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REVIEW

Muco-Adhesive Hydrogels-Based Exosome Delivery for Periodontal Tissue Regeneration and Inflammation Reduction: A Review

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Abstract: This review highlights the potential of muco-adhesive hydrogel-based exosome delivery vehicles for the regeneration of periodontal tissue and the reduction of inflammation in periodontitis. Exosomes, mainly produced from mesenchymal stem cells (MSCs), represent nano-sized vesicles loaded with bioactive molecules that can stimulate tissue repair and modulate inflammatory pathways. The review provides a thorough view for the synthesis of the in vitro, in vivo and clinical-pilot studies on exosome-loaded muco-adhesive hydrogels, encompassing the physicochemical characterization, exosome delivery and biological efficacies. In vitro studies highlight the regenerative potential of exosomes on periodontal ligament cells and on alveolar bone cells. In vivo animal models have shown significant improvements in tissue regeneration with effective inflammation control. Preliminary clinical pilot studies similarly show promising results for periodontal tissue healing. The use of exons in combination with muco-adhesive hydrogels provides an effective and non-invasive approach for the targeted, prolonged therapeutic delivery for the treatment of periodontal disease. The main conclusion of this review is that exosome loaded muco-adhesive hydrogels represent a promising strategy for developing strategies to treat periodontitis, setting up as its double aims to enhance the regeneration of tissues and reduce inflammation.

Keywords: exosomes, muco-adhesive hydrogels, periodontitis, tissue regeneration, inflammation modulation, drug delivery systems, regenerative medicine

Introduction

Periodontitis is an inflammatory disease of the gums that starts with gingivitis and continues with the loss of the tooth-supporting structures.[1] This involves the destruction of both the periodontic ligament and alveolar bone, which can usually result in the loss of teeth. Periodontitis occurs due to a synergistic association of bacterial biofilms and host immune response. It is among the most common chronic conditions around the globe, it is reported that a global prevalence of periodontitis is of ~61.6% (2011–2020), with about 23.6% having severe periodontitis.[2] It is more widespread among people over 30 years old, and the level of its severity grows with age.[3] The disease is not only associated to local oral health issues but also to systemic related diseases, including cardiovascular diseases, diabetes and respiratory infections thereby impacting on overall health and wellbeing.[4]

Periodontitis appears clinically in the form of swollen gums, bleeding gums, deep pockets of gums, and resultant tooth loss, as illustrated in Figure 1. With its development, the disease can become a source of severe discomfort, dysfunction (impossibility to chew or speak), and aesthetic unattractiveness caused by moving or loss of teeth.[1,5] Besides these oral challenges, the inflammatory mediators that are released in periodontitis have been linked with the risks of developing systemic disorders. At the same time, studies proved the connection between periodontal and diseases such as

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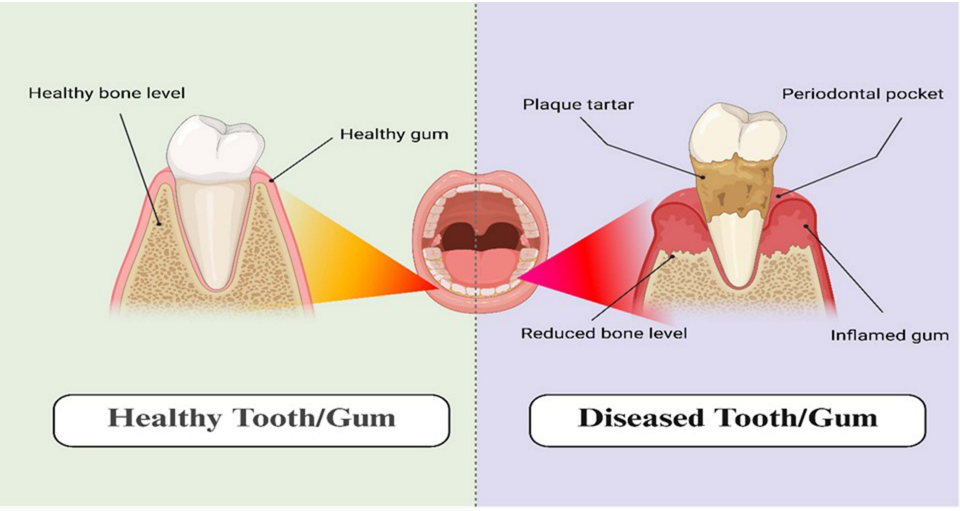

Figure 1 This schematic describes the difference in terms of anatomy and pathology between healthy (left) and periodontitis affected (right) tissue. There is complete gingival structure of the healthy tooth and gums with healthy bone topography and no infection/inflammation. Conversely, the pathological condition is characterized by quintessential indicators of the disease such as the presence of plaque and tartar, periodontal pockets, decrease in the alveolar edge, and swollen gums. This ends up in degeneration of the tissues and loosening of the teeth when gone unchecked.

