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Original Research Paper

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GELATIN METHACRYLOYL HYDROGEL (GELMA) IN DENTISTRY: A NARRATIVE REVIEW

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ABSTRACT Gelatin methacrylate (GelMA) has gained significant attention in dentistry as a versatile biomaterial with broad applications in tissue engineering and regenerative therapies. This review explores the role of GelMA in dental applications, emphasizing its unique properties such as biocompatibility, tunable mechanical characteristics, and photocrosslinkability. GelMA serves as an ideal scaffold for the regeneration of dental tissues, including dental pulp, periodontal ligaments, and alveolar bone, promoting cell adhesion, proliferation, and differentiation. The material's ability to be functionalized with bioactive molecules further enhances its regenerative potential. Additionally, its application in 3D bioprinting and drug delivery systems holds promise for creating patient-specific treatments and improving outcomes in conditions like periodontitis and pulpitis. This review also addresses the future perspectives in highlight on the opportunities for advancing GelMa hydrogels as innovative materials in modern dentistry. Overall, GelMA represents a promising biomaterial in the field of dentistry, with ongoing research focusing on overcoming current limitations and expanding its clinical applications.

KEYWORDS : Gelatin Methacrylate, Biocompatible material, Hydrogel, Tissue regeneration, Photocrossslinking

INTRODUCTION

One of the most often used media for the three-dimensional (3D) culture of mammalian cells is hydrogel. In dental science research hydrogels have a broad range of uses, from treating oral disorders to restoring lost tissues. These are amphiphilic polymer networks with a high fluid absorption capacity that maintain structural integrity. They can be produced in situ via chemical or physical cross-linking. In oral therapeutic applications, hydrogels demonstrate exceptional antibacterial capabilities. In the first place, they physically distinguish pathogens, stopping them from invading and spreading. Second, hydrogels work well as drug release vehicles, making it easier to distribute different antimicrobial compounds and get the desired results (1). Its distinct properties in structure and function set it apart from other biological materials. Because of the high moisture content, the hydrogel's polymer network can bind water, which in turn exhibits good biocompatibility (2). Drug delivery and tissue regeneration are two areas in which hydrogel excels since it is a biocompatible substance with easy shape adaptability. Hydrogels typically have a porous structure because of their internal network, which creates a large number of microscopic holes and pores. By altering the setting and preparation procedure during gel synthesis, it is possible to change the size and shape of these holes and voids. It is feasible to match the structure of the pores with the surrounding tissues by controlling their structure, which encourages cell attachment and proliferation (3).

Oral health is seen as an essential element of overall health and quality of life. Oral disease continues to be a significant public health issue in developed countries and a growing burden in developing nations (4). Periodontitis, caries, pulp necrosis, oral mucositis, and other common oral disorders are among them. Recent years have seen a significant development in the field of oral science research, with hydrogels emerging as a focal point. To exert biological effects precisely and effectively, various hydrogels ranging from natural ones, and synthetic ones to composite hydrogels are being studied (5).The arginylglycylaspartic acid (RGD) peptide sequence and the matrix metalloproteinase (MMP) degradable motifs found in gelatin are both advantageous for cellular proliferation and regulate the enzymatic destruction of cells, respectively (6).

Van den Bulcke *et al*. created GelMA(gelatin methacryloyl) in 2000 to advance research on gelatin. GelMA, also known as photo-cross linkable gelatin, has a great deal of biocompatibility, biodegradability, and moldability, which makes it a popular choice for biomedical applications (6). GelMA is a typical semi-synthetic hydrogel, which enables the exploitation of the biological signals inbuilt in the gelatin molecule, while allowing control of mechanical properties. Under UV light, GelMA can generate three-dimensional (3D) structures through photocrosslinking in the presence of a photoinitiator. The crosslinked GelMA with excellent and controllable mechanical properties could meet the requirements for scaffolds under variety of conditions (7). This narrative review article aims to provide a concise view on structure, the status of biomedical applications and future scope of GelMA hydrogels in dentistry.

