



A Review On Use Of Polymeric Hydrogel For Cartilage Regeneration.

D. Jebasurya, Uppuluri Varuna Naga Venkata Arjun and Shanmugarajan T.S.*

Department of Pharmaceutics, School of Pharmaceutical Sciences, Vels Institute of Science,
Technology & Advanced studies (VISTAS), Pallavaram, Chennai - 600117, India.

Abstract: The therapy for articular cartilage trauma was a major challenge in the medical field. However due to their 3D cross linking capability and tissue mimicking nature, hydrogel played a crucial role in cartilage regeneration. However, when compared to traditional gels, hydrogels have many distinct properties that make them desirable for several biomedical applications. Firstly, the compact size of the hydrogels enables it to pass through the compact needles and catheters, which is useful for minimally invasive cells and biological deliveries in case of cartilage tissue regeneration. Further, the physical interactions among the polymers also lead to shear thinning behavior that enables the solid-like consistency in case of hydrogel scaffolds without the need for chemical modifications. In general, the polymeric hydrogels thus approaching the ideal characteristics must adhere to the site of the application, relieve traumatic signs, facilitate the faster rate of cartilage regeneration and seek to restore the normal daily activities of the preclinical or clinical subjects. Furthermore, in this review addresses past and current efforts with a brief overview of the highlighted properties for cartilage repair applications of hydrogel scaffolds made from both natural and synthetic polymers. We reviewed the multi scale properties of the hydrogel scaffolds such as mechanical properties and porosity. Moreover, this review focuses primarily on illustrating the characteristics of ideal polymeric hydrogels that are compatible with cartilage repair.

Keywords: Hydrogel, Silanized Hydroxypropyl methylCellulose, Gelatin, Alginate, Polycaprolactone, Poly ethylene glycol.

*Corresponding Author

Shanmugarajan T.S.*, Department of Pharmaceutics, School of Pharmaceutical Sciences, Vels Institute of Science, Technology & Advanced studies (VISTAS), Pallavaram, Chennai - 600117, India.



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1. INTRODUCTION

Hydrogels are used as substrates for cartilage regeneration, due to their high water content, diverse properties and resemblance to the native cartilage tissue. Generally, hydrogels were cross linked in continuous volumes with large millimeter scale dimensions that enabled a molecular diffusion. Different processing methods such as physical crosslinking and chemical crosslinking etc. can be used to incorporate a micrometer porosity into the hydrogel scaffold.^{1-2; 16-18} However, when compared to traditional gels, hydrogels have many distinct properties that make them desirable for several biomedical applications. Firstly, the compact size of the hydrogels enables it to pass through the compact needles and catheters, which is useful for minimally invasive cells and biological deliveries in case of cartilage tissue regeneration. Further, the physical interactions among the polymers also lead to shear thinning behavior that enables the solid-like consistency in case of hydrogel scaffolds without the need for chemical modifications. However, interparticulate cross linking methodologies can also be implemented to further modify the properties of the hydrogel scaffolds. Secondly, hydrogels were essentially

flexible 3D cross linked structures of varying sizes and shapes and that can be mixed to produce several diversified materials for different regenerative approaches. Moreover, in the previous studies it was also revealed that both natural and synthetic polymer based hydrogels with various range of shapes and sizes showed excellent consistency with biological encapsulation (e.g. cells and drugs). Thirdly, owing to its excellent porosity in case of previous studies hydrogels had shown excellent rate of cell proliferation and migrations in case of both growth factor loaded and drug loaded hydrogel scaffold for cartilage regeneration.^{3-5; 19-21} In this review we addressed the polymers involved in designing the hydrogels for cartilage regeneration. Next we presented the role of each polymer in the cartilage regeneration. Finally we reviewed the multi scale properties of the hydrogel scaffolds such as mechanical properties and porosity. Moreover, the ultimate aim of this review is to demonstrate the role of several polymer based hydrogels in cartilage tissue regeneration.^{6-9; 22-24} Further in the current study Figure 1. Pharmaceutical and physiological characteristics of hydrogels for cartilage regeneration and Figure 2. Represents role of hydrogel on cartilage defects.

