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Recent Advances in Hydrogel Based Scaffolds for the Cardiac Tissue Regeneration.

[1]S. Gowtham, [1]R. Subash Chandra Bose, [1]B. Rajkumar, [1]Dr.T. S. Shanmugarajan*

[1]Post Graduate, [1]Professor,

[1] Department of Pharmaceutics, School of Pharmaceutical Sciences, Vels Institute of Science, Technology & Advanced Studies (VISTAS), Chennai, 600 117, Tamil Nadu, India.

mailshanmuga@gmail.com

ABSTRACT

In light of the limited efficacy of existing treatments for myocardial regeneration, tissue engineering techniques have been examined for their ability to provide mechanical support to damaged cardiac cells, circulate cardio-protective molecules, and augment cell-based treatment approaches. In recent years Hydrogel based delivery systems have found clinical applicability of cardiac tissue engineering concepts through which it .can leverage potentially beneficial therapeutics outcomes. Moreover, these hydrogels plays a significant role in promoting the controlled release in spatial and temporal manner for the variety of therapeutic agents, including drug molecules, peptides, and cells. This review highlights the importance of the hydrogels along with recent advancements in hydrogels meant for cardiac tissue engineering. Further various polymers involved in the fabrication of the hydrogels meant for cardiac tissue regeneration were also discussed.

Keywords: Cardiac regeneration, Hydrogels, Scaffolds, Tissue engineering, Injectable hydrogels.

INTRODUCTION

The cardiovascular system includes the heart and blood vessels. Endocarditis, rheumatic heart disease, conduction system anomalies, and cardiovascular disease (CVD) or cardiovascular disease are just a few of the cardiovascular system's illnesses. CVD has been one of the leading causes of death in the United States since 1975, accounting for 633,842 fatalities (1 in every 4 deaths). Heart disease, followed by cancer, were the top causes of death in 2015. (595,930 deaths). CVD is the biggest cause of death worldwide, and according to World Health Organization (WHO), with 17.7 million deaths predicted in 2015.

A blocked coronary artery causes myocardial infarction (MI), which lowers or prevents blood circulation to a part of the heart, leading to lower oxygen supply to the cardiomyocytes and eventually destruction. The ischemia event causes severe damage to the infarcted zone at initially, but following the MI, the nearby heart wall thins, causing to ventricular dilatation and the development of Heart Failure (HF). The heart muscle's inefficiency to pump blood properly to the rest of the body is caused by cardiomyocyte (CM) loss, cardiac matrix deterioration, and fibrosis. Heart failure is associated with a poor quality of life, significant medical costs, and a high mortality rate.[1, 2]

Tissue engineering

Tissue engineering incorporates engineering and life science concepts to yield biological spares that rebuild, uphold, or strengthen cellular activity or the performance of an entire body part. The core components in tissue engineering are cells, scaffolds, and growth factors. The cell generates new tissue matrices, while the scaffold affords the suitable circumstances for cells to perform their best. Growth factors enable cells regenerate tissue by making it easier for them to do so. Tissue engineering is characterised by its ability to replicate a patient's native organs and tissues that are entirely of poor biocompatibility, low biofunctionality, and autoimmune rejection. Tissue engineering is commonly regarded as the ideal medical assistance because of its massive benefits. Body tissues and organs possess unique structural and functional characters, any designed material must be capable of imitating the properties of the target tissue

and organ. In designing a tissue or organ, several strategies are employed in order to adapt their form and function. Decellularization and recellularization of tissues prior implantation have shown vast potential, since they eliminate immunogenic cells thereby retaining the original ECM's structure and elemental composition.

Tissue engineering methods may be divided into a set of unique techniques, which include the injection of patient-derived cells into the damaged tissue, the distribution of biomolecules like growth factors that can convey impulses to the patient's original cells. The degradation of the scaffold is vital for tissue engineering therapies to work effectively. Once the scaffold has performed its purpose of delivering a framework for tissue formation, it should ultimately resorb. Moreover, the deterioration must progress at a rate which is compatible with the development of new tissue. To minimize the impacts of an inflammatory reaction, the degraded products must not be hazardous and should be immediately removed or resorbed. It is important to remember that the local pH should not be considerably less than the physiological pH during scaffold breakdown; otherwise, apoptosis and protein degradation might arise.[3]