Architecture Of Gelatin Methacryloyl

As a gelatin derivative containing many methacrylamide groups and few methacrylate groups, GelMA undergoes photoinitiated radical polymerization to produce covalently crosslinked hydrogels. Due to its easy and controllable fabrications, it is largely used in biomedical applications with semi-industrial management (20). Figure (1) summarizes the GelMA modification route as described previously (6). The illustration demonstrates how unsaturated boundaries were grafted onto gelatin by a straightforward one-step procedure that transformed an anhydride into an amino and hydroxyl group. Because gelatin contains eighteen different kinds of amino acids, it is difficult to determine the amount of methacryloyl that has been substituted. Nevertheless, a number of methods have been developed to quantify this amount in order to further control the mechanical properties and morphology of the GelMA hydrogels (7). One strategy to determine the amount of methacryloyl that has been substituted is to use, ^{1}H NMR (Proton nuclear magnetic resonance) to evaluate the change in the lysine amino group after the reaction. However, this method only calculates the methacrylamide groups during grafting, including amidation of the amino group and esterification of the hydroxyl group. This suggests an underestimation of gelatin methacryloyl substitution. Other methods can estimate total methacryloyl substitution but cannot distinguish between methacrylamide and methacrylate groups (8). Southan et al. carried out 2D NMR (Nuclear magnetic resonance) studies to obtain detailed information on the signals found in the ^{1}H NMR spectrum. Methacrylamide from the methacrylate groups and unbound contaminants such methacrylic acid could be discovered using this technique. This quantification technique made it possible to precisely manage GelMA substitution, further altering hydrogel properties to meet the needs of scaffolds in bone regeneration (9).

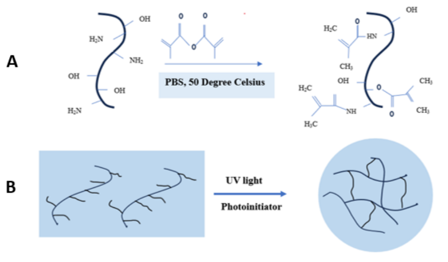

Figure 1: Synthesis of methacrylated gelatin. Gelatin macromers consisting primary amino groups were reacted with methacrylic anhydride (MA) to add methacrylate pendant groups (A). To produce a hydrogel network, the methacrylated gelatin (GelMA) was crosslinked using UV irradiation in the presence of a photoinitiator (B).
Source: Redrawn taking reference from Bulcke *et al* (6)

Uses Of Gelma Hydrogel In Oral Cavity

1. Use of GelMA Hydrogels for regeneration of dental pulp

The innermost cavity of the tooth contains the dental pulp, also known as the endodontium. Pulp tissue is mostly made up of odontoblasts, which are positioned on the pulp's outer periphery and are responsible for producing dentin, as well as it hosts nerves, blood vessels, lymphatic and connective tissues. The preservation of blood flow and homeostasis, sensory transmission, and dentin regeneration are all dependent on dental pulp (10). The pulp-dentin complex is essential for immunological defence, sensory system function, and regeneration. The permanent damage of the dental pulp can result from dental caries, trauma, and developmental abnormalities (11). After conventional root canal treatment due to pulp necrosis and irreversible pulpitis, the pulpless teeth lose their natural biological defense, which may raise the risk of serious caries, apical periodontitis, and ultimately tooth loss. Therefore, it is crucial to regenerate the dentin- pulp complex in order to prolong the life of teeth without pulp and to restore the biological function of teeth (12).