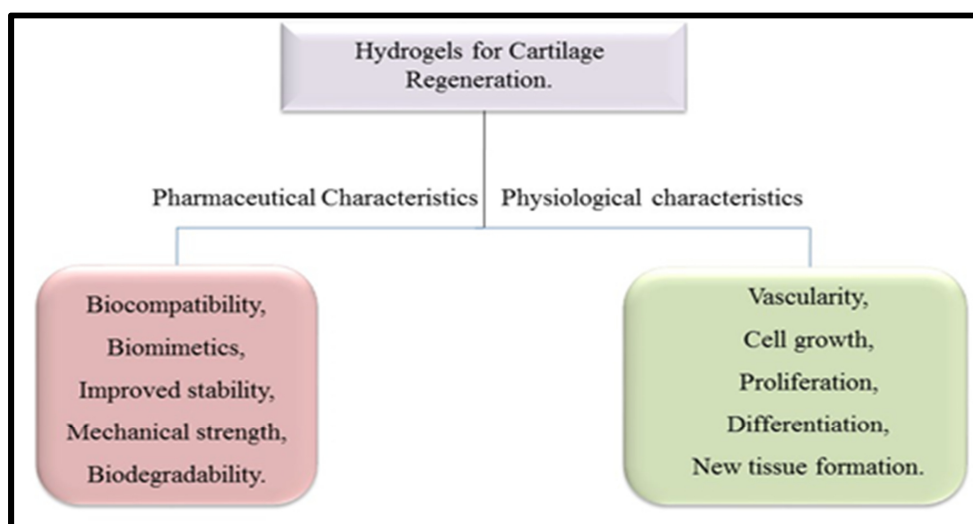


Fig 1. Depicts about Pharmaceutical and physiological characteristics of hydrogels for cartilage regeneration.

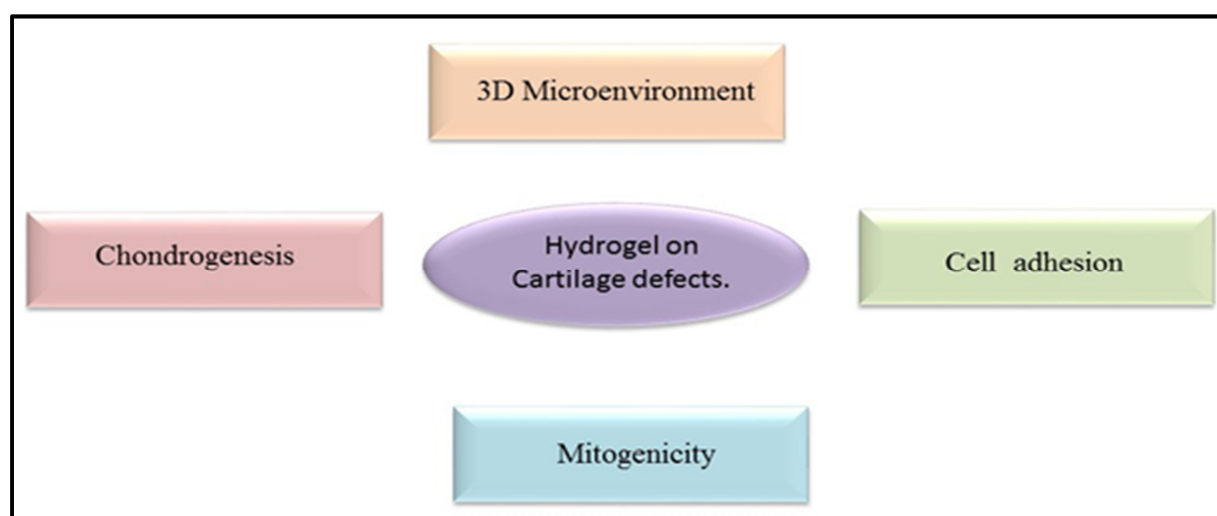


Fig 2. Represents role of hydrogel on cartilage defects.

