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## Bioresponsive Injectable Hydrogels for On-demand Drug Release and Tissue Engineering

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### Abstract

The emergence of injectable hydrogels as biomaterials has been a revolutionary breakthrough in the field of on-demand drug delivery and tissue engineering. The promising features of these systems include their biodegradability, biocompatibility, permeability, ease of the surgical implantation, and most importantly exhibit minimally invasiveness. These hydrogels have been explored as sustained and on-demand release carriers for the various bioactive agents, growth factors, live cells, various hydrophobic drugs and as extracellular matrices for tissue engineering. Present review is an attempt to highlight the recent systems explored for on demand drug release and tissue engineering. It also gives an overview of the role of nanotechnology in the advancements of injectable hydrogels. The future prospects and challenges of these hydrogels have also been addressed.

### Keywords

Injectable hydrogels; biomaterials; Nanomedicine; Pluronics; Chitosan; Drug delivery; Nanotechnology

## 1. INTRODUCTION

Injectable hydrogels by definition are the hydrogels which are in the form of sol or liquid at room temperature (20–25° C) and gel at body temperature (37° C). Since 1960 hydrogels have been explored for biomedical applications [1–4] and the recent demand has urged to develop injectable hydrogel systems, which can be synthesized by using various biopolymers, temperature sensitive polymers and loaded with the pharmaceutical excipients or live cells to form a hydrogel depot that undergo sol-gel transition. The excellent features

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### CONFLICT OF INTEREST

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of these hydrogels in comparison to the other forms of the hydrogels include their simple implantation process which limit the surgical procedures and also their ease of synthesis methods have highlighted their potential application as a drug carrier [5–8], seal-ants [9], tissue engineered products [10], surgical glues [11].

The field of regenerative medicine has come up with the novel approaches to improve, restore and replace the damaged tissues of the various parts of the human body. Various combination of therapies are being explored for this translational application. Cell therapies as well as immunomodulation therapies are in high demand. Interestingly hydrogel based scaffolds have taken upper hand in mimicking the extracellular matrix for the structural support resemblance and artificial organs and tissues [12]. The basic features that a synthetic scaffold should fulfill the properties that include the exact mechanical strength, porous structure and the free diffusion of the various nutrients across the cells. The cytocompatibility of these artificial scaffolds takes on the major concern. Hydrogels fulfill these criterion by having all the features with the three dimensional network of polymeric chains and have proven to be promising artificial extra cellular matrices (ECMs) [13]. The synthesis methods of the hydrogels especially the injectable hydrogels which are the most demanding comprise of simple, non-toxic chemical crosslinkers and enzymes for the crosslinking. These hydrogels can be made in desired shape and have the capability to adhere to the surrounding tissues during their formation. Researchers are involved in developing more advanced injectable systems for long-term cell encapsulation and on demand drug release which exhibit high stability when injected in the body [14]. Nanomedicine is making more precise dominant steps in applying nanoformulations for specific applications including drug delivery for on-demand, sustained release, gene delivery, tissue engineering, imaging and sensing applications [15–18]. The various routes of administration like transdermal, vaginal, intranasal, intra-pulmonary and one of the preferred route is parenteral route, which is opted for last many years exhibited many limitations such as frequent administration which results in poor patient compliance [19, 20]. In the last few years, broad and intensive research with the emergence of nanotechnology the invention of nanomedicine as well as to prolong the release of the bioactives for extended time has been suggested. This requirement is being fulfilled by soft injectable hydrogels. There are many biopolymers used for the synthesis of these hydrogels like chitosan, Polyethyleglycol (PEG), Poly (N-isopropylacrylamide) (PNIPAAm), Polylactic acid (PLA), Polyglycolic acid (PGA), Hydroxyethylcellulose (HEC), Pluronics,  $\alpha$ ,  $\beta$ -glycerophosphate have been extensively explored. The general synthesis methods employed for the synthesis of injectable hydrogels is via physical crosslinking methods using the hydrogen bond formation or ionic interactions. The temperature sensitivity of certain polymers for example PNIPAAm, are exploited in the synthesis method by modulating their properties of swelling and elasticity by the addition of hydrophilic polymers like PEG.[21] Other synthesis methods include the chemical crosslinking methods using the enzyme crosslinking [22], free radical polymerization or high energy radiations as well as condensation reactions [23]. These methods vary to the different type of polymers used and diverse biomedical applications of the synthesized hydrogels [24]. Table 1 highlights few recent noteworthy studies of stimuli responsive injectable hydrogels used for different biomedical applications. Literature showed the use of PEG–PNIPAAm based hydrogel for the parenteral administration. These

hydrogels exhibit good gelling mechanical strength and thus have least effects on the initial burst effect of the drug.

The increased bioavailability by having the on demand drug release these injectable gels are being extensively explored in drug delivery.

The present article gives an overview of the injectable hydrogels explored recently for tissue engineering and drug delivery. The ability of cell encapsulated hydrogels to get implanted into the body to eradicate the bone and cartilage defects for tissue restoration [25]. The addition of the nanofillers like metal nanoparticles, silica nanoparticles, clay, carbon nanotubes (CNT) etc. in the nanocomposite hydrogel matrices increases the mechanical strength of the hydrogels and play a major role in improving the shape, irregular bone defects and the osteoinductive properties.