diabetes mellitus, atherosclerosis and Alzheimer.[6–8] Moreover, chronic oral health complications, including periodontitis, may have a psychological effect, causing social silence and lower quality of life.[9]

Conventional periodontitis treatment methods basically involve mechanical cleaning, ie, such procedures as scaling and root planing (SRP) are aimed at dislodging bacterial colonies, ie, biofilms, on roots. Nonetheless, SRP is not sufficient to restore lost tissues, and it may need the support of additional treatment such as the usage of antibiotics or the performance of surgical operations in the severe cases.[10] Though surgical operations, such as the one with flap surgery or bone grafting can assist in restoration of some of the tissues, they can lead to certain complications, including post-operative pain, swelling, prolonged recovery process.[11] Such therapies also do not respond to the unclear inflammation process, which results in the re-occurrence of the disease. Hence, a more constructive and extensive treatment method, which not only treats diseases, but also leads to subsequent tissue regeneration and decreases inflammation, is required.

Given the limitations implicit in conventional periodontal therapies, recent years have seen an advancing interest in optimized therapeutic approaches that combine tissue regeneration with the achievable and well-targeted modulation of inflammatory processes. Hydrogels have proven to be especially promising drug delivery platforms given their biocompatibility and biodegradability, and their intrinsic muco-adhesive properties.[12] These materials can provide strong adhesion to mucosal surfaces and deliver a sustained and controlled release of therapeutics for longer durations. Among therapeutic agents contemplated for such delivery systems, exosomes, which are nano-centred extracellular vesicles, are of special interest because of their key roles in intercellular communication, inflammation pathway regulation, and tissue repair promotion.[13] When used within the framework of hydrogel matrices, exosome therapy promises to revolutionise the treatment of periodontal diseases by delivering regenerative and anti-inflammatory markers site-specifically to the tissues that need them most.

Exosome-laden hydrogels offer several advantages over conventional modalities such as oral administration or systemic injections. These include an increased targeting specificity, prolonged retention at the site of action, and enhanced bioavailability, cumulatively resulting in the enhanced therapeutic efficacy of exosomes in periodontal tissues.[14] By preserving the proximity of the therapeutic agents to the compromised mucosal architecture, hydrogel-based exosome delivery can improve tissue regeneration efficiency while at the same time attenuating the inflammatory responses.

Furthermore, modern advances in regenerative medicine provide attractive alternatives to traditional therapies. Amongst them, mucoadhesive hydrogels have been recognized as novel drug delivery systems due to their ability to remain adhered to mucosal surfaces and control drug delivery to the submucosal tissue in a sustained manner. This

property makes them particularly beneficial in local treatment of periodontal tissues.[15] The simultaneous delivery of muco-adhesive hydrogels with exosomes allows for directed, non-invasive delivery of content which has potential to revolutionize periodontal disease management and can improve results for regeneration while being a better controlling process for inflammation compared to current conventional methods.[16]

This review therefore highlights the combined treatment of exosomes and muco-adhesive hydrogels as an innovative strategy for periodontitis treatment, with a special focus on their ability to effortlessly rebuild periodontal entities and provide appropriate inflammation control.

Exosomes and Their Role in Regenerative Medicine

Exosomes are small (30 to 150 nm) nano sized vesicle produced by all kinds of cells such as immune cells, fibroblasts, epithelial cells among so many others.[17] These vesicles take part in intercellular communication and are significant in the mediation of tissue inflammation and homeostasis.[18,19] Exosomes are formed in multivesicular bodies (MVBs) in the cytoplasm and after they fuse with the plasma membrane are released to the extracellular space. They include different bioactive molecules (including proteins, lipids, RNA (including mRNAs, microRNAs) and metabolites) that regulate cellular functions.[20,21] Exosomes have the natural propensity to crosstalk between cells, and this potential works in both directions in terms of delivering functional cargo to a cell and receiving any functional cargo from the cell.[22] These characteristics place exosomes in an ideal situation, like a vehicle to carry treatment or medical information to a cell.

Exosomes have increasingly become a topic of interest in the field of regenerative medicine since they have been found to regulate inflammation in addition to enhancing the repair of tissues.[23] The mechanism of action entails the exchange of specific biomolecules that control other processes in the cells, such as cell migration, cell proliferation, differentiation, and even apoptosis.[24] Growth factors, including vascular endothelial growth factor (VEGF) and bone morphogenetic proteins (BMPs), can be loaded into exosomes and are crucial to tissue regeneration and angiogenesis.[25] In addition, exosomes are extremely important in the anti-inflammatory reaction as they regulate the immune cell activity. As an example, mesenchymal stem cells (MSC) exosomes have the potential to decrease pro-inflammatory cytokine release and polarise macrophages, switching the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype.[26] Such ability to regulate inflammatory environment renders exosomes as very eligible in the medicinal treatment of inflammatory disorders like periodontitis, in which one of the most pathological conditions is long-lasting inflammation.