Murray *et al.* originally suggested pulp regeneration, commonly referred to as regenerative endodontic treatment, in 2007. The goal of this optimal type of regenerative therapy is to replace unhealthy or necrotic pulp tissue with vital, healthy pulp tissue (11). Studies on pulp regeneration mainly take histoengineering principles and means to initiate differentiation of pulp–dentin complex through stem cells–scaffold growth factor complexes, so as to repair damaged pulp tissue and restore physiological function (5). Biomaterial scaffolds play a crucial role in pulp regeneration by giving a 3D scaffold for stem cell adhesion, migration, proliferation, differentiation and function (13). Hydrogel-based pulp regeneration has been demonstrated and validated by developmental and molecular biology, as well as biomimetic concepts and histological techniques (14). UV light-crosslinked GelMA hydrogel has been used to create tissue-engineered pre-vascularized dental pulp-like structure. GelMA is widely used synthetic hydrogel for endodontic regeneration, especially when modified with bioactive molecules. When GelMA hydrogels are encapsulated with hDPSCs (Human dental pulp stem cells) and human umbilical vein endothelial cells (HUVECs), they facilitate the adhesion, proliferation and differentiation of host cells and promote the establishment of well-organized pulp like tissue and neovasculature (15). Additionally, research has demonstrated that HyStem-C, an injectable composite hydrogel made of gelatin, hyaluronic acid and polyethylene glycol diacrylate, exhibited good compatibility with DPSCs (16). Dental tissue engineering is anticipated to be the best biological solution in endodontic medicine and the use of growth factors and hydrogel scaffolds enhances this process (14). In the field of pulp engineering, only a small number of hydrogels with particular components have been studied in vivo and no clinical research report has been made thus far. Additionally, comparative studies of various hydrogels are still lacking and more research is needed to advance our understanding of pulp tissue.

2. Use of GelMA Hydrogels for regeneration of Periodontal Tissue

Periodontal disease is a complex ailment wherein pathogenic bacteria trigger the immune system of the host, resulting in the degeneration of the tissues that surround and support the teeth, including the cementum, gingiva, and periodontal ligament (17). Superficial gum inflammation gives way to deeper gum inflammation, which creates a periodontal pocket of bacteria that consumes away at the teeth's supporting ligaments until the teeth fall out. While gingivitis can be reversed with better dental hygiene practices, not receiving treatment at proper time can, lead to periodontitis, characterized by the breakdown of collagen fibres, resorption of alveolar bone, and the creation of soft tissue pockets between the gingiva and tooth root. This condition can develop into severe periodontitis if still left untreated, which can lead to loose teeth, difficulty chewing, and eventually tooth loss (18). In the past, periodontal tissue damage and inflammation have been effectively cured by mechanical debridement and flap surgery that intended to remove plaque .While these treatments reduce symptoms and stop the disease from getting worse, they cannot replace all the tissues that have been lost, including the periodontal ligament, so patients still have cosmetic and functional consequences remaining (19). The ideal goal of treatment for periodontal regeneration is to reconstruct the morphology and function of the injured periodontal tissue, although this is still a difficult task. Restoring periodontal tissue destroyed by inflammation is now mostly accomplished with a variety of scaffold materials that have been developed in recent years to encourage the creation of alveolar bone. The best biomaterials are those that can draw in functional cells linked to regeneration, encourage their growth and differentiation, and help create new periodontal tissues (20). The materials comprise of membranes, sponges, fibres, hydrogels, and 3D-printed scaffolds. Particularly when it comes to sustained drug administration and tissue mimicking, hydrogels are superior to other types of scaffolds in a number of ways. While several hydrogel types can be employed for the regeneration of dentoalveolar tissue, effective methods are frequently needed for their modification or combination (21).

Natural hydrogels have a structure similar to that of native tissues, are biocompatible, bioactive, and exhibit minimal cytotoxicity. However, hydrogels have weak mechanical characteristics and exhibit compositional fluctuation from batch to batch, which makes it difficult to fine tune the material's properties. Conversely, synthetic hydrogels like polyvinyl alcohol (PVA), polyethylene glycol (PEG), polyacrylic acid (PAA), or polyacrylamide (PAAM) don't have these drawbacks, but they also don't have the endogenous components needed to encourage cell behavior like migration, proliferation and differentiation (22).