2. POLYMERS INVOLVED IN FORMULATION OF HYDROGELS MEANT FOR CARTILAGE TISSUE REGENERATION

2.1 Silanized Hydroxypropyl methylCellulose (Si-HPMC)

Various injuries, including traumatic lesions, lead to osteoarthritis, may damage the articular cartilage (AC). There is no effective cure for lesions in the cartilage. New strategies to regenerate AC are being regarded with interest in this regard. In this context, Boyer *et al* intend to develop and characterize a mechanically reinforced injectable, self-hardening hydrogel (Si-HPCH) consisting of silanized hydroxy propyl methyl cellulose (Si-HPMC) mixed with silanized chitosan. The Si-HPCH cytocompatibility in vitro has been tested with human stromal adipose cells (hASC). Initially, they first mixed Si-HPCH with hASC to observe the viability of cells in nude mice subcutis after implantation. Si-HPCH, or not associated with canine ASC (cASC), was then tested for osteochondral defect repair in canine femoral condyles. Further, their data showed Si-HPCH supports the viability of hASC in culture. Besides, Si-HPCH allows the transplantation of hASC into the nude mice subcutis while maintaining its viability and secretory activity. A major osteochondral regeneration was discovered in the canine osteochondral defect model while the empty defects were only partially filled with fibrous tissue, defects filled with Si-HPCH with or without cASC.¹ In his research Buchtova, *et al* demonstrated that Si-HPMC related hydrogels tend to have a highly porous morphology with chemically cross-linked Si-HPMC polymer, comprising just 2 % wt of the polymer. When 3 % wt of silica nanofibers have been applied, a cross-link of the silica nanofibers occurs with the Si-HPMC polymer leading to a hybrid silica-polymer matrix with enhanced mechanical properties. However, Si-HPMC hydrogel encloses two distinct water populations, such as, "hydration" and "bulk like water." Whereas, Hydration vapor, with and without NFs, interacts with the hydrophilic hydrogel matrix. Consequently, its thermodynamic behavior is modified: even at very low temperatures (at least -60°C), hydration water does not display solidification. On the other hand, bulk-like water contained within these hydrogels exhibits a normal transformation of the solid-to-liquid process at temperatures

close to 0°C , and its dynamics at room temperature are very similar to that of bulk water. In Si-HPMC hydrogels, the molecules of bulk-like water can disperse over micrometric distances without being affected by the matrix. These hydrogels thus appear as promising materials for use in tissue engineering for cartilage, intervertebral disks or fibrillated heart, both due to potential micro-invasive surgery and due to sufficiently high water dynamics that are advantageous for the diffusion of nutrients, thus for the viability of cells.² A prerequisite in cartilage engineering is the production of biologically and mechanically competent hydrogels. Rederstorff *et al* recently demonstrated that a marine exopolysaccharide, GY785, is stimulating the in vitro chondrogenesis of stromal adipose cells. Moreover, in this research, it was also hypothesized that enriching the silated hydroxypropyl methylcellulose hydrogel (Si-HPMC) with GY785 may offer new prospects for the production of cartilage regeneration scaffolds. Surface plasmon resonance (SPR) has tested the interaction properties of GY785 with growth factors. MTS test, cell counting, and qRT-PCR assessed in vitro the biocompatibility of Si-HPMC / GY785 against rabbit articular chondrocytes (RACs) and their ability to maintain and recover a chondrocyte phenotype. Finally, the assessed potential of Si-HPMC / GY785 associated with RACs for the development of cartilaginous tissue in vivo via transplantation into nude mice subcutis for 3 weeks. Moreover, the SPR data showed that GY785 was able to interact physically with BMP-2 and TGF β . Further this study also showed that, when compared to Si-HPMC alone, three-dimensionally (3D)-cultured RACs in Si-HPMC/GY785 strongly expressed type II collagen (COL2) and aggrecan transcript. Besides, RACs also developed large quantities of glycosaminoglycans (GAG) and COL2-containing extracellular matrices (ECM). When dedifferentiated RACs in Si-HPMC/GY785 were substituted in 3D, the COL2 and aggrecan transcript expressions were recovered and that of type I collagen decreased. The immunohistological study of Si-HPMC/GY785 constructs transplanted into nude mice revealed the manufacture of a cartilage-like extracellular matrix (ECM) containing high GAG and COL2 levels.³ Table I. Represents the role of Silanized Hydroxypropyl methylCellulose (Si-HPMC) in Cartilage regeneration.

Table I. Represents the role of Silanized Hydroxy propyl methyl Cellulose (Si-HPMC) in the hydrogels meant for Cartilage regeneration.