## 2. IN SITU FORMING GELS: SYNTHESIS, POLYMERS, ROUTES OF DELIVERY

The general methods for the synthesis of in situ hydrogels involve the use of non-toxic chemical cross linkers as well as physical interactions. The physical interactions include the hydrophobic and ionic interactions which are quite popular. The recently opted techniques are using the supramolecular chemistry [12]. These techniques offer potential benefits like the easy route for delivery, non-invasive techniques for better patient compliance. The other fascinating and potential chemical crosslinking techniques employed for the synthesis are Michael addition utilizing thiols and amine as nucleophile and added to  $\alpha$ ,  $\beta$  unsaturated carbonyl compounds [33]. Moreover click chemistry [34] is also explored for the development of injectable gels for rapid reactivity in physiological conditions. The other methods for chemical crosslinking is by Schiff base reactions as well as by enzyme interactions [35] and self-assembly [36]. The biopolymers already mentioned above including chitosan and alginate use the electrostatic interactions between them and the polyionic molecules for the formation of the gels [37]. PNIPAAm have the property of phase transition with temperature change and have been extensively exploited for in situ gels.

The most important aspects of the in situ gels system are that these gels can be delivered in a non-invasive manner using diverse route for administrations. Intrathecal [38], buccal, intraperitoneal (i.p.), vaginal [39], ocular [40, 41], nasal [42] and rectal routes of administrations for in situ gels are being exploited for various drugs. The natural polymers used for the synthesis of in situ gel systems, owing to their biocompatible and biodegradable nature include pectin [43], hydroxypropyl methylcellulose (HPMC) [44] guar gum, xyloglucan, cellulose [45, 46], and sodium alginates [47]. The calcium ions are used for pectin gelation. The property of thermal reversibility exhibited by the biopolymer like xyloglucan is used for i.p. and oral delivery [48]. The metal ions divalent or trivalent are important for alginates gelation. The use of pH responsive features of the polymers are exploited for the buccal adhesion. The time of contact is extended for the antifungal drugs. One of the important pH responsive polymer is Carbopol which shows liquid form at acidic pH and forms gel in alkaline pH [49]. Pluronics and polyols, glycerophosphates are extensively exploited for in situ gels [39, 50].

### 3. APPLICATION OF INJECTABLE GELS AS ON-DEMAND DRUG RELEASE SYSTEMS

The drug delivery systems that have the ability to allow the remote, and reliable drug release are in high demand. Their ability to imbibe large amount of the drug inside it and deliver the drugs to the target site when in ON-state and do not release any of the amount of the drug in off state and may be frequently converted to ON state is ideal system. Though these systems are being synthesized by novel technologies yet none of the systems is in clinics. The methodologies lack their effective application *in vivo* because of the absence of the local implanted heat source and their multiple thermal cycles as well as the slow response time and exact drug dosing. Though few successful investigation using radiofrequency – activated microchips have shown very promising on demand drug release. Cheng *et al* [51] reported an interesting injectable hydrogel which has multiple features like near infrared (NIR) responsiveness as well as on demand degradable supramolecular hydrogel for controlled drug delivery. These stimuli responsive hydrogel based systems have the ability to yield a local high-dose and to overcome the limitation of non-specific distribution in normal tissues for best efficacy. This NIR responsive supramolecular hydrogel consisted of alpha-cyclodextrin ( $\alpha$ -CD) and poly (ethylene glycol) (PEG)-modified dendrimers and the encapsulation of the platinum (Pt) nanoparticles (DEPt-PEG). The synthesis methodology of the gels comprised of host- guest inclusion by threading the PEG chains inside the cavities of  $\alpha$ -CD. The physical crosslinking by hydrogen bond formation was seen for the formation of hydrogels [52]. It was shown that these gels were able to degrade on the exposure of NIR and showed the potential as a local delivery system for spatiotemporally controlled drug release. The main feature of these gels were their photo thermal responsiveness and the biocompatibility, which make them potential candidate to be used in chemotherapy.

A very recent study carried out by research group demonstrated the use of the in situ gelling hydrogels developed using superparamagnetic iron oxide nanoparticles (SPIONs) and thermoresponsive microgels showed pulsatile release of the model drug (4 kDa fluorescein labeled dextran). These particles have gained recent attention owing to the fact that they are inorganic actuating nanoparticles capable to be used in a non-invasive manner and also exhibit thermo-responsive characteristics. Their tendency to regulate the release of the drug by outer control over the extended period of time have been explored.

The group showed that these injectable gels have ~4-fold enhancement of release when in on state as compared to the off state. Fig. 1 shows the synthesis of these microgels has 90 % decrease in volume when heated from 37 to 43°C. This is the temperature range for the physiological temperature to the highest temperature before which the local tissue damage is observed. The application of the alternating magnetic field (AMF) the generation of heat by SPIONs raises the local temperature of the microgels and hence create free volume within the composites and thus increased drug release occurs through diffusion [53]. Other important studies show the application of the on demand drug release using the injectable hydrogels by exploiting the NIR responsive feature of the hydrogels.