GelMA, a photosensitive hydrogel biomaterial that is photosensitive, has garnered interest as a scaffold designed to replicate the three-dimensional cell microenvironment. In order to encourage bone repair, Pan *et al.* studied periodontal ligament stem cells encapsulated in GelMA hydrogels. They assessed the impact of GelMA hydrogel containing embedded human PDLSC(Periodontal ligament stem cells) both in vitro and in vivo and when the hydrogels were applied to rat alveolar defects, they saw increased PDLSC proliferation and differentiation as well as the production of new bone (23). Bioprinting has been utilized to regenerate periodontal tissue using a mix of GelMA and polyethylene glycol (PEG). Ma *et al* in their study combined gelatin methacrylate (GelMA) and poly ethylene glycol dimethacrylate (PEGDA) to create injectable, photocross linkable composite hydrogels that included periodontal ligament stem cells (PDLSCs). GelMA/PEGDA hydrogels loaded with PDLSC and of different composition were effectively created using a 3D bioprinting platform by adjusting the GelMA to PEGDA volume ratio. Due to its superior in vitro osteogenic differentiation capability, the 4/1 GelMA/PEGDA composite hydrogel was chosen. Ultimately, an in vivo investigation revealed that, when compared to hydrogel alone and saline ones, the defects treated with the PDLSC loaded hydrogel had a maximal and strong new bone growth. The method established was helpful in understanding 3D cell-ECM(Extra cellular matrix) interaction and opening the door for functional tissue regeneration (24).

3. Use of GelMA Hydrogels for Drug Delivery in Oral cavity

For the complete and effective treatment of oral disorders, an appropriate drug delivery system (DDS) shows to be a potent therapeutic tool. This requires biomaterials with exceptional performance as drug-delivery platforms (25). While oral sprays and lozenges, which are considered conventional oral drug delivery systems, because of their short half-lives and instability in saliva, are effective in delivering active medications topically and there are controversies regarding them. The only way to effectively control an infection is to maintain a long-term and stable medication concentration in the infected zone (26). A great deal of research has been done recently to modify the pore size, swelling, degradability, stimulus-response characteristics and other characteristics of hydrogels in order to better tailor them to the intricate oral and maxillofacial milieu. Many studies have attempted to load drugs, cytokines, and stem cells into hydrogels for use as drug delivery carriers in the oral and maxillofacial regions for tissue regeneration, antibacterial, and anticancer applications (21). The bulk structure of hydrogels can be adjusted to produce a variety of therapeutic features. Drugs can be shielded from hazardous environments by crosslinked hydrogel networks, such as from enzymes and low stomach pH. Hydrogels provide site specific distribution by employing basic physiological alterations and offer a platform for preserving the therapies through the GI (Gastro intestinal tract) tract's complicated environment. The main obstacles to the oral delivery of medicines, especially protein and peptide medications, are as follows: (i) inactivation in the GI tract as a result of denaturation by digestive enzymes or an acidic pH (ii) inadequate permeability into the bloodstream through the cell membrane (27).

Complexation pH-sensitive hydrogels, like the poly ethylene glycol (PEG) grafted on poly methacrylic acid (PMAA) family of grafted copolymers, also known as P(MAA-g-EG) and other polyacids, adapt to their surroundings, shielding the medications from the harsh stomach environment and releasing them in the small intestine (28). According to a recent review, environment-sensitive hydrogels are the "smart" hydrogels because they can react to a wide range of stimuli, including pressure, temperature, pH, light, enzymes, and so forth. As a result, this is a promising method for application in the clinic (29).

Yan *et al.* used GelMA hydrogel to deliver metronidazole (MTR) and chlorhexidine (CHX) and clear antibacterial actions against *P. intermedia*, *S. mutans*, and *E. faecalis* were observed (30). In a related application involving GelMA and CHX, Ribeiro *et al.* created an injectable gelMA hydrogel modified with nanotubes loaded with chlorhexidine (CHX), allowing for the prolonged release of CHX to treat dental infections caused by *E. faecalis* (31). Drugs with sustained release properties for periodontal disease can act longer and require fewer doses to be effective. Ribeiro *et al.* created an injectable and photo-cross-linkable gelatin methacryloyl (GelMA) hydrogel with ciprofloxacin (CIP) eluting short nanofibers for the ablation of oral infections. The hydrogels demonstrated good efficiency in reducing *E. faecalis* inflammation by promoting localized, prolonged action in efficient cell friendly antibiotic dosages (32).