Sl.No	Author	Polymer	Application	Reference
1.	Boyer <i>et al</i>	Si-HPMC	Exhibits ideal mechanical properties in the developed hydrogels.	1
2.	Buchtova, <i>et al</i>	Si-HPMC	Demonstrates highly porous morphology in case of 3D crosslinked hydrogels.	2
3.	Rederstorff <i>et al</i>	Si-HPMC	Develops cartilage-like extracellular matrix (ECM) containing high GAG and COL2 levels.	3

2.2. Gelatin

Reconstruction in plastic surgery of segmental costal cartilage defects that result from autologous cartilage grafts remains a problem. Moreover, in his research, Dai *et al* developed a bioinspired, multifunctional hydrogel SGII / H-AND for the reconstruction of costal cartilage defects, which had components identical to the hyaline cartilage matrix, such as collagen and HA. A chemical-curing, forming and light-curing gelation system, including an SGII/PEG-4SS amide condensation reaction and a HAMA photo-initiated free-radical polymerization reaction, was developed to balance

the SGII/H-AND hydrogel's operability and mechanical properties. The first network's chemical crosslinking with a delayed gelation time of 5 ~ 7 min ensured tailored and adaptable filling of defects that was highly appropriate for repairing grafting defects. The subsequent implementation of light-curing for the construction of the second network increased the hydrogel's mechanical strength to 11 MPa (near the natural resistance of the costal cartilage) for long-term repairs. Biologically, the hydrogel SGII / H-AND displayed dual immunomodulatory activity on the neutrophils and macrophages proinflammatory/anti-inflammatory phenotypes. The hydrogel could sustain a well-improved and

chondrogenic microenvironment, with lower levels of pro-inflammatory factors and increased levels of anti-inflammatory factors and pro chondrogenic cytokines. Eventually, the SGII / HA-DN hydrogel may up regulate the level of expression of chondrogenic genes and cartilage matrix and down regulate the rates of dedifferentiation genes and proteins through direct stimulation and the M2 macrophage / TGF- β /Smad pathway. Eventually, the segmental costal cartilage defect rabbit model achieved adequate regeneration. With the combination of ease of action, excellent mechanical properties, and functionality, it was concluded that novel SGII / HA-DN hydrogel will be a valuable tool for the reconstruction of costal cartilage by defect-site and could be a promising method of replacing autogenous/xenogenous tissue grafts in the clinical setting.⁴ Chondroprogenitor cells encapsulated in a three-dimensional, chondrogen supporting hydrogel scaffold represent a promising, regenerative approach to restoring articular cartilage. In this research, Hang *et al* produced an injectable, biodegradable methacrylated gelatin (mGL)-based hydrogel that is capable of rapid gelation through visible light (VL)-activated air or aqueous solution crosslinking. The mild conditions of photo cross-linking allowed the cells to be integrated during the gelation cycle. Encapsulated mesenchymal stem cells (hBMSCs) derived from the human-bone marrow demonstrated high, long-term viability (up to 90 days) throughout the scaffold. To determine the applicability of the mGL hydrogel to cartilage tissue engineering, hang *et al* assessed the effectiveness of encapsulated hBMSC chondrogenesis using agarose-seeded hBMSCs as control. Moreover, the in-vitro cartilage repair model was used to further examine the ability of hBMSC-laden mGL constructs to integrate with host tissues after implantation. The findings showed that the mGL hydrogel, which may be photopolymerized in air and aqueous solution, supports the growth of hBMSC and chondrogenesis induced by TGF- β 3. MGL constructs laden with hBMSCs are mechanically stronger over time relative to agarose, and combine well with native cartilage tissue upon implantation based on mechanical push-out testing. Therefore, the VL-photo cross linked mGL scaffold represents a promising scaffold for the repair and resurfacing of articular cartilage defects dependent on cells.⁵ According to Bogdan *et al*, given their injectability and ability to fill defects with irregular shapes, hydrogels (HGs) are desirable matrices for the regeneration of cell-based cartilage tissues. Nevertheless, most HGs produced to date still lack macroporosity of the cell scale, which restrains the encapsulated cells, resulting in delayed new deposition of the extracellular matrix restricted to pericellular regions. Besides, tissue-engineered cartilage using traditional HGs typically suffers from poor mechanical integrity and fails to recover articular cartilage's load-bearing properties. The purpose of this study was to evaluate the potential of macroporous gelatin-based microribbon (μ RB) HGs in 3D with improved mechanical properties as novel 3D matrices for accelerating chondrogenesis and new formation of cartilage by human mesenchymal stem cells (MSCs). These μ RB HGs, unlike conventional HGs, are inherently macroporous and exhibit cartilage-mimicking mechanical properties which absorb shock. After 21 days of cultivation, MSC-seeded μ RB scaffolds display a 20-fold increase in the compressive module to 225 kPa, a range approaching native cartilage level. By comparison, HGs resulted only in a modest increase of 65 kPa compressive modulus. Macroporous μ RB