The nanomedicine is actively involved in utilizing the features like spatiotemporal sensitivity of the biological systems. These sensitivity provides platform for developing the novel therapeutics. The various natural and synthetic polymers have been exploited for the localized therapy. For example a recent report suggests that the ultrasound sensitivity of the gels can be used to obtain a digital drug release of the bioactive molecules. These devices result in the constant release of the drug [54]. The ionically crosslinked hydrogels have been disrupted by applying the ultrasound and release of the drug takes place. This study also highlighted that by applying regular ultrasound, stimulated drug release substantially reduce the growth of the tumor as compared to the native sustained release of the drug. The amount of ultrasound used for the disruption is not that high to cause permanent damage to the materials but it is sufficient to release the small molecules or bioactives. This type of systems has direct application to the clinics as they provide approach to directly deliver the drug to the tumor site. These systems have significant advantage in providing outer control on the dose and timing from outside and greatly benefit the implantable systems [54].

The injectable hydrogels have also been exploited for the disease rheumatoid arthritis, this disease treatment poses potential challenges owing to the flexible disease activity consisting of exacerbations of inflammation punctuated by periods of remission. Thus a preferred localized system which is able to release the drug specifically during the period of exacerbation, as well as self-titrating in response to the level of inflammation. A perfect example of self-assembled nanofibrous hydrogel system developed by Vemula *et al* [55] showing the encapsulation of the specific enzymes and their release which are significantly upregulated in the diseased state including matrix metalloproteinases (MMP-2 and MMP-9) and esterases. The study showed that fibrous gels can withstand the shear force experienced during the joint, when injected into healthy joints of mice and get dis assembled to release the agents. This type of systems provides great platform for the future localized treatment of the proteolytic diseases [55].

Various natural polymer based materials are being exploited for bone defect repair. For example in a recent study regenerated silk fibroin (RSF) [56] has been explored for bone defects. This group demonstrated the use of laponite nanoplatelet (LAP) which is known to promote the osteoblast growth when incorporated in RSF hydrogel (Fig. 2). An injectable hydrogel of RSF/LAP formed showed cell proliferation and improved osteogenic differentiation.

The ability to release the drug by the change in the stimulus have been explored to great extent for clinical applications. Among the various stimuli light has been the major triggering source for activating remote controlled operations and ability to completely control on the release of the cargo. Ultraviolet (UV), near infrared (NIR) light [57] have been explored for the stimuli. Though UV and NIR radiations are accompanied by many drawbacks and certain limitations are associated with them [58, 59]. Such as premature aging by the disruption of the cellular response in the dermis by the application of UV light. The hydrogels in the form of beads have been explored by many groups. A recent study show the visible light induced volume change at body temperature by the hydrogel beads many hundreds micrometer sized and synthesized using alginate templating method. These light sensitive hydrogel beads are successful examples of remotely triggered drug release

system. The DEX drug release rate can be controlled by adjusting the intensity of the visible light. These beads possess potential application in transdermal patch. These type of system lay platform for the on-demand sequential as well as sustained release of the drug using light as an external stimuli [60].

The research undergoing in the field of stimulus responsive delivery systems show that light sensitive hydrogels owe a great potential in the transdermal controlled drug delivery. The most important factor to apply them safely is to control the exposure time as well as the power of the light [61]. These systems give an added advantage over the drug delivery systems using subcutaneous injections, which can act as an on demand transdermal patch. NIR as an external response has also been exploited for specifically on demand drug release systems. These systems are generally classified on the basis of the presence of photosensitive groups o-nitrobenzyl and azobenzene [62]. These groups are responsible for triggering the drug release when NIR is applied. Moreover when nanofillers like nanorods based on Carbon nanotubes (CNT) are incorporated in the hydrogel matrix, photo degradation is observed which is responsible for the drug release. The structural variations in these nanostructure occurs like the swelling and deswelling of the gels is responsible for release of the drug.

The main concern behind using the photocontrolled drug delivery systems is to overcome the limitation associated with light source such as the UV light is accompanied by the drawback of not penetrating inside the skin deeply and result in major absorption with the fat tissues [63, 64]. This results to poor reaction and effects the drug release. Similarly NIR is also followed by the limitation to be directly used and also consumption of high energy. The suggested platform to overcome these issues is to create an in situ environment for the UV by using a transducer which can convert the NIR to UV radiations. The high penetration of NIR is a very crucial aspect utilized in drug delivery application [65].

One of the recent studies by Jalani *et al.* [64] showed the doping of Lanthanide in nanoparticles results in converting them as transducers having the ability to convert the NIR to shorter wavelength to UV to Vis regions of the spectrum. Present study developed a photocleavable crosslinker (PhL) bearing the succinimidyl group and an acetylene group on respective ends. Lanthanide doped upconverting nanoparticles (UCNP) were capped by using oleate and was used to coat the chitosan hydrogel. This group demonstrated the use of the lanthanide doped  $\text{LiYF}_4:\text{Yb}^{3+}/\text{Tm}^{3+}@\text{SiO}_2$  encapsulated by fluorescent-bovine serum albumin (FITC-BSA) inside the hydrogel and showed the release completely dependent on the light source. It also showed that the upconverted NIR permits the particle tracking under the tissue (Fig. 3). This study showed the potential of these systems in theranostics, and imaging [64].

