C, the polymeric chain changes the conformation to form nanoparticles, entrapping molecules to deliver the actives, like as cell or protein cultured

system, loaded drugs [22]. Injectable polymeric hydrogels are stimuli sensitive used as the delivery vehicles for the controlled release of bioactive agents. These polymers get change sol to gel in aqueous solution. This response to various stimuli such as enzyme, temperature, pH, light and magnetic field. Hydrogel scaffolds encapsulated with therapeutic agents such as growth factors, fillers or cells are used in filling or regeneration of the defect area. Injectable hydrogels are used in biomedical applications like tissue engineering and drug delivery [23,24]. Stimuli responsive polymers mimic the biological systems in a primitive way and changes occur in properties because of external

stimulus. Stimuli responsive polymers are used in the biomedical field due to their ability to respond stimuli that are inherited by the *in vivo* method. This polymer is able to apply these stimuli in a non-invasive manner in a living body. The internal stimuli include a change in pH or temperature or external stimuli include electric or magnetic field, light and ultrasound [25]. Figure 1 shows the schematic diagram to describes the different formulation used in bone tissue engineering while Table 1 summarized the different formulation of stimuli responsive polymer used for tissue engineering.

**Table 1.** Different formulation of stimuli responsive polymer used for tissue engineering.

Formulation	Work done
Scaffolds	The scaffolds based on starch and chitosan are stimuli responsive for bone tissue engineering. Biomimetic calcium phosphate coated chitosan based scaffolds incorporated with lysozyme make an interconnected network of the pore <i>in situ</i> coupled which shows positive effects of scaffolds upon osteogenic differentiation of rat marrow stromal cells and mineralized matrix which confirms the effect of this scaffolds in bone tissue engineering [26].
	A natural biodegradable material in the form of chitosan-alginate-hyaluronate complexes was used in the preparation of scaffolds used in tissue engineering. Their surface can be modified by an Arg-Gly-Asp containing protein a cellulose binding domain used for cartilage regeneration [27].
	Poly(vinyl alcohol)-Chondroitin sulfate hydrogel scaffolds was prepared by using cross-linking agent glutaraldehyde by a chemical cross linking method used for the regeneration of articular cartilage. Poly(vinyl alcohol) increases the bioadhesive and mechanical properties to native tissue. Chondroitin sulfate increases the content of glycosaminoglycan in the extracellular matrix [28].
	Chitosan was used in the preparation of scaffold for tissue engineering. This can be used to regenerate the injured or damaged tissue. Chitosan scaffolds are also used for cartilage, bone, skin, vascular, corneal, cardiac tissue and nerve [29].
	Porous silicon was used for the preparation of scaffold in the field of ophthalmological tissue engineering and orthopedic applications. Porous silicon helps in the form of accompanying adjuvant drug release and as self reporting in the adjuvant [30].
	Scaffolds can be acts as the center of new tissue engineering when added with isolated cells or loaded with drugs to stimulate the ability of the body to generate or repair the injured tissue. Fabrication techniques were used in the preparation of scaffolds which can be used in the tissue engineering [31].
	Bone tissue engineering uses an artificial extracellular matrix called the scaffold. The highly porous scaffolds play a significant role in cell seeding, proliferation and new 3D-tissue formation. For bone tissue, engineering different biodegradable polymer materials and scaffolding techniques were explored [32].
Hydrogels	Scaffolds based on the extracellular matrix that was induced synthesis of organs and tissues. For restoration or regeneration of tissue, a scaffold is necessary which can act as a temporary matrix for cell proliferation and extracellular matrix deposition, with consequent growth until the tissues were totally restored or regenerated. The scaffold was used for tissue engineering like as cartilage, bone, skin, ligament, neural tissues, vascular tissues and skeletal muscles and also used as a vehicle for the controlled delivery of drug, protein and DNA [33].