scaffolds significantly increased the total amount of neocartilage provided by MSCs in 3D, with improved interconnectivity and mechanical strength compared with traditional HGs.⁶ Chondrocyte-loaded hydrogel bioprinting enables the manufacture of constructs with controlled structure and form e.g. articular cartilage implants. A promising bio-ink is the gelatin-methacryloyl (gelMA) combined with gellan gum. The rheological properties governing the printing process, however, and the effect of gellan gum on the mechanical properties and the blend's chondrogenesis are still uncertain. Here Vivian *et al* examined the suitability of gelMA / gellan for bioprinting cartilage. Several concentrations, ranging from 3-25 percent gelMA with 0-1,5 percent gellan gum, were assessed for their printability, defined as the ability to form filaments and integrate cells at 15-37 ° C. To help the assessment of the printability, the hydrogels were assessed to yield stress and viscosity. The rigidity of UV-cured constructs, as well as the development of cartilage-like tissue by embedded chondrocytes, were determined in vitro. A wide range of gelMA / gellan concentrations was printable with cell inclusion and formed the bio printing window. The addition of gellan gum enhanced deposition of filaments by inducing yielding behavior increased build stiffness and chondrogenesis. Nevertheless, high concentrations of gellan gum have impaired the production and distribution of cartilage matrixes, and even higher concentrations have resulted in excessive yield stresses allowing for cell encapsulation. This study shows the high potential of gelMA / gellan blends for cartilage bio printing and recognizes yield stress as the dominant factor for bioprintability.⁷ Emily *et al* developed cross-linkable hydrogels entirely derived from ECM, native cartilage. Next, the cartilage was solubilized and then methacrylated to form photocrosslinkable gels. Compared to traditional GelMA hydrogels, these MeSDCC gels supported rBMSC development, ECM production, caused significant up regulation of chondrogenic genes 1 day after crosslinking, and surprisingly, the mechanics of the MeSDCC gels were characteristically similar to those of native porcine cartilage until their failure. MeSDCC concentration has been found to affect chondroinduction and mechanical properties where the 20 %MeSDCC gels are superior in mechanical efficiency and encourage ECM synthesis whereas the 10 %MeSDCC gels are superior in chondroinduction. Clinically, such findings could potentially result in a surgeon being able to inject the MeSDCC paste into a cartilage defect where the treatment could be done as a source for stem cells in combination with micro fracture. The materials could then be cross linked into a gel with sufficient strength to enable the patient to follow the treatment, where both the MeSDCC materials and the biomechanical stimulation obtained by the cells from walking would result in chondrogenesis. Future work will, therefore, tackle the enhancement of mechanisms for fractures, and in vivo chondrogenesis and immune function. Also, it will be important to consider in future work the ability of these materials to support the zonal organization through in vivo biomechanical stimulation, as well as their ability to promote superficial zone lubrication. Overall, it was shown that MeSDCC can prove to be a promising biomaterial for application in cartilage tissue engineering.⁸ Table 2. Represents the role of gelatin and alginate in the hydrogels meant for cartilage regeneration.

Table 2. Represents the role of gelatin and alginate in the hydrogels meant for Cartilage regeneration.