Many studies suggest the use of on demand drug delivery systems using stimuli responsive hydrogels for the treatment of local infections, tumors, and wound healing applications [66, 67].

### 3.2. Application of Injectable Gels as Tissue Engineering

The emergence of the injectable hydrogels as smart materials is mainly due to their effective application in comparison to the traditional surgeries, which have come up with lowering down of the cost on the healthcare and improving the patient compliance. The development in the field of tissue engineering have come up with novel injectable hydrogel based systems with improved properties covering the ease of their handling and repairing the defects. The injectable hydrogels have come up as biomaterials. The ability of encapsulating various therapeutic agents by injectable hydrogels have been used for drug delivery to various human tissues. For example application of injectable hydrogels for bone tissue engineering and cartilage tissue engineering have taken up an upper hand for replacement of defected organs. Injectable hydrogels have been synthesized using wide range of natural polymers as well as synthetic polymers. Among natural polymers hyaluronic acid [68], alginate [69], decellularized ECM [70], agarose [71], matrigel [72], chitosan and fibrin [73] have been extensively exploited. In this section, we are going to highlight few important and noteworthy injectable hydrogel based systems used for cardiac, bone and cartilage repair.

Hyaluronic acid (HA) is found in many tissues and biological fluids of various bacteria and vertebrates. This natural polymer is known to have high molecular weight and consist of alternating D-gluconic acid and N-acetyl D-glucosamine. This polymer plays an important role in the functioning of various tissues and cells. It is known for its features like biocompatibility, gel forming ability, ease of modification and hence employed for tissue engineering [75]. The degradation of HA by hyaluronidases is an added advantage to be used for controlled release of the drugs.

There is an immense work going on for the improvement of the mechanical strength of HA based hydrogels. Many nanofillers are being used for increasing the strength like Carbon nanotubes, or nanocrystals of cellulose. A recent report showed the development of injectable hydrogel of adipic acid dihydrazide-modified HA (ADH-HA) and aldehyde, which was improved by HA (a-HA) and also added content of the aldehyde modified nanocrystal (Fig. 4). These hydrogel showed improved mechanical properties such as compact network and stiffed properties having a storage modulus  $E'$ , of 152.4 kPa when nanocrystal concentration is 0.25wt% and this content was responsible for the improvement of the elastic modulus by 135% in comparison to hydrogels without the crystal. A distinct proliferative activity was observed when human adipose derived stem cells (hASCs) were encapsulated in it [74].

The field of tissue engineering and regenerative medicine have emerged with novel technologies, which give innovative approach to the organ transplant as well as repair of the damaged tissues in heart [76]. These approaches utilize the injectable forms of cells to the myocardium. This technology have explored stem cells, which resemble the cardiac cell type, the differentiated cell type or the full cardiac cells [77]. Hydrogels as a biomaterials have been extensively exploited to support the injured heart tissue. Many upcoming research articles pose the absence of any biomaterials for the cell types are grown in situ by tissue engineering for repair of the damaged cardiac tissue. Many injectable hydrogel based systems are compared to those using no biomaterial which possess certain limitation such as low cell retention on the desired site. The additional support delivered by the hydrogel

matrix have shown effective regeneration of cardiac tissues [78]. The complete control on the release kinetics by modulating the characteristic features of the hydrogel matrix gives an excellent platform for tissue engineering. Certain growth factors, cell types, proteins, DNA plasmids for the promotion of the anti-apoptosis and angiogenesis are being encapsulated in the injectable hydrogels [79]. Hydrogels are applied for the scaffold engineering owing to the porous structure and moreover the rubbery tissue like morphology support the resemblance and integrity for the tissue formation and act as potential adhesives for the interface between the biomaterial and the tissue. They can serve as scaffolds that provide structural integrity to tissue constructs, control drug and protein delivery to tissues and cultures, and serve as adhesives or barriers between tissue and material surfaces. A number of studies show the application of injectable hydrogels for the stem cell delivery of infarcted myocardium. A very interesting study [80] demonstrated the use of four injectable hydrogels for left ventricle remodeling. Tetronic-fibrinogen (TF) and polyethylene glycol (PEG)-fibrinogen (PF) conjugates were employed in this study. The utilization of multiple properties of the biomaterial like stiffness and highest modulus showed the best neovascularization [80]. HA nanoparticles are also exploited as nanofiller in the hydrogel systems for the encapsulation of stem cell mesenchymal MSCs. These cells showed the existence of the live cell up to 27 days after the encapsulation. The hydrogel mineralization was supported by the combination of the encapsulated MSCs. This type of systems promotes and gives a very potential platform for the in situ forming nanocomposite hydrogels which simultaneously promote the cell delivery as well as mineralization which is the most important condition for craniofacial bone tissue engineering [81].