As the medical demand for tissue engineering and wholly regenerative medicine has expanded over the years, which is evidently depicted by the tremendous rise in the number of participants on the contributor standby. Furthermore, it is essential to remember the contributor's mismatch with the patient's tissues, along with mobility barriers and the limited time available for implantation. Many studies have been undertaken to regenerate various types of tissue; nevertheless, there are multiple crucial components engaged in the tissue repair process, including source of stem cells, scaffold fabrication, cell seeding, culture environment, matrix production analysis, mechanical characteristics of the cell–scaffold framework, and adequate laboratory experiments. In the upcoming years, a biopsy will be used to extract cells, that could then be cultivated in culture, implanted onto a 3D scaffold, and inplanted into the patients.[4]

As a result, innovative ways to help rebuild diseased heart tissues are urgently in need. Injectable hydrogels have emerged as a viable regenerative medicine technique for heart repair.The capacity to use designed or regenerated myocardial tissues instead of a donated heart would be a huge step forward in terms of improving patient survival and advancing the discovery of new therapies for myocardial infarction (MI) and other life-threatening cardiac diseases. After a cardiac arrest, the body's typical response is to restructure fibre, which leads to scar formation rather than the forming effective tissue. As a byproduct of scarring the heart is unable to operate effectively, which eventually leads to heart failing. Injectable hydrogels have the ability to deliver bioactive molecules, cells, or engineered tissues precisely to the affected area of the heart in order to regenerate healthy cardiac tissue, providing them a effective therapy choice for MI. They make an alternative and novel delivery strategy that has the capability to alleviate the drawbacks of current therapies. Many injectable hydrogels have been synthesized in recent decades, and many of them have been investigated for use in myocardial repair post MI (Table 1.) (Figure 1.).[5]

Hydrogel

Hydrogels are "water-swollen polymer networks" with a high water content similar to that of human tissues. It could be delivered as a fluid and crosslinked into a gel phase with the use of physical or chemical stimulation. They can also be administered as part of a partially crosslinked gel. After injection, the gel forms, allowing for a less invasive introduction of the material into the body as well as the inclusion of bioactive molecules prior to injection. Thermo-sensitive hydrogels are made to gel at body temperature. As a result, the shift from fluid to gel can happen after the injection is made.Photo crosslinking, pH-dependent crosslinking, and ionic crosslinking are some of the other in situ crosslinking techniques. Because some hydrogels have structures that are comparable to those of extracellular matrices, they can aid in the development of a novel extracellular matrix and promote integration inside the body if injected in the defective area. Hydrogel characteristics and behaviour are heavily influenced by design factors used during synthesis. These design parameters must be selected based on the hydrogel's key features and, as a result, on the hydrogel's intended application (Figure 1).

Injectable hydrogels are good for cardiac compatibility because they may be modified to give precise physical, chemical, and electrical qualities, the latter of which may be vital for supporting the heart's conductive capabilities. Their ability to give structural support of variable stiffness may also make them compatible with the heart muscle's constant contractions, which make it a particularly difficult tissue to physically recover. Hydrogels injected into injured heart tissue could be used to deliver cells, growth factors, therapeutic peptides or medicines, and other substances. Hydrogels can also be utilised to support a variety of gene targeted delivery, including viral and nonviral approaches, allowing for targeted delivery and efficient localised therapy. These deliverables could be targeted to a specific tissue, reducing nonspecific distribution to other nearby tissues.[6]

While the scientific community has made significant progress in producing injectable hydrogels that are excellent for heart regeneration, more work needs to be done before these biomaterials can be fully optimised for routine clinical usage. Injectable hydrogels, in particular, should be engineered to closely imitate cardiac muscle signals and have qualities that allow them to promote cell viability and/or retain biological molecules activity even in the severe, damaged localised tissue conditions that exist following a MI. Utilizing extreme levels of biocompatibility, especially signals responsive of cell integration into cardiomyocytes, and conditioned fragmentation, so that the hydrogel could indeed promote new cell rejuvenation but then non toxic degradation process to leave no foreign particles inside the tissue which might eventually trigger an autoimmune reaction, can be vital for the enhancement of all such intravenous hydrogels. Further to that, for such hydrogels to be beneficial, maintaining the integrity over the phase transition parameters and strategy is intended. It may be preferable for them to be fluid while inside a syringe to provide uninterrupted delivery, and then convert to a gel form within few seconds following injection on to the specific location to contribute to better hydrogel integration. Since heart muscle is always contracting and thus continuously in constant movement, the ability to accurately assimilate into the tissue is extremely important.[7]