Exosomes have been found to have significant potential in the treatment of periodontitis, monitored by their regenerative and anti-inflammatory effects. Several studies have demonstrated that MSC- or other stem cell-derived exosomes can induce periodontal tissue regeneration (several types of periodontal tissues: periodontal ligament, alveolar bone, and cementum).[27] Exosomes derived of MSC have been identified to stimulate the proliferation and differentiation of periodontal ligament cells that are essential in tissue repair in periodontitis.[27] Moreover, exosomes were identified to induce other regenerative cells to migrate to the injury site to regenerate the tissue at a faster rate.[28] This regenerative capacity is especially critical where there is periodontitis, and the lost tissues are not effectively replaced by the regular treatment.

Moreover, there is a possibility of combining exosome therapy with muco-adhesive hydrogels to maximize the delivery and retention of exosomes on the location of the infection. The biocompatible materials muco-adhesive hydrogels can adhere to the mucosa and release the therapeutic agent, the exosomes, in a specific and sustained way.[29] The combination has numerous benefits compared to the traditional ways of delivering drugs like oral delivery or systematic injections that tend to post low bioavailability of the drugs at the target site. Through the encapsulation of muco-adhesive hydrogel, one can also enjoy the benefits of controlled release and of a prolonged release since the muco-adhesive hydrogel has a lengthy duration, thus enabling the exosomes to have a greater contact force with the problematic periodontal tissues.[29]

This combination of exosomes and muco-adhesive hydrogels has shown the ability to drastically curtail inflammation at the location of the periodontal infection, and at the same time, encourage the tissue regeneration process. As an example, in an animal model of periodontitis (as mentioned in the literature), the topical delivery of exosomes derived of MSC mutated in muco-adhesive hydrogels significantly decreased the inflammation indicators and enhanced tissue

repair.[30] Exosomal-based treatment in conjunction with muco-adhesive hydrogels may be a viable technique of periodontitis management and provide the benefit of therapeutic benefit coupled with a decreased chance of the disease reoccurrence.

The Need for Innovative Approaches

Traditional methods of treating periodontitis, including scaling and root planing (SRP), antibiotics and surgical management, have been basic in the management of the disease. These methods, however, are not enough to handle the underlying issues of tissue regeneration and disease recurrence. SRP is highly capable in lightening up the microbial load and controlling inflammation, but it is incapable of restoring lost periodontal structures such as alveolar bone or the periodontal ligament. Likewise, although antibiotics are effective in controlling bacterial infection, they do not heal the tissues, and their indiscriminate use increases the problem of antibiotic resistance. Surgery is effective to use in late stages, but it is invasive, and it has a risk of post-surgical complications and subsequent long recovery periods. The above limitations speak to the necessity of higher levels of treatment, such as the regenerative type that is more than purely symptom management, because it is long-term and rather than putting bandages on the wound, it is healing the wound.

The subject of regenerative medicine has received a lot of attention because it offers a good approach in restoring and regenerating periodontal tissues. Therapies such as stem cell therapy, gene therapy, and tissue engineering have been used to induce the regeneration of periodontal tissues, such as bone, ligament and cementum. Although these strategies are highly promising, there are difficulties in improving delivery structures and demonstrating safety and efficacy in clinical practice. The use of muco-adhesive hydrogel with respect to exosome-based therapy can be offered as a novel solution to the problem. Muco-adhesive hydrogels are effective presentation vehicles of exosomes, which carry bioactive molecules to influence wound repair and the balancing of inflammation. These hydrogels offer a regulated, focused delivery, which guarantees prolonged exposure of the periodontal tissues, regenerative success and recovers the constraints of the customary therapies.

Muco-Adhesive Hydrogels: An Emerging Tool for Drug Delivery

Characteristics of Muco-Adhesive Hydrogels

Muco-adhesive hydrogels represent polymers that form networks of hydrophilic crosslinked polymers with a unique property of adhesion to mucus membranes, including the mouth, gut tract and respiratory system. These materials expand when the aqueous environments are present to give the gel like consistency, which allows the storage and release of therapeutic agents in a controlled manner. Their ability to bind strongly to mucosal tissue and hold water makes them deliver long-term drug amid the locality thus they are more helpful in the treatment of conditions that needed long-acting therapeutic effects at the point of infection or injury like periodontitis, ulcers, or chronic inflammation.[31]