	Hydrogels were the three-dimensional structure obtained from the class of natural or synthetic polymers. This can absorb and retain the amount of water. Polymer based hydrogel was used in the field of biochemical and biomedical. Stimuli-responsive hydrogels were used in tissue engineering and drug delivery. They can possess the different properties which include swelling in aqueous medium, pH, temperature, biocompatibility or sensitivity towards other stimuli, these properties can be utilized for their controlled zero-order release [34].
	Hydrogels composed of naturally derived macromolecules have the potential of biocompatibility, cell-controlled degradability and cellular intrinsic interaction. It was found that mechanical signals can be used to control the growth factor released from hydrogels, which could provide a new approach to tissue formation in stressed environments [35].
	Tissue engineering has the ability to engineer the shape and size of biologically pertinent hydrogels. Tissue engineering was used as tissue architecture, cell seeding and vascularization. These approaches used in the engineer tissue architecture and microvasculature inside cell-containing hydrogels. It was anticipated that the modular approach of tissue engineering can be used to generate the small building blocks which can be assembled to produce large tissues with relevant structure and function [36].
	For tissue engineering, the encapsulating cells in biodegradable hydrogels were used. This can be easy to handle, act as a hydrated tissue like environment for cell and tissue growth and have the ability to form <i>in vivo</i> . Hydrogels were having important properties like mechanical, swelling, diffusion and degradation which was closely linked to the crosslinked structure of the hydrogels. These hydrogels were used in the cartilage and bone tissue engineering [37].
The injectable and cell containing hydrogel was developed that supports growth and cell proliferation to allow <i>in vivo</i> engineering of new tissues. Derivatives of two thiolated hyaluronan derivatives were coupled with four $\alpha$ , $\beta$ -unsaturated amide and ester derivatives of poly(ethylene glycol) 3400. The crosslinking of 3-thiopropionyl hydrazide derivatives with poly(ethylene glycol)-diacrylate was used as <i>in situ</i> crosslinking applications that were used in the preparation of hydrogel for tissue engineering [38].	
Hydrogels scaffold	Biodegradable, injectable hydrogels are a captivating scaffold because of their similar structure to the extracellular matrix of many tissues. It can be processed under relatively mild conditions and may be delivered in a minimally invasive manner. The synthetic and native polymer both can be used in the preparation of hydrogels which can be used in soft and cartilage tissue engineering [39].
	Hydrogels were good scaffolding materials used for the regeneration of tissue. The hydrogel provide a highly swollen 3-D environment similar to soft tissue. The natural extracellular matrix model was used in the design and fabrication of bioactive scaffolds for tissue engineering. Extracellular matrix derived bioactive molecules to poly(ethylene glycol) hydrogels, different strategies for the integration of main extracellular matrix biofunctions were developed like proteolytic degradation, specific cell adhesion and signal molecule-binding [40].
	Tissue engineering scaffolds have similarity similarities to the native extracellular matrix, hydrogels were a leading candidate for engineered tissue scaffolds. Traditional techniques were used for preparing bulk porosity in polymers which have been used in success of hydrogels for tissue engineering. This technology was capable of regulating porosity and microarchitectural features in hydrogels in order to prepare engineered tissue with similar structure and function to native tissues [41].