This article provides a complete analysis of distinct injectable hydrogels for potential use in cardiac repair or rejuvenation. A brief summary of existing clinical therapies and associated limitations. The feasibility of injectable hydrogels for cardiovascular regeneration

has been studied, along with the crucial parameters to be considered while designing the hydrogel, distribution network, and drugs to be injected. Furthermore, significant innovations in the field are discussed, followed by thoughts on future perspectives for resolving the barriers that inhibit injectable hydrogels from being routinely used in the healing of injured cardiac tissues.[8]

Classification:

Natural polymers

Collagen:

Hydrogels synthesized using collagen are biodegradable, readily accessible, and multipurpose. Moreover, when treated with heart cells, they exhibit remarkable tissue compatibility and promote cell adhesion and longevity. Collagen-based gels can be manufactured maybe using decellularized techniques that retain the tissue's basic shape, or extraction methods that allow the protein to be further coupled with other substances. Collagen's morphology and sturdiness, can be affected significantly when exposed to high temperatures and perhaps other types of irradiations because it is a protein.[9]

Fibrin:

Fibrin is synthesized from the proteolytic enzyme thrombin and fibrinogen monomers by fast polymerization process. The proportion of these two main components can indeed be adjusted to modify the fibrin scaffold's gelling rate and mechanical parameters. The fact that fibrin is exceedingly elastic makes it perfect to use in cardiovascular tissue engineering. Fibrin-based hydrogels have a moderate inflammatory and foreign body reaction, and they can be absorbed spontaneously during healing process. Although fibrin-based gels have such a big future for synthetic biology, polymers have poor mechanical characteristics and a tend to shrink, which could be a concern when delivered into the heart.[10]

Chitosan:

Chitosan are chitin-derived natural polysaccharides with high biocompatibility, bactericidal, and fungicidal effects. Chitosan is readily accessible as it may be isolated from shellfish and fisheries debris. Chitosan-based hydrogels react to a series of environmental stimuli, specifically light and temperature, and develop integrated nanostructures that enhance cell infiltration. Temperature-responsive chitosan-based hydrogels are promising because bioactive molecules and/or cells can be rapidly absorbed into the hydrogel without affecting their behaviour. When exposed to elevated temperatures similar to body temperature, the polymeric solution solidifies in a brief period, permitting these cells/compounds to be confined within the injected tissue.[11]

Alginate:

Alginate is a natural polysaccharide formed from bacteria and brown seaweed. With it's structural similarities to the natural ECM, it has a greater standard of biomedical applications and is frequently used in tissue engineering scaffolds. The coupling of alginate with divalent cations that promote hydrogel bridging is the most prominent step to generate alginate-based hydrogels, but they can also be synthesized through free radical polymerization. Alginate is also biodegradable, non-antigenic, and has been recognized for human use by the US Food and Drug Administration (FDA). Alginate's mechanical and gelation abilities can be easily adjusted by adding other materials, inactivating specific ligands such peptides and monosaccharides, and crosslinking.[12]

Synthetic polymers

Polyethylene glycol (PEG):

Polyethylene glycol, a biodegradable synthetic polymer that has now been broadly utilized in tissue engineering. As it is soluble in water and organic solvents, has limited protein adhesion, and nontoxic, PEG has a major hit in tissue regeneration. Further, by combining drug moiety to the polymer backbone, PEG can be easily adapted to fit in the expectations of different applications. Compared to natural polymers, its tensile performance are more easily managed. As a byproduct of these properties, injectable PEG hydrogels are increasingly used in heart regeneration techniques.[13]

Poly(N-isopropylacrylamide):

Poly(N-isopropylacrylamide) is a thermo - responsive hydrophyllic homopolymer that has attained a considerable interest in the biomedical applications due to its steep, reversible solution-to-gelation (hydrogel) transition point of 32°C, which in itself is high enough to make it a solution at room temperature and yet low enough to make it a gel at body temperature, makes it incredibly useful for a diverse range of medical applications. This polymer system can be introduced into the injection site and will gel in order to respond to the abnormalities of the injured area. Drug delivery technologies, cell scaffolding and grafting, and also in vitro culture procedures have mostly been utilized with PNIPAAm-based polymer systems in cardiac tissue regeneration.[14]

Polyvinyl alcohol:

PVA is synthesized from polyvinyl acetate after it has been hydrolyzed. Physical or chemical crosslinking is used to create the PVA hydrogel. Since chemical crosslinking seems to have the potential to be dangerous, some studies have concentrated to use

photocrosslinking to substitute chemical bridging. Because of its elasticity and effectiveness in increasing mechanical signal diffusion, it could be employed as a matrix. Since PVA is a neutral hydrogel, its adhesion characteristics are minimal, which can be augmented by combining it with biological factors. The material strength of PVA hydrogel is firm, and it has a low friction rate.[15]