Sl.No	Author	Polymer	Application	Reference
1.	Dai <i>et al</i>	Gelatin	Enhanced mechanical strength so that hydrogel could sustain a well-improved and chondrogenic microenvironment with increased levels of anti-inflammatory factors.	4
2.	Hang <i>et al</i>	Gelatin	Developed long-term viability in case of encapsulated mesenchymal stem cells (hBMSCs) derived from the human-bone marrow.	5
3.	Bogdan <i>et al</i>	Gelatin	Significantly increased the total amount of neocartilage provided by MSCs in 3D, with improved interconnectivity and mechanical strength.	6
4.	Vivian <i>et al</i>	Gelatin	Enhanced deposition of filaments by inducing yielding behavior increased build stiffness and chondrogenesis.	7
5.	Emily <i>et al</i>	Gelatin	Enhanced ECM production, caused significant upregulation of chondrogenic genes	8
6.	Rami <i>et al</i>	Alginate	Acts as a biomimetic biomaterial for cartilage, which induces cell proliferation while retaining the encapsulated chondrogenic phenotype.	9

2.3. Alginate

During monolayer expansion, the loss of expression of chondrogenic markers remains a stumbling block for cell-based treatment of cartilage lesions. Here Rami *et al* introduced sulfated alginate hydrogels as a biomimetic biomaterial for cartilage, which induces cell proliferation while retaining the encapsulated chondrogenic phenotype. Alginate hydroxyl groups were converted to sulfates by incubation with the sulfur trioxide – pyridine complex (SO₃/pyridine), resulting in a sulfated substance that can be cross-linked with calcium chloride. Passage 3 bovine chondrocytes were encapsulated for up to 35 days in hydrogels of alginate and alginate sulfate. For alginate sulfate, cell proliferation was five-fold greater than in alginate ($p=0.038$). Blocking beta1 integrins within alginate sulfate hydrogels in chondrocytes significantly inhibited proliferation ($p=0.002$). Compared with unmodified alginate, sulfated alginate increased chondrocyte RhoA activity, an improvement blocked by $\beta 1$ blocking antibodies ($p=0.017$). Type II collagen, type I collagen, and proteoglycan expression and synthesis were not significantly affected by the encapsulation content shown by a quantitative reverse transcription-polymerase chain reaction (qRT-PCR) and immunohistochemistry. In culture, alginate sulfate structures displayed an opaque presence, while the unmodified alginate samples remained translucent.⁹

2.4. Polycaprolactone (PCL)

Cartilage is a semi-solid, resilient and smooth connective tissue, and its repair is almost impossible upon the damage or occurs with a very slow process of recovery. Polycaprolactone (PCL), used as a biocompatible polymer, retains all necessary mechanical properties, except due to its hydrophobicity, ideal for cell adhesion. To solve this problem, Pourbashir *et al* tried to introduce suitable semi-IPNs into the device to recover its hydrophilicity base by enhancing the hydrophilic polymer. In this research PCL-PAA-CNW, semi-IPNs were prepared for use for the synthesis of artificial cartilage. The PCL solution distributed CNWs which were isolated from cellulose microfibrils by acid hydrolysis with length and diameter of approximately 100 and 10 nm, respectively. AA was crosslinking in the presence of a CNW suspension in the PCL solution in DMF via a novel acrylic-urethane crosslinker. The AA, CNW, AIBN, and MS concentrations were constructed using the Taguchi process. The maximum amount of monomer was around 46 percent based on the results. Incorporating the

optimal volume of CNW, which was 0.5 percent, improved the artificial cartilage's mechanical properties. The synthesized cartilage was correlated with adequate water content (higher than 26%) and ideal biocompatibility (100%). The results of the contact angle indicated that the semi-IPN nanocomposites become more hydrophilic by increasing the concentration of monomers and CNWs. Therefore the improved hydrophobicity of the PCL provided an acceptable characteristic of cell adhesion. The findings of this study suggest that PCL-PAA-CNW semi-IPNs are good candidates for use in cartilage regeneration.¹⁰ Articular cartilage is a lack of vascular distribution in nature. Once the cartilage is broken or sick it cannot heal on its own. Surgical therapies do not fully cure articular cartilage defects. The most possible solution to this problem is tissue engineering. In this analysis, Hsieh *et al* demonstrated that methoxy poly (ethylene glycol)-block-poly(γ -caprolactone) (mPEG-PCL) and hydroxyapatite were mixed by layer to form a solid scaffold at a weight ratio of 2:1 through fused deposition modeling (FDM). The scaffolds were further infiltrated with hyaluronic acid loading of glycidyl methacrylate with 10 ng/mL of Transforming Growth Factor- $\beta 1$ and a photo cross-linked on top of the scaffold. For 12 months, an *in vivo* study was conducted on Lanyu miniature pigs' knees. PC tomography (CT) accompanied the healing process of osteochondral defects. The defect was fully covered in the control pig with regenerated tissues, whereas in the experimental pig's knee defect different tissues were grown. The scaffold stayed in the subchondral position in the gross anatomy of the cross-section, while the surface cartilage was regenerated. Hematoxylin and eosin staining were applied to the cross-section of the knees of both the control and experimental pigs. The knee cartilage in the experimental pig was partly matured, e.g. the lacunae produced few chondrocyte cells. The deficiency had been entirely grown with fibrocartilage in the control pig's knee. The combination of the TGF- $\beta 1$ -charged hydrogel and scaffolds has been found to regenerate hyaline cartilage in another *in vivo* experiment in a rabbit and a pig. However, the healing process can be disrupted by scaffolds which remain in the subchondral lesion. The structural architecture of the scaffold should, therefore, be reconsidered to suit both the cartilage and subchondral bone regeneration processes.¹¹ In his research, Stichler *et al* explore the use of allyl-functionalized poly(glycidol)s (P(AGE-co-G)) as a cytocompatible cross-linker for thiol-functionalized hyaluronic acid (HA-SH) and the optimization of this hybrid hydrogel as a bioink for 3D bioprinting. A UV-induced radical thiol-ene coupling between the thiol and allyl groups accomplished the chemical cross-