Formulation	Work done
	The hydrogel scaffolds overcome the various challenges in tissue engineering which include vascularization, tissue architecture and seeding of multiple cells. These hydrogel scaffolds were also able to control the shape, surface morphology, porosity and size. It can help to preserve, restore and enhance tissue function [42].
	The conducting polymers were used as scaffolds for tissue engineering, applied in bone tissue engineering. Conducting polymers have electrical properties that can enhance muscle and nerve cell growth and regeneration. Because of hydrated nature, biocompatibility and tissue like mechanical properties the hydrogels were used as scaffolds for tissue engineering [43].

## 5. APPLICATIONS OF STIMULI-RESPONSIVE POLYMERS FOR BONE TISSUE ENGINEERING

Scaffolds prepared by using the polymers are used for the bone tissue engineering application. It includes biodegradability and biocompatibility with non-toxic products and also adequate resorption rate for the repair of bone. It can also include an adequate surface for cell adhesion and proliferation, vascularization, an interconnected porous structure that enables tissue ingrowth, nutrition, oxygen and metabolites exchange and suitable mechanical properties matching those of the native tissue [44]. Stimuli responsive polymeric hydrogels used as biomedical and biological applications and includes tissue engineering, biological sensors, drug release systems, microassays, imaging and actuators. Temperature sensitive hydrogels are the important class of stimuli responsive polymers for the delivery of the drug. Polysaccharide based pH-responsive hydrogels used for tissue engineering and control delivery applications [21]. In the study, Lin *et al.* were prepared thermoresponsive ABA triblock copolymers that are poly(acrylic acid)-phosphoethanolamine-poly(N-isopropylacrylamide) by using atom transfer radical polymerization. This can possess low cytotoxicity in the cell viability test so it can be used in the application of bone tissue engineering [45]. Thermo responsive polymers are used in tissue engineering which is derived from the proteins, natural polysaccharides, synthetic origins and their conjugation. The most effective biomaterials are derived from the different functional monomers, macromolecules and oligomers by crosslinking with the biodegradable segments. These systems are responsible for the interaction with the cells and promote cell-cell communication in response to stimuli. This can be used for the functional tissue generation and also acts as a delivery agent for the fast curing purpose. The self-assembly peptides are used as biomaterials that respond to physico-chemical stimuli and also achieved for the 3D cell culture and tissue engineering [46]. The thermo responsive polymer poly(N-isopropylacrylamide) is used in the preparation of the hydrogels which is used in the application of tissue engineering. They can provide softness, nutrients, and permeability for water, metabolites and pharmaceutically active agents. It can show a certain mechanical strength which can enable them to stimulate the living tissue. So they are used for tissue engineering and drug delivery devices [47]. Four dimensional bioprinting can be used to fabricate dynamic three dimensional patterned biological architectures that change their shapes by using stimuli responsive materials. In four dimensional bioprinting, time is integrated with the three dimensional bioprinting as the fourth dimension. It is used as the next

generation of tissue engineering technology because it represents the possibility of functional structure and constructing complex. The functional transformation and maturation of printed cell-laden constructs over time are also considered as four dimensional bioprinting, providing the unrivaled potential for bone tissue engineering [48]. Scaffold prepared by biomaterial can enhance the osteogenic differentiation for bone repair. Scaffolds are composed of synthetic or natural materials and their combination incorporated in bone progenitor cells and growth factors to display osteoconductive and osteoinductive potentials and helps to repair and replace bone defects [49]. Magneto-responsive biomaterials have emerged as candidates effective candidates as scaffolds for advanced drug delivery and tissue regeneration applications, which can be controlled spatiotemporally through an external magnetic field. These magneto responsive biomaterials are synthesized by the chemical or physical method by incorporating magnetic nanoparticles into biomaterial structure. This can be used in the preparation of tissue engineering scaffolds, artificial muscles and as controlled drug delivery system [50]. Stimuli responsive polymer respond to the various stimuli that include biological molecules, light intensity, temperature, pH, magnetic or electric fields which induce macroscopic responses in the material like collapse, swelling or sol-gel transitions, depends on the physical state of the chains. All these changes can be used in the design of smart devices for tissue engineering [51]. In the study, it was observed that the stimuli responsive polymers were allowed the dynamic changes of the structure used for the tissue engineering approaches. Recent advances in shape memory polymers enabled the study of programmable, shape changing, cytocompatible scaffolds used in bone tissue engineering [52]. Different types of stimuli responsive biomaterials organized into different shapes which are used as temporary support for cells in tissue engineering. The manufacturing procedure used in the production of particles in drug delivery issued for the manufacturing of microparticles in the fields of tissue engineering and regenerative medicine [53]. Stimuli responsive actuators, sensors to microfluidics, pharmaceutical and biomedical devices are having potential towards the nanocomposite polymer hydrogels. The responsive hydrogels change their properties and function as a response to external stimuli like artificial muscles are often inspired by natural systems. The injectability and precise drug delivery that cannot be controlled by macroscopic hydrogels are achieved with nanocomposite microgels and nanogels [54].

## 6. CONCLUSIONS AND FUTURE PERSPECTIVE

The stimuli responsive polymer has been used in bone tissue engineering which can respond to various physical and chemical stimuli. The various formulations have been prepared by using supramolecules for bone tissue repair and regeneration. This

has the ability to respond to the physical and chemical stimuli and also has the biotechnological approach. In this review mainly three formulations were described hydrogels, scaffolds, hydrogel scaffolds. The application of stimuli responsive Supramolecules

was also described. In future 3D scaffolds, 3D Bioprinting and 4D Bioprinting were prepared with advancements that respond to

the stimulus.

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