In the last few decades the musculoskeletal problems are growing at major scale and human healthcare has been affected largely by it. Economically also the cost on the bone and joint care have been recognized by the world health organization (WHO) predominantly [82, 83]. Joint replacement surgeries are on high demand with existing style of living. The large defects are major concern for the restoration of the complete function of the bone. The similar kinds of osteoconductive matrix release the similar kind of the progenitor cells and factors. The use of degradable polymers to design this matrix as a three dimensional scaffold was being opted and now the upsurge is to develop in situ scaffolds. The emergence of in situ forming scaffolds have come up with advantages and thus eliminating the defect site and provides better contact between the scaffold and their surrounding tissues. Methyl acrylates and PMMA are used as bone cements. The injectable hydrogels are being intensively explored for the bone grafts. An interesting study shows the development of hydrogel using 1, 4-butanediol diacrylate and tricalciumphosphate. Strontium chloride and Zinc chloride were added for increasing the osteoblast cell density [84]. The recent research is more focused on the development of nanocomposite hydrogels having organic and inorganic composite materials that have similar properties of bone.

Collagen, one of the known natural polymer is extensively used for the bone tissue engineering [85]. The injectable form of the gelatin gel has provided great platform for filling the bone defects. One of the very recent study highlighted the use of gelatin- water-glycerol gel for broad spectrum carrier. This gel was highly biocompatible *in vivo*. This gel was injected with the demineralized bone matrix and it showed high osteogenesis performance. The study highlighted the property of degradability as well as hydrophilicity.



The study demonstrated the ternary gel as irradiation sterilized and universally applied injectable system [86]. The recent approaches utilizes the degradation of the many hydrogel based materials for the *in vivo* development of the scaffold materials. The overall motive is to develop such system which have a matching rate with the development of the new scaffold with the degradation of the scaffold. The injectable hydrogel systems are preferred as they can carry the imaging agents along with them and make easy for the imaging the *in vivo* journey of the carrier and hence reduce the number of animals required for the study. One of the very recent study show the development of in situ HA based gel by the Michael addition and thiol sulfide exchange reactions [87]. The study show the structure–degradation relation very important parameter to decide the development of the new *in vitro* scaffold models for tissue engineering.

Other techniques used to synthesize injectable hydrogels is by using the ring-opening copolymerization. Interestingly, nanohydroxyapatite when incorporated into the biodegradable triblock copolymer poly (ethylene glycol)–poly( $\epsilon$ -caprolactone) –poly (ethylene glycol) formed injectable nanocomposite and showed potential in orthopedic tissue engineering (Fig. 5). Thus these systems are important platforms for the development of key biomaterials which have the excellence in recapitulating the environment for the *in vivo* tissue engineering.

## CONCLUSION AND PERSPECTIVES

From the overall discussion in the present review, we can conclude that the forms of the hydrogels have critical impact on the route of administration as well as the entire characteristics of the hydrogels for different application. The present article gives an overview of the injectable form of the hydrogel for the on demand and sustained release of the drugs. These hydrogels have been innovatively designed for the tissue engineering applications. The most important fact about these systems is their stimuli responsiveness such as they can be designed responsive to light, temperature, electric and magnetic field. The modulation of the dose and release by using external control has a great perspective in drug delivery. Various nanofillers are being introduced to increase the encapsulation efficiency and also the carbon based nanomaterials are being explored for better efficacy of the hydrogel systems. The flexibility to functionalize the hydrogels these systems hold a great potential in diagnostics and imaging. The novel system pave the way for developing hybrid injectable hydrogels with specific bioactives and molecular response. The targeted drug delivery uses the features of the hydrogels to be modified structurally and can provide precise control on the drug release and recognition of molecular agents. The article discuss various stimuli such as light, NIR, UV, magnetic field as well as electric field for on demand drug release systems, There is an immense need to develop such systems using these sources and improving their efficacy and eliminating all the drawbacks associated with them such as heat generation, carcinogenic properties as well as the increased risk of toxicity when these stimuli responsive hydrogels are retained in the body for long term.

The efforts by the physicist, chemist and materials scientist have already layed a platform for the triggered release systems which comes with the synergism in development of the novel material, fabrication of the device and the mechanism behind the stimuli triggering. The

overall motive behind these efforts is that these systems should exhibit the features before they are in market or in clinics. The tunability in the on state should have wide window and it could be adjusted as required for therapeutic relevance. The off state should be very stable which shows no leakage for the longevity of the implanted device. These systems should be checked for inflammatory response [89]. The main emphasis of the research community working in the field of engineered hydrogels for the delivery of the various growth factors to the endogenous progenitor cells *in vivo* is on working on the subsequent resorption of the hydrogel matrix and thereby promoting the tissue regeneration. Scaffold degradation, appropriate tracking of the system and sensing diagnostics are the demanding future topics that need to be addressed more critically.