Biocompatibility is one of the characteristics that make up muco-adhesive hydrogels, and it makes sure that the hydrogel induces no immune system reaction when encountering biological tissues and it is also not toxic. This is an important attribute especially when it comes to oral use since mouth tissues of the mucosa are very sensitive.[29] As well as being biocompatible, biodegradability is a necessary characteristic of muco-adhesive hydrogels, as illustrated in Figure 2. Controlled release is also possible as the hydrogel can gradually degrade with time, releasing the encapsulated drugs pharmacologically at a sustained rate, and in anti-inflammatory drugs, growth factors or antibacterial substances.[32]

Muco-Adhesion Mechanism and Its Relevance in Targeting Oral Tissues

Muco-adhesion is a characteristic which allows material to be attached to mucosal tissues through a synergy of physical, chemical, and electrostatic interactions. Muco-adhesion mechanism is central to effective use of hydrogels in drug delivery systems since it helps in keeping the therapeutic agent in the area where needed, leading to enhanced therapeutic contact.[29] The glycoprotein-rich layer on the Mucosal surfaces (eg, in the oral cavity) are called mucins and these are important in the protective barrier mechanism of the mucosal tissues. These mucins are anionic; thus, they can connect with positively charged functional groups within the hydrogel, the various examples being chitosan (poorly understood muco-adhesive polymer).[29]

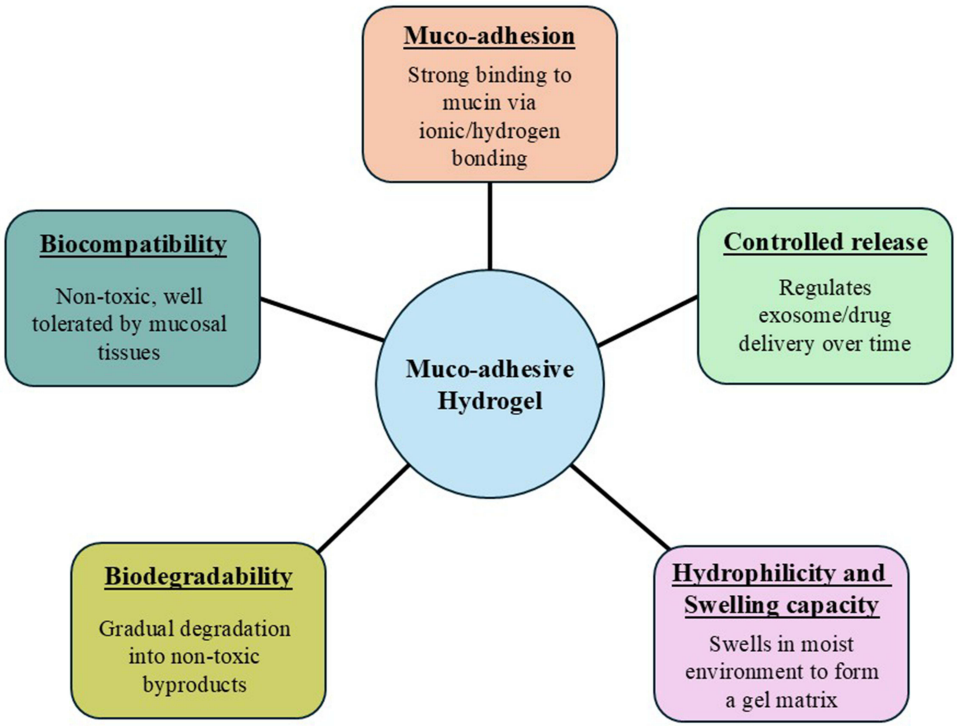

Figure 2 This figure outlines the key features of muco-adhesive hydrogels that make them effective in therapeutic-medical purposes.

Muco-adhesion process is based on few forces such as: hydrogen bonding, electrostatic forces and the van der Waals forces and this is what enables the hydrogel to create a stable bond with the mucosal layer.[29,33] In particular, the polysaccharide chitosan contains amino groups; the strong interaction it develops with mucin promotes the increase in the retention of the complex on the surface of the mucosa. Such retention plays a very important role in oral drug delivery, especially in the treatment of periodontal diseases where the drug has to stay in contact with the gums, teeth and nearby tissues over a long period of time so as to result in effective therapeutic treatment.

Regarding oral tissues, the muco-adhesive characteristic of hydrogels can make it possible to maintain the focused site of activity, ie, the therapeutic substance, whether exosomes or anti-inflammatory agents, can be placed in places where it is required. As an example, periodontal tissues are rather vascular and are under steady inflammatory responses as far as periodontitis develops.[34] Muco-adhesive hydrogels compensate this property by stickiness to the mucosal tissue, which may extend the dwell time of the active compound reducing its metabolism thus maximizing its effect.[29]

This localized delivery is important in preventing systemic side effects and ensuring that the therapeutic agents can act directly at the site of inflammation and tissue degradation.[35] Additionally, the controlled release of these agents over time helps in reducing the frequency of administration, which improves patient compliance, especially in chronic conditions like periodontitis.