Polyphosphazene:

Polyphosphazene is a biodegradable polymer. The pace of its decomposition process can be controlled by manipulating its sidechain. Interchanging phosphorus and nitrogen atoms, along with two side groups attached to each phosphorus atom, constitute the polyphosphazene polymer. Upon preparing the actual polymer, an intermediary product called polydichlorophosphazene is formed. The resulting product's gel phase is attributed to its hydrophilic core and adaptability developed through several replacement mechanisms. Only a thermosensitive hydrogel can be manufactured out of it. Nonionic and ionic hydrogels can also be synthesized from polyphosphazenes.[16]

Recent advancement in hydrogel

Acellular Hydrogels for Treatment of Myocardial Infarction

Being delivered unilaterally, acellular hydrogels studies have revealed promising effect in cardiac remodeling as a filler material to lend structural stability to the infarcted heart, and often a carrier for biomolecules such like growth factors, cytokines, and nucleic cassettes. Many research teams have indeed emphasized on acellular biocompatible hydrogels completely lacking of pharmaceuticals in favor of focusing on materials that provide the appropriate biochemical signals to resemble the instinctual habitat.

Fibrous tissue is noncontractile, which affects the heart's potential to circulate blood effectively, thereby limiting fibrosis is extremely important for heart regeneration. The tissue implanted with the ECM hydrogel further showed foci of angiogenesis, denoting cardiac reconstruction due to sudden rush of blood to the ischemic injury area providing oxygen required for cardiomyocyte progress, clarifying that the ECM by itself doesn't trigger an immune response as long as the framework is effectively decellularized. This explains how ECM elements will be used to construct cardiac tissue.[17]

Myocardial Remodeling employing Cell-Laden Hydrogels

Hydrogels effectively protect the cells against being drained by the body's protective mechanisms by facilitating them with a mechanical stablity and biocompatible surroundings. As a result of these flexible characteristics, hydrogels have a big future to be an essential consideration for cell therapy's ability to relieve coronary artery disease. To enhance the productivity of stem cell injection in infarcted myocardium, different intravenous hydrogels have just been implemented. In a latest studies, an antero-lateral incision would be used to conduct a left thoracotomy, which would be proceeded by a injection of hydrogel precursor solution on four sides of the infarcted zone. De monstrated that injecting the left ventricle with hydrogel significantly improved wall thickness, which enhanced the survival of undamaged heart cells in the occurrence of myocardial infarction.[18]

GelMA Hydrogels containing Carbon Nanotubes enabling Cardiac Constructs

Scaffolds that are used to construct cardiac tissue sparingly have the ability to conduct electrical impulses. Purkinje fibres in the native tissue, on the other hand, transmit electricity and allow the heart to pump.In a recent study, mesenchymal stem cells (MSCs) were generated into cardiomyocytes using a carbon nanotube loaded GelMA hydrogel with effective electromechanical performance. The addition of carbon nanotubes into a photo-cross-linkable GelMA hydrogel is a promising method for increased myocardial tissue engineering.[19]

Gene Transfer Techniques Involving Injectable Hydrogels

Gene therapy provides an ability to improve local restoration of injury prone myocardial tissue, predominantly by enabling the growth of new blood vessels and limiting stiffness. Amplifying or ceasing certain host genes, or plainly overexpressing effectively targeted genes, are all standard strategies for transferring specific therapeutic genes employing injectable hydrogels. A research conducted used a gene delivery platform to boost the biofunctionality of injectable hydrogels. Better mechanical strength, improved the composite hydrogels' network infrastructure, and generated significant biomaterials affinity for ultimate translation to the host tissue The biocompatibility of the formed hydrogel was evaluated, had no cytotoxic or inflammatory effects, as shown by quantitative measurement of proinflammatory tumor necrosis factor.[20]

CONCLUSION

For myocardial tissue engineering, hydrogels represent a relatively powerful class biomaterials. Regulating and controlling cellular fu nctions with hydrogel platforms has become routine. Engineering the heart and producing cardiac tissue replacements in the future wil l need functional hydrogels with responsive qualities. Hydrogels that can replicate the mechanical behavior of heart muscle can be use d to make effective myocardial rejuvenation scaffolds. Because of the dynamic nature of the cardiac region, elastic products are expected to best match the tissue responsiveness. Elastic biomaterials can indeed enable the adaptability and endurance for recurrent expansion and contraction episode. Resistant and flexible hydrogels will therefore contribute to myocardial restoration.