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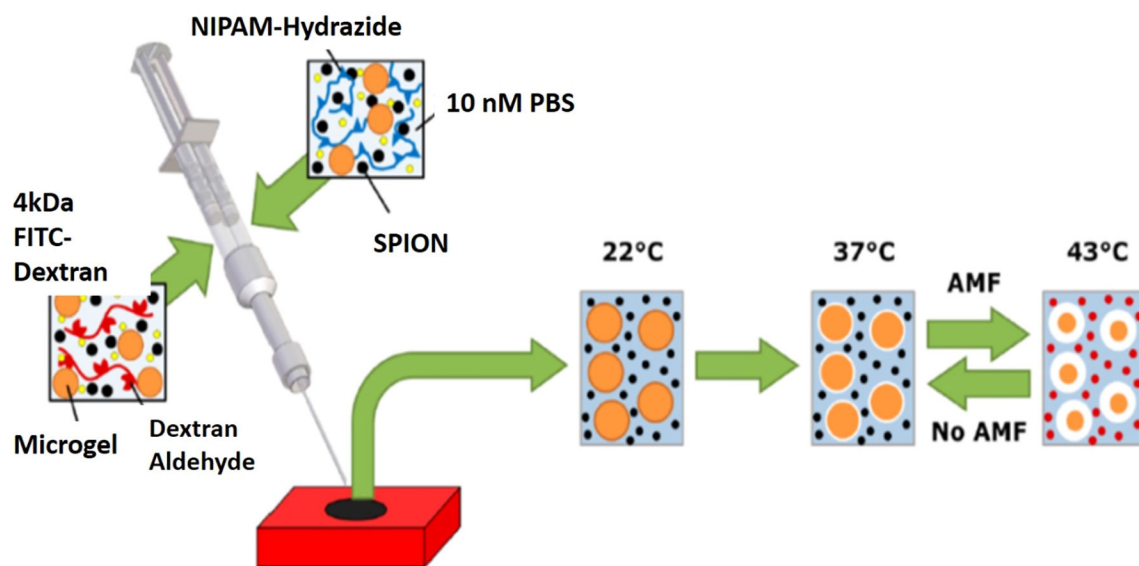
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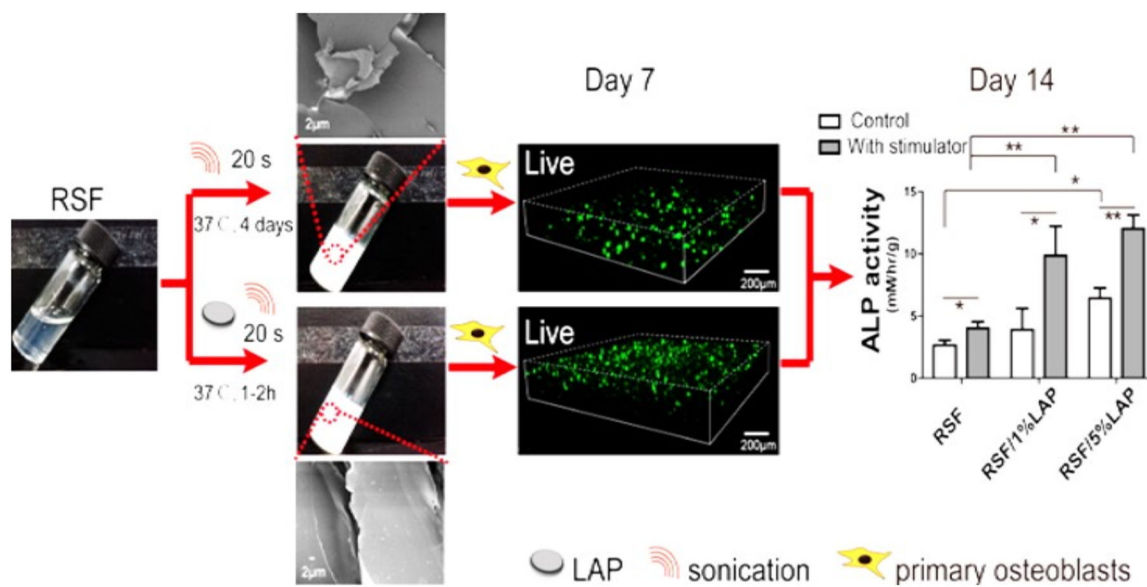
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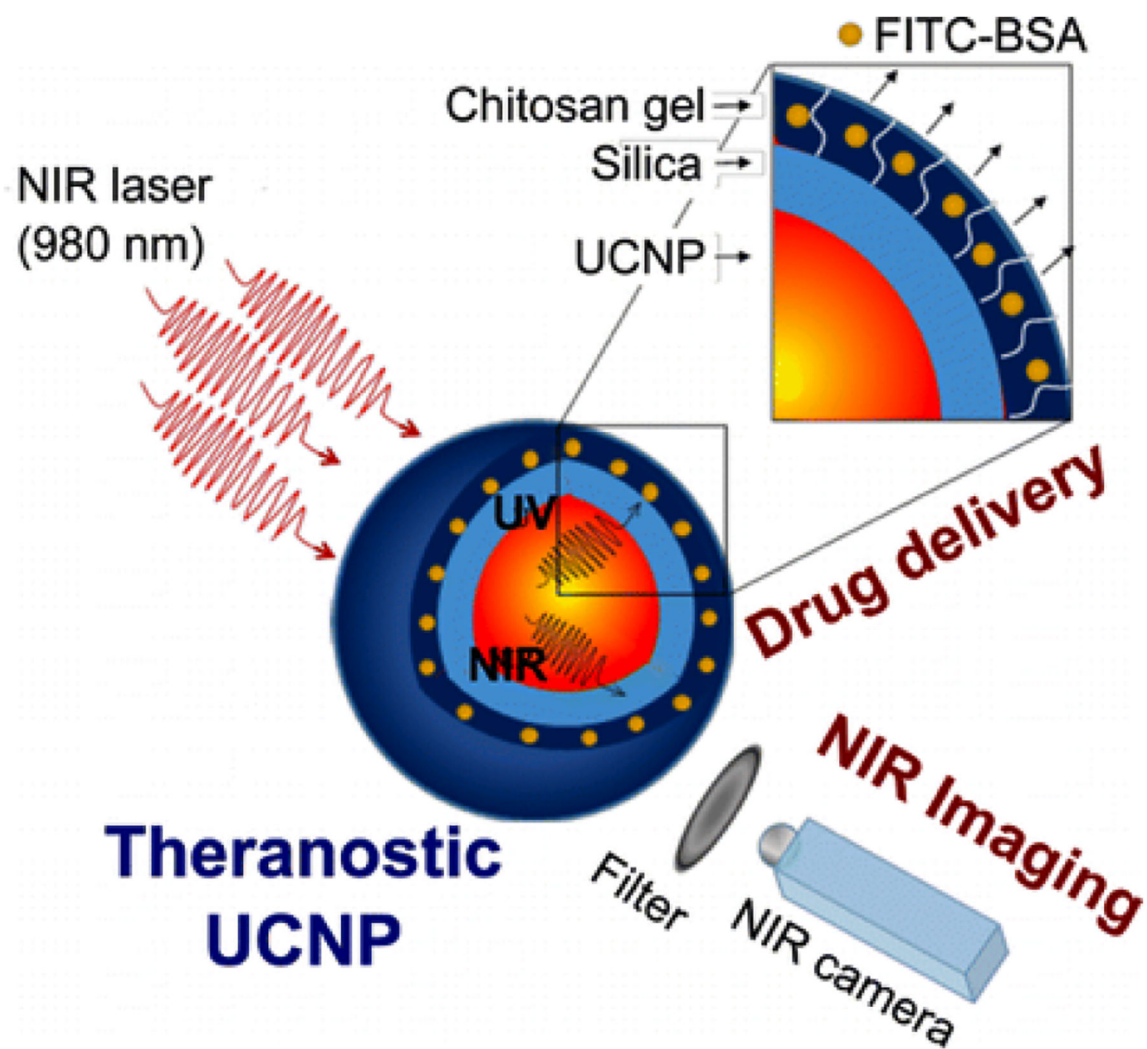