Types of Muco-Adhesive Hydrogels

Muco-adhesive hydrogels are emerging as an important drug delivery system particularly local application over mucous tissue. This specific property to attach to mucosal surfaces and deliver controlled bioactive agents release, ie, exosomes, has led to their promising prospects as tissue repair in periodontitis and inflammation minimization carriers.[36,37] These hydrogels mostly fit into two categories, namely, natural and synthetic polymers. The advantages of each drug category in terms of biocompatibility, muco-adhesion, and release control are essential for practical periodontal applications.

Natural Muco-Adhesive Hydrogels

Muco-adhesive hydrogels have also been developed using natural polymers, eg chitosan and pectin. Chitosan, a chitin-derived product, is among the most popular natural polymers used in hydrogel composition because it is biocompatible, biodegradable, and positively charged.[38] The positively charged amino groups of chitosan bind to mucosal surfaces that are negatively charged with the formation of ionic bonds, thereby increasing the muco-adhesive properties of the substance.[39] This high muco-adhesion property renders chitosan-based hydrogels useful in local drug delivery systems, including the targeted system of exclusive drug delivery into the periodontal tissues included in the delivery of exosomes.[40–43] In addition, it is easy to customize and adjust chitosan to increase its muco-adhesive capabilities, and this aspect makes it a promising material to develop effective systems of tissue regeneration and inflammation modulation delivery in periodontitis.[44,45]

Besides chitosan, pectin, another natural polymer has also shown significant prospects in muco-adhesive hydrogel formulations. Pectin can be located inside the cell wall of various fruits and gel under the influence of divalent cations such as calcium.[46] This property enables the hydrogels based on pectin to stick well on mucosal surfaces, thus increasing the holding time of therapeutic agents.[47] Pectin has carboxyl groups and due to this it is muco-adhesive in nature and the properties allow the delivery of exosomes using pectin-based hydrogels with a decrease in inflammation in periodontal diseases and tissue regeneration.[48,49] Biocompatibility and biodegradability of pectin provides further evidence of its application to periodontal, where long-term interaction of the tissue with the key substances.[50]

Synthetic Muco-Adhesive Hydrogels

Synthetic polymers such as polyvinyl alcohol (PVA) and polyethylene glycol (PEG) are also widely used to make muco-adhesive hydrogel formulations. PVA is resistant to water, meaning that it is a water-soluble polymer and does not interfere with water; it also possesses good mechanical properties, water retention, and biocompatibility.[51–53] The physical properties of PVA hydrogels, including viscosity, swelling, and degradation rate, can be controlled in any measure: they can be cross-linked chemically or physically.[54] The degree of control renders PVA-based hydrogels suitable to achieve prolonged effect, release of bioactive molecules such as exosomes, in a periodontal tissue regeneration application.[55]

Another common synthetic polymer in muco-adhesive hydrogels is PEG. The presence of highly hydrophilic molecular structure in PEG leads to swelling as well as improving the queer of the muco-adhesive characteristics of the hydrogels produced.[29] They are applicable in periodontal drug delivery due to the ability of PEG-based hydrogels to sustainably release therapeutic agents at a controlled rate up to exosomes.[56] Furthermore, PEG-based hydrogels are particularly beneficial for applications requiring long-term retention and localized drug release, as they can be designed to respond to physiological changes such as pH and temperature.[57,58]

Properties That Enhance Tissue Adhesion and Controlled Release

Muco-adhesive hydrogels have several properties that may be regarded as essential to the successful use of those applications as drug delivery systems. The main activity that enables hydrogel to stick on mucus tissue is their ability to exhibit muco-adhesion making them remain in place by delivering therapeutic agents to a local area over time. The chemistry between the functional groups of the polymer (amino, carboxyl, and hydroxyl) and the mucous leads to firm adhesion, which guarantees the long-term retention of the hydrogel and its active components.[59] As an example, chitosan interacts highly with mucosal tissues due to the cationic component of its structure, whereas the carboxyl groups of pectin support its muco-adhesion. Such interactions play significant roles in the sustenance of therapeutic effects of exosome in periodontal therapy.[60]

Besides muco-adhesion, controlled release is one more indispensable characteristic of muco-adhesive hydrogels. Controlling the release rate of bioactive agents like exosomes is essential in making sure that there is a continuous therapeutic effect with time. Hydrogels have such release kinetics that may be altered by regulating the physical state of the hydrogel, including cross-linking density, swelling characteristics, and degradation kinetics.[61–63] Moreover, the control over the release of a drug can be further increased with a response of hydrogels to changes in pH or temperature, which would maximize the therapeutic potential of exosomes in periodontitis.[63,64]