4. Uses of GelMA Hydrogels for Mandible Regeneration

Nowadays, mandibular defects are treated through various methods such as traction osteogenesis, metal implants, and bone grafting. The fibular free flap graft is considered the gold standard for mandibular reconstruction. However, the limited availability of bone and donor site morbidity are the primary limitations of this method (33) .There have been attempts at mandibular rebuilding using hydrogel and the results are quite promising. Because they facilitate the release of antibiotics, hydrogel systems are important in the treatment of infected jaw deformities. For example, Kumar *et al.* developed a bone tissue engineering biphasic construct packed with bone BMP2. They used a gelatin–HA (Hydroxypatite) hydrogel to bind to the osteogenic cue BMP-2, which was then loaded onto a PCL (Polycaprolactone) scaffold. The construct mimicked native bone and consisted of cortical bone and cancellous bone for vertical jawbone augmentation. In vitro studies showed that the cell viability of BMP-2 was maintained in the hydrogel for 21 days, and bone markers increased on the third and fourteenth days (34). In order to improve the mechanical strength and stable network of traditional GelMA hydrogel, DN (Double-network) hydrogels doped with magnesium ions have been successfully formulated by crosslinking, through in situ free radical polymerization and magnesium ionic coordination strategies. With the introduction of DN networks and POSS-Mg (Polyhedral oligomeric silsesquioxane nanoparticles, and active Mg^{2+} ions) composite, the maximum compressive strengths are enhanced by about 6-folds, showing a promising bone formation and vascularization in calvarial defect of rats (35).

5. Uses of GelMA Hydrogels for Soft Tissue repair

Soft tissue regeneration stands a major challenge in contemporary medicine and dentistry. Periodontitis, gingival recession and chronic inflammation of the gums can result in tooth loss. In the cases of long term tooth loss, proper dental restoration and aesthetic outcomes heavily rely on critical soft tissues (36). Functional hydrogel dressings have the capacity to incorporate bioactive molecules like growth factors and antimicrobial agents. This enables targeted and sustained delivery of therapeutics directly to the wound site, addressing the multifactorial nature of chronic wounds and enhancing the healing trajectory (37). Yi *et al.* developed a bioink made up of injectable platelet-rich fibrin, alginate and gelatin that can be moulded according to individual patient requirements (38). Kim *et al.* prepared artificial oral mucosal tissue models employing GelMA hydrogels cocultured with human gingival fibroblasts (HGFs) and human oral keratinocytes (HOKs). After 14 days of culture on the surface of the hydrogel, the number of HOK cells raised and showed continuous cell proliferation. Histological evaluation demonstrated that bilayer GelMA hydrogels of HGFs and HOKs could be used to develop artificial oral mucosal tissues (39).

Future Scope Of Gellma In Dentistry

The future scope of GelMA in dentistry includes advancements in 3D bioprinting for custom dental implants, enhanced tissue regeneration techniques, and targeted drug delivery systems. It may also lead to innovations in bioactive materials for dental restorations and improved scaffolds for periodontal and craniofacial tissue engineering

CONCLUSIONS

Oral health is closely related to general health and quality of life. Trauma, genetic disorders, cancer, and infections can all cause tissue abnormalities in the dental, oral, and craniofacial structures. Hydrogels have a wide range of uses in oral science research, from treating oral diseases to reconstructing damaged tissue. Many studies on biomaterials for dentistry have been conducted recently with the aim of improving patient quality of life and clinical outcomes. Overall, the future of GelMa hydrogels in dentistry hinges on ongoing research efforts to refine their properties, explore new applications and validate their efficacy through rigorous clinical studies. As these technologies evolve, they have the potential to revolutionize dental care by offering more effective, personalized and minimally invasive treatment options. This article reviews the potential of Gelma hydrogel to cure pathogenic disorders of the oral cavity.

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