**Fig. (1).** Fabrication of nanocomposites and their proposed mechanism of externally AMF-controlled enhanced drug release. “Reprinted (adapted) with permission from [53]. Copyright (2015) American Chemical Society.”

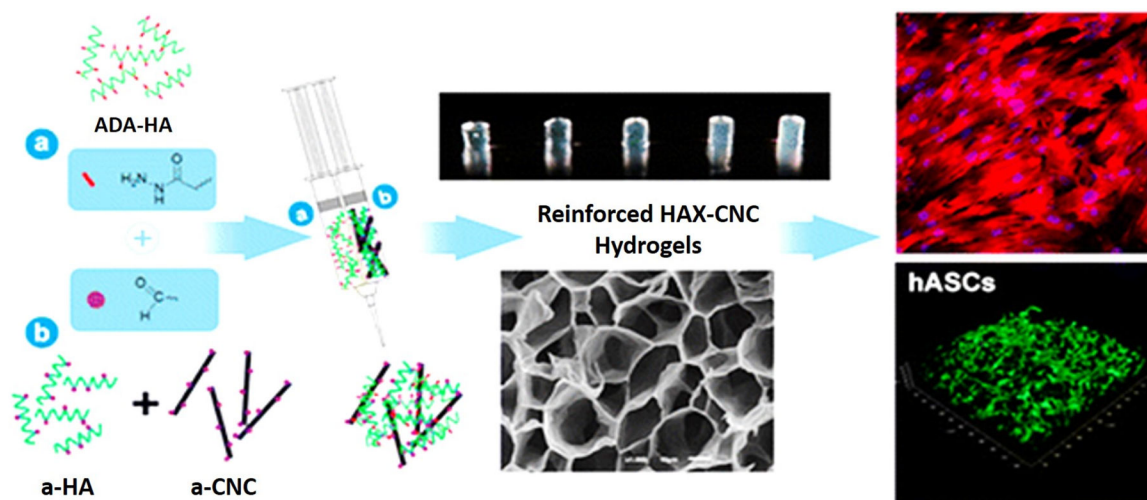


**Fig. (2).** Injectable Silk Fibroin Hydrogel with Laponite Nanoplatelets “Reprinted with permission from [56]. Copyright (2016) American Chemical Society.”