Lastly, muco-adhesive hydrogels have been shown to be biocompatible and bio-degradable, and this makes them safe and effective when used in vivo even in the long term. The body tolerates them well and there are no adverse effects to their intracellular accumulation because of their safe biodegradation at the end of the activity procedure.[65] These characteristics are especially relevant in the context of periodontal diseases, in which the hydrogel must be adsorb on tissues and react over prolonged periods without triggering any negative phenomena.[66]

Role of Muco-Adhesive Hydrogels in Drug Delivery Systems

Muco-adhesive hydrogels have gained significant attention in recent years as an innovative platform for drug delivery, particularly in the treatment of diseases affecting mucosal tissues. These hydrogels are designed to adhere to the mucosal surfaces, ensuring prolonged retention and enhanced bioavailability of the therapeutic agents at the target site. In the context of periodontitis, this feature is especially beneficial, as it allows for localized treatment of periodontal tissues, thus promoting tissue regeneration and reducing inflammation.[67]

One of the main advantages of muco-adhesive hydrogels is their ability to provide controlled and sustained release of bioactive compounds over extended periods. This characteristic significantly improves the therapeutic efficacy of drugs, particularly in conditions like periodontitis, where frequent dosing is often impractical. Muco-adhesive hydrogels, by adhering to mucosal surfaces, enable the slow and steady release of the encapsulated drugs, which is crucial for maintaining therapeutic levels at the site of action.[29,35]

Recent studies have explored various formulations of muco-adhesive hydrogels for the sustained delivery of both small molecules and biologics, including proteins, peptides, and nucleic acids. For example, Ashfaq et al, (2025) prepared muco-adhesive, meloxicam-loaded hydrogels based on nanostructured lipid carriers which have substantive eliminating the inflammation implications of periodontitis. The results of their in vitro release studies also validated sustained release of drug within 24 hours; this is important in ensuring delivery of a stable therapeutic concentration at the site of action. This kind of prolonged release is beneficial because it reduces the peaks and valley effect that is normally common with standard oral drug delivery to improve the efficacy of local treatment and the overall patient compliance.[68]

Advantages in Oral and Periodontal Tissue Targeting

The oral cavity, especially the periodontal tissue, poses unique challenges in drug delivery due to its complex anatomy and dynamic environment. Muco-adhesive hydrogels have shown great promise in overcoming these challenges. The hydrogels can be formulated to adhere to the mucosal surfaces of the oral cavity and periodontal tissue, ensuring that the drug is effectively delivered to the site of inflammation and tissue degeneration.[69] This is particularly beneficial for periodontal diseases like periodontitis, where the localized application of therapeutic agents is essential for managing chronic inflammation and promoting tissue regeneration.

In addition to enhancing drug retention, muco-adhesive hydrogels can be tailored to respond to the physiological conditions of the oral cavity. For example, pH-sensitive muco-adhesive hydrogels have been developed to release their payloads in response to the acidic microenvironment of inflamed periodontal tissues.[70] The ability to design hydrogels that release drugs in a targeted manner in response to specific triggers further improves the precision and efficacy of drug delivery in periodontal therapy.

Synergy with Nanoparticles and Exosomes

An encouraging note in muco-adhesive hydrogel-based drug delivery system development is the introduction of nanoparticles and exosomes to improve their functionality. Liposomes, polymeric nanoparticles, and solid lipid nanoparticle are just but a few examples of nanoparticles that have been extensively explored in encapsulating and delivering various kinds of drugs like anti-inflammatory drugs and growth factors.[71–73] When incorporated in muco-adhesive hydrogels, the nanoparticles can further enhance the stability, solubility and bioavailability of the drugs besides permitting the controlled and targeted drug release to the periodontal tissues.

Natural nano-sized vesicles, exosomes, are the new innovative option of drug delivery in regenerative medicine. It can be said that exosomes possess bioactive substances (proteins, lipids, RNAs, and growth factors), which are

instrumental in tissue regeneration and regulating inflammation.[74,75] They have a distinctive potential to induce a cell-to-cell communication and tissue repair, which makes them a perfect solution in their inclusion in muco-adhesive hydrogel-based formulas. Researchers have indicated that a combination of exosomes and muco-adhesive gels increases the potential of therapeutic intervention of tissue reconstruction and management of inflammation in periodontitis. Moreover, exosome-loaded muco-adhesive hydrogels can be effectively used to target inflamed periodontal tissues and induce tissue repair by loading regenerative factors.[14] Moreover, muco-adhesive hydrogels loaded with exosomes demonstrated the capacity to lessen an inflamed condition, synchronizing the immune reaction within the periodontal microenvironment.[65]

The synergistic activities between nanoparticles and exosomes once synthesized into muco-adhesive hydrogels do not only augment drug delivery to the desired target but also produce the required biological cues to heal tissue.