linking of gels with a total polymer concentration of 10 wt. percent. Adding unmodified high molecular weight HA (1.36 MDa) allowed tuning of the rheology for extrusion-based bioprinting. The introduction of additional HA resulted in hydrogels with a lower Young's modulus and a higher swelling ratio, particularly in the first 24 h, but after 24 h a comparable swelling of the equilibrium for all gels. The integration of human and equine mesenchymal stem cells (MSCs) into the gels and subsequent in vitro culture

demonstrated positive chondrogenic differentiation after 21 d for cells of both origins. Besides, cells could be imprinted with these gels, and hMSCs embedded showed good cell survival in culture for at least 21 d. To obtain mechanically stable and robust constructs for the intended use in articular cartilage, the formulations were modified for double printing with thermoplastic poly(γ -caprolactone) (PCL).¹² Table 3. Represents the role of polycaprolactone in hydrogels meant for cartilage regeneration.

Table 3. Represents the role of polycaprolactone in hydrogels meant for cartilage regeneration.

Sl.No	Author	Polymer	Application	Reference
1.	Pourbashir <i>et al</i>	Polycaprolactone	Improved the artificial cartilage's mechanical properties with adequate water content and ideal biocompatibility.	10
2.	Hsieh <i>et al</i>	Polycaprolactone	Exhibits ideal tensile strength and biocompatibility.	11
3.	Stichler <i>et al</i>	Polycaprolactone	Demonstrates ideal thermoplastic nature in th	12

2.5. Poly ethylene glycol

Osteoarthritis (OA) is a painful joint disorder that is caused by chronic joint inflammation and deterioration of the articular cartilage. Platelet-rich plasma (PRP) intraarticular administration is a promising biologic treatment for OA. Moreover, bolus' immediate release of growth factors limits the beneficial therapeutic effects of PRP and therefore necessitates the need for continuous platforms for release. The therapeutic effect of PRP released from a polyethylene glycol (PEG) hydrogel on articular chondrocytes / cartilage explants isolated from OA patients was demonstrated in this study by Jain *et al*. Therefore, the hydrogel properties were slightly influenced by the PRGF encapsulation in 10 per cent w / v PEG hydrogels. In addition, the analysis on Chondrocyte proliferation (pico-assay), gene expression for COL1A1, COL2A1, MMP13, COX2, and NFKB1 (real-polymerase chain reaction) and nitric oxide measurement (Griess ' assay) further substantiated the effect of PRGF releases and PRGF bolus (1% w / v PRGF) on explants or chondrocytes in patients. Similar to the PRGF bolus, PRGF promotes increased proliferation of chondrocytes, suppresses gene expression such as MMP13, NFKB1, COL1A1, and COL2A1, and decreases nitric oxide levels.¹³ Glucosamine (GA) was an important precursor of the cartilage matrix for glycosaminoglycan biochemical synthesis and has a positive effect on cartilage regeneration, especially in osteoarthritis. Hence this was not widely used in cartilage repair scaffolds as a bioactive material. In this study, Yao *et al* synthesized modified polyethylene glycol (PEG) hydrogel with glucosamine and then encapsulated mesenchymal human bone stem cells (hBMSCs) into the hydrogel to induce the differentiation of hBMSCs into three-dimensional chondrocyte culture. HBMSC chondrogenesis was promoted by the GA-modified PEG hydrogels, especially in concentrations of 5mM and 10 mM. The subcutaneous transplantation of 10 mM GA-modified hydrogels within vivo cartilage-like blocks developed by hBMSCs for 8 weeks. Importantly, with an increase in glucosamine the modified