Insulating materials offers unique ability to promote the transfer of electrical inputs during cardiac cell pulsing owing to the electrophysiology of the heart. As a response, there is an expanding necessity for hydrogels biomaterials that can augment the

electrophysiological parameters of myocardial cells within synthetic scaffolds. Hybrid hydrogels will be developed by indulging conductive components into the frameworks to facilitate the process. Oxygen-releasing hydrogels, in combination to elastomeric and electrical hydrogels, are likely to have a profound influence on the formation of biocompatible cardiac structures. It is vital to provide adequate oxygen over a long stretch of time in a steady and coordinated manner in order to build up photorealistic structures of clinically relevant proportions. As an outcome, nanostructured oxygen-releasing hydrogels will support in the minimisation of diffusion barrier and the initiation of vascularized tissue analogues.

Engineering biomaterials with coupled elasticity and conductivity abilities would be very beneficial in the long run. Conducive elastomers are an efficacious next- generation technology for cardiac tissue regeneration. Incorporating microfabrication mechanisms with biomaterial styling to produce additional vascularized cardiac scaffolds with controlled functionalities would be another promising alternative. Another potential future research field is the refinement of modified bioreactors that can carry synchronized electro - mechanical activity to artificial cardiac tissues. Functional hybrid hydrogels are designed to assist us troubleshoot the myocardium following an injury. Implementation of renewable cell sources and comparatively small biomolecules are also vital factors in replicating innate cardiac tissue. Using stem cells as well as bioactive molecules in association with micropatterning strategies to activate cardiogenic differentiation and vascularization workflows will be vital. Pre-vascularized off-the-shelf heart cells will match the prevailing necessities of regenerative programming and open up new pathways for the design of novel tissue alternatives. Hydrogel-based scaffolds with elevated electrical conductivity, flexibility, vasculogenic power, and oxygen enrichment are believed to regulate and modulate cellular functions, leading to the establishment of responsive cardiac cells.

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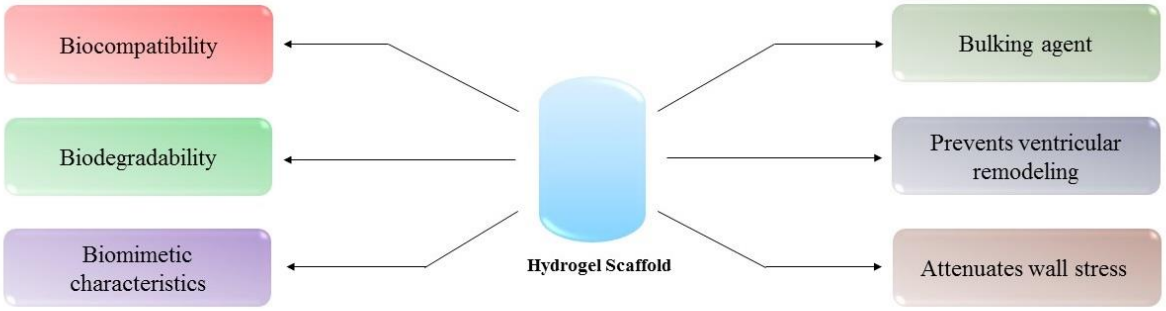

Figure 1. Represents the importance of the hydrogel scaffolds in the cardiac tissue engineering.

Table 1. Product based on hydrogels are available on the market.

PRODUCT	COMPOSITION OF HYDROGEL	INDICATION
SQZ Gel™ oral controlled release system	Chitosan and polyethylene glycol	Hypertension
Cervidil® Vaginal insert	Poly(ethylene oxide) and urethane	Cervical ripening begins and/or continues.
Smart Hydrogel™	Poly(acrylic acid) and poly(oxypropylene- co-oxyethylene) glycol	Ophthalmic, buccal, nasal, vaginal, transdermal, injectable, implantable, and non-aerosol pulmonary medication delivery systems have all been developed using this technology.
Aquamere™	PVP and PVP interpolymers—grafted copolymers with urethane	Topical and oral medicinal therapy, skincare
Aquatrix™ II	Chitosan–PVP	Adhesive gels for the skin, treatments for wounds and burns, implants, and drug carrier matrices
Hypan®	A novel multiblock structure hydrophilic acrylate derivatives	Soft contact lenses and hydrating wound creams and dressings are made with it.