Exosome Delivery in Tissue Regeneration and Inflammation Reduction

Exosomes have the capability to package diverse types of bioactive molecules, such as proteins, lipids, and the types of RNA (mRNA, miRNA, and lncRNA). These bioactive molecules are very vital in the regulation of different cellular processes like cell proliferation, differentiation, migration and apoptosis. There is a significant therapeutic potential of exosomes of various origins, most notably of the stem cell type, in tissue repair and immune system modulation.[76–78]

Biological Functions of Exosomes

Exosomes have varying and situation-specific biological roles. They play the role of intercellular communication mediators and move bioactive chemical substances between the cells. As an example, exosomes released by mesenchymal stem cells (MSCs) contain various growth factors, including VEGF, FGF, and TGF-B, necessary during the angiogenesis, collagen production, and extracellular-matrix remodeling during tissue regeneration.[79] miRNAs present in the exosomes may also regulate the activities of the cells receiving them by altering their expression of certain genes by binding to the mRNA molecules.[80] Moreover, it is shown that exosomes can induce the reprogramming of cells to a particular phenotype, that supports regeneration and restores damaged tissues.

Besides having regenerative properties, the exosomes also play a role in immune modulation. MSC-derived exosomes have demonstrated the presence in exosomes contents, the presence of anti-inflammatory properties that make them a tempting option as a therapeutic protocol to diseases such as periodontitis due to the high rates of periodontitis-related inflammation.[81] Inhibiting the activation of pro-inflammatory cytokines, including TNF-a, IL-1β, IL-6, exosomes have the potential to diminish their activity through the provision of immunomodulatory effects.[82–84]

Exosome Isolation, Purification, and Functionalization for Therapeutic Use

Exosome therapy can only be performed through the isolation, purification, and functionalization of exosomes so that they can be effective. Isolation of exosomes in biological fluids is typically completed using different protocols comprising ultracentrifugation, density gradient centrifugation, and size-exclusion chromatography.[85]

Once isolated, the exosomes may be functionalized and thus increase their treatment efficacy. Selective targeting a specific tissue or cell type can be achieved by means of surface modifications eg conjugation of targeting ligands or peptides to the exosome membrane. For example, the specificity and efficacy of treatment can be enhanced, by targeting peptides, including RGD (Arg-Gly-Asp) sequences, which can target exosomes, to bone tissues or periodontal ligament cells.[86,87]

In addition to that, the potential of encapsulation of exosomes in muco-adhesive hydrogels offers a highly valuable method of providing guidelines through controlled and sustained release at the desired site. Hydrogels are biocompatible water-swollen materials that can be designed to stick to mucosal surfaces thus enabling localized treatment. These properties of muco-adhesive hydrogels guarantee more prolonged stays of exosomes at the point of application and, consequently, improve their therapeutic effectiveness when used in the treatment of periodontal lesions.[65,88]

Mechanisms of Exosome Action in Periodontitis

Periodontitis is an inflammatory process, which involves destruction of the periodontal tissues such as the bone and cementum as well as periodontal ligament. The most significant capability of the exosome in the treatment of

periodontitis is to contribute to the tissue-repair and the regulation of inflammation, as illustrated in Figure 3. The processes by which exosomes have appeared to have their therapeutic action in periodontal regeneration and anti-inflammatory action are multimodal and incorporate regenerative attributes, immune modulation, and tissue-specific restorative.

Regenerative Properties

Exosomes also stimulate angiogenesis, cell proliferation, and cell migration in multiple tissues which makes them a potential candidate to regenerative medicine. It has been revealed that MSC-derived exosomes have the capacity to promote the migration and proliferation of periodontal ligament cells, osteoblasts, and fibroblasts, which play a crucial role in the repair of periodontal tissues in periodontitis.[89,90] Moreover, exosomes have the potential to induce angiogenesis, ie, the growth of new blood vessels, which plays a crucial role in the supply of nutrients and oxygen to the damage-regenerating tissues. It has been demonstrated that animal models with angiogenic factors such as VEGF enclosed in exosomes encourage new blood capillary generation in animal models of periodontal defect and portend enhanced healing.[91]

Moreover, they could promote osteogenesis (bone formation) as well as cementogenesis (development of the attachment of the teeth roots) within periodontal tissues in the form of exosomes. Exosomes have the capability to induce the formation of periodontal stem cells into osteoblasts and cementoblasts through using growth factors like bone