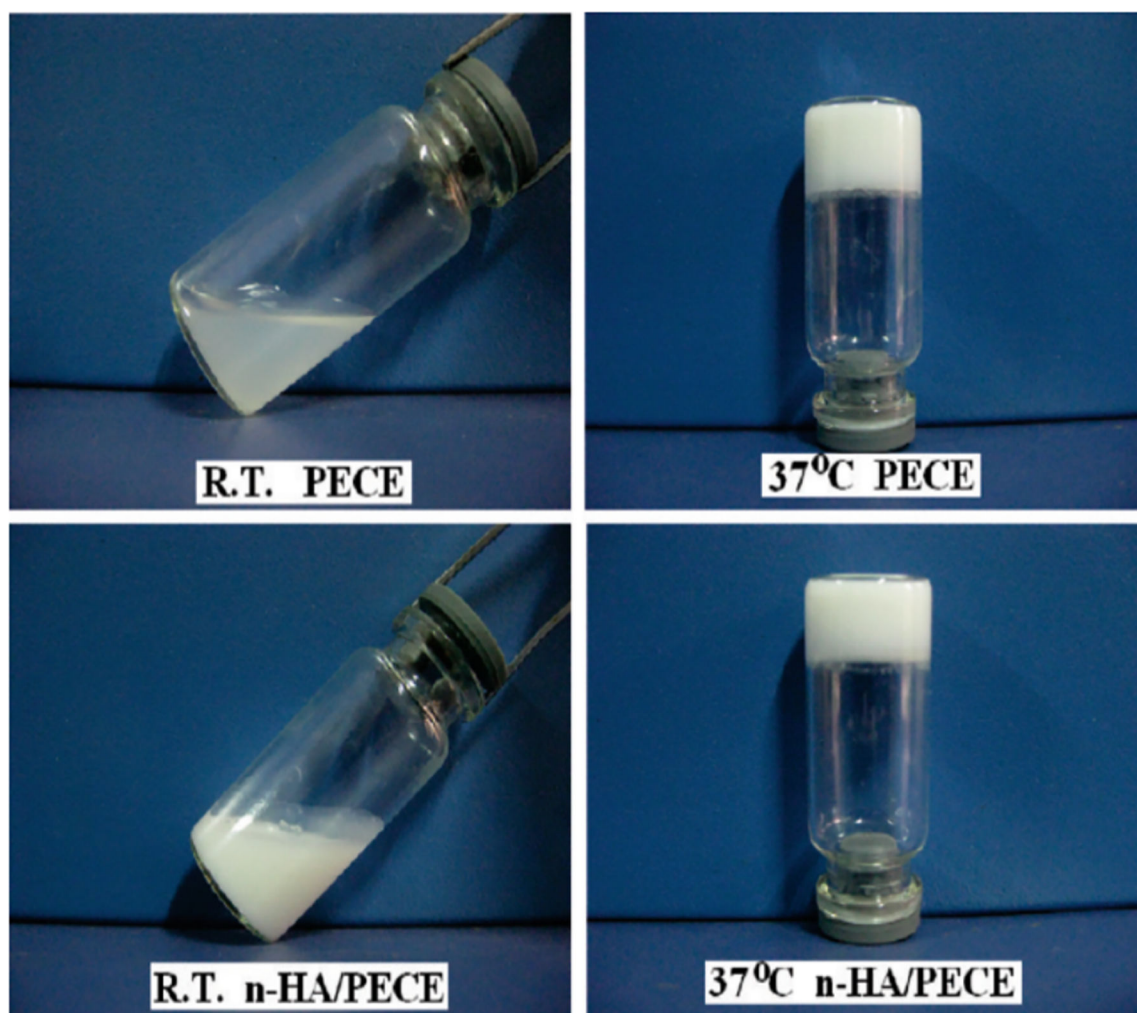




**Fig. (3).** Multifunctional Theranostic Platform for NIR Imaging and On-Demand Macromolecular Delivery. "Reprinted with permission from [64] Copyright (2016) American Chemical Society.



**Fig. (4).** Injectable hyaluronic acid/cellulose nanocrystals bionanocomposite Hydrogels for tissue engineering Applications. “Reprinted with permission from Reference [74]. Copyright (2015) American Chemical Society.”



**Fig. (5).** Thermosensitive hydrogel formation of pure PECE and n-HA/PECE nanocomposites with 20 wt % HA at room temperature (R.T.) and 37 °C. Reprinted with permission from Reference [88]. Copyright (2009) American Chemical Society.”

**Table 1.**

Stimuli responsive injectable hydrogels for different biomedical applications.

Biopolymers	Gel Processing	Stimuli response	Application	References
Chitosan-beta glycerophosphate-hydroxyethyl cellulose (CH-GP-HEC)	Sol-gel transition at 37 °C	Temperature responsive	Cartilage Tissue engineering	[26]
Dextran sulfate (DS)	Coupling of a cysteine terminated peptide to HA-maleimide	Bio-responsive	On-demand matrix metalloproteinase inhibition	[27]
Methacrylate-poly(lactide (MAPLA), N-isopropylacrylamide (NIPAAm) and 2-hydroxyethyl methacrylate (HEMA)	sol-gel transition	Thermally responsive	Hydrolytic Lability	[28]
Heparin-bearing poly( <i>ε</i> -caprolactone- <i>co</i> -lactide)- <i>b</i> -poly(ethylene glycol)- <i>b</i> -poly( <i>ε</i> -caprolactone- <i>co</i> -lactide) (Hep-PCLA)	Temperature-induced sol-to-gel transitions	Thermally responsive	Protein Delivery	[29]
Poly(ethylene glycol)-poly(sulfamethazine carbonate urethane) (PEG-PSMCU) copolymers	sol-gel transition	pH and temperature sensitive	Sustained delivery of cationic proteins	[30]
Hyaluronic acid methyl cellulose	Sol-gel transition	Pressure sensitive	Spinal cord injury repair	[31]
Phenylboronic acid (PBA) and glucose.	Complexation	Glucose responsive	Sensing application for monitoring blood glucose levels.	[32]