hydrogels down-regulated the protein-level fibrosis and hypertrophic cartilage markers. Consequently, glucosamine-modified PEG hydrogels allowed hBMSC chondrogenesis, which could represent a new type of cartilage repair using a tissue-engineering technique.¹⁴ According to Chang *et al* Tissue engineering can surmount tracheal reconstruction limitations. Auricular chondrocytes were encapsulated in a photocurable poly (ethylene glycol)/poly(γ -caprolactone) (PEG / PCL) hydrogel to tissue engineer tracheal cartilage. After 2 weeks of in vitro culture in the PEG/PCL hydrogel, chondrogenic genes, including Sox9, Acan, and Col2a1, were up-regulated in auricular chondrocytes. Co-cultivation of 70 percent auricular chondrocytes and 30% mesenchymal stem cells (BMSCs) of the bone marrow increased the expression of chondrogenic genes in the hydrogel PEG / PCL. After 4 weeks of in vitro cultivation, cartilaginous matrix markers including proteoglycans and type II collagen were detected in the chondrocyte-encapsulated PEG / PCL hydrogel. In the PEG / PCL hydrogel, the higher expression level of cartilaginous matrix markers was observed with co-cultivation of 70 percent chondrocytes and 30 percent BMSC. The cylindrical PEG / PCL structure was maintained with the use of a luminal silicone stent after 4 weeks of ectopic cultivation in rabbits. Nevertheless, the build collapsed under a compressive force without the stent. After 4 weeks of ectopic cultivation, no fibrosis or vessel ingrowth was found in the PEG/PCL hydrogel, whereas the auricular chondrocytes showed accumulation of proteoglycans and type II production of collagen. Rabbit auricular chondrocytes may live under both in vitro and in vivo conditions, and maintain chondrogenic capacity in the PEG/PCL hydrogel. While the PEG / PCL hydrogel did not show adequate mechanical properties to maintain the construct's cylindrical shape, the high chondrogenesis level of chondrocytes in the PEG / PCL hydrogel demonstrated this material's potential for tracheal tissue engineering.¹⁵ Table 4. Represents the role of polyethylene glycol in hydrogels meant for cartilage regeneration.

Table 4. Represents the role of polyethylene glycol in hydrogels meant for cartilage regeneration.

Sl.No	Author	Polymer	Application	Reference
1.	Jain <i>et al</i>	Polyethylene glycol	Enhances the proliferation of chondrocytes.	13
2.	Yao <i>et al</i>	Polyethylene glycol	Facilitates the mesenchymal human bone stem cells chondrogenesis.	14
3.	chang <i>et al</i>	Polyethylene glycol	Exhibits the high chondrogenesis level of chondrocytes	15

3. CONCLUSION

The most recent development of the use of polymeric hydrogel for cartilage regeneration was recollected and outlined in the current review. However, the polymeric hydrogels thus approaching the ideal characteristics must adhere to the site of the application, relieve traumatic signs, facilitate the faster rate of cartilage regeneration and seek to restore the normal daily activities of the preclinical or clinical subjects. Moreover, the current review also highlights the need for a more rational approach to cartilage repair, so that the anatomical and biochemical characteristics of the cartilage were taken into consideration when choosing the optimal hydrogels for cartilage regeneration.

4. ACKNOWLEDGMENTS

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5. AUTHORS CONTRIBUTION STATEMENT

Conceptualization, writing was done by Shanmugarajan T.S. and Uppuluri Varuna Naga Venkata Arjun whereas, review and editing were done by Shanmugarajan T.S., Jebasurya D. and Uppuluri Varuna Naga Venkata Arjun. In general, all the authors had agreed to the publishing this review article in International journal of Life Science and Pharma Research.

6. CONFLICTING INTEREST

The authors report no conflicts of interest.

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