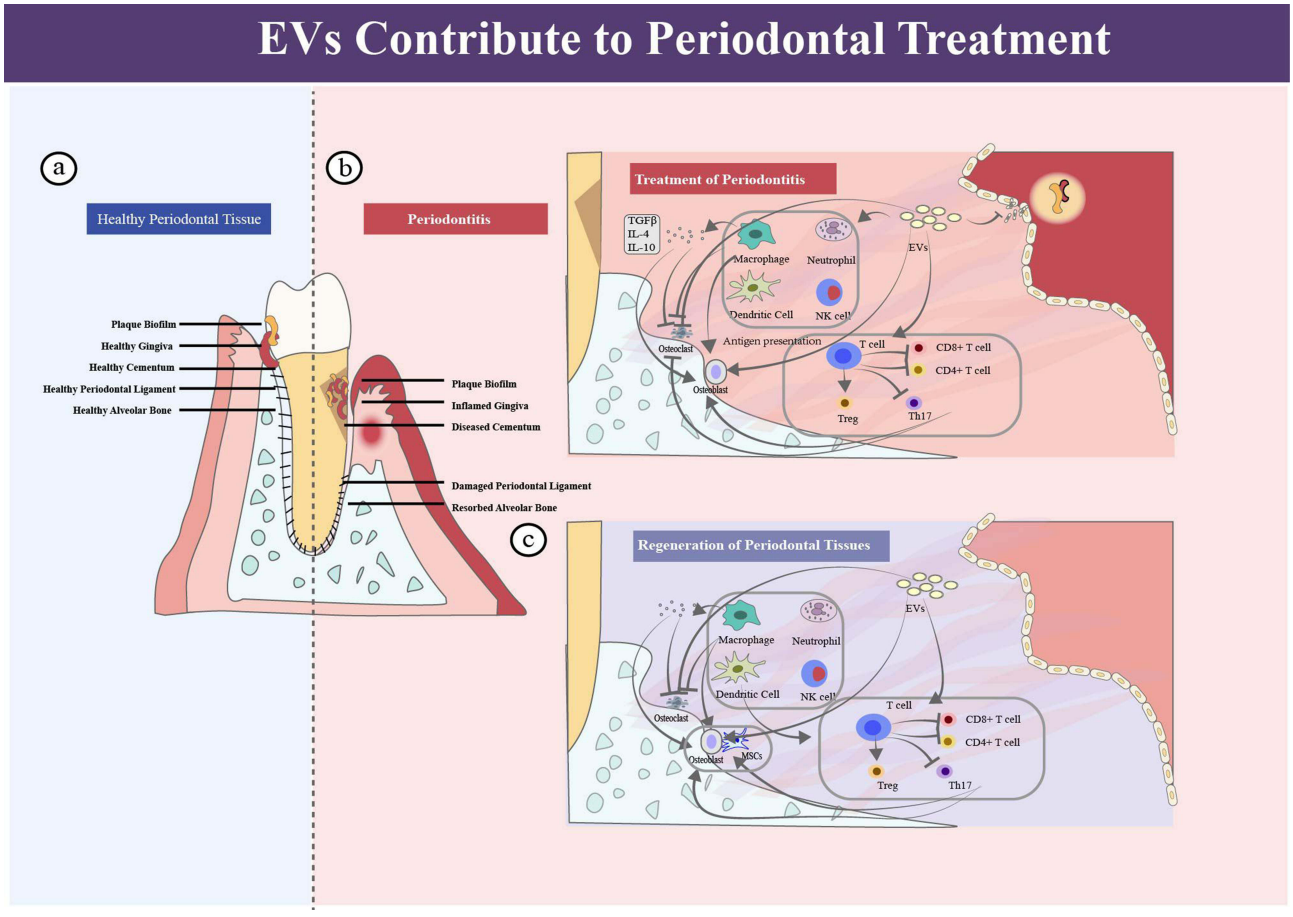

Figure 3 Periodontium, Periodontitis and Periodontal Regeneration. (a) Within healthy periodontal tissues, a biofilm (plaque) derived from commensal microorganisms is present within the gingival sulcus and all four of the constituent structures, gingiva, periodontal ligament, cementum, and alveolar bone, remain physiologically intact and stable. (b) In periodontitis, inflammatory processes are disrupting periodontal architecture and the role of EVs in targeted therapeutic strategies aimed at improving disease progression. (c) EVs - an additional principal factor in the regeneration of the periodontal tissues. Adapted from reference[30] under a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

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morphogenetic proteins (BMPs) and FGF, which facilitate the regeneration of bone and periodontal ligament tissues in the damaged regions.[37,92] This repair capacity assumes exosomes to be an outstanding choice of clinical use in periodontitis.

Anti-Inflammatory Effects

The immune system is hyperactivated in periodontitis and results in chronic inflammation and the destruction of tissues. Exosomes have helped tremendously as a barrier to immune response and calming of inflammation in periodontal tissues. MSC-derived exosomes are considered to have anti-inflammatory molecules possibly cytokines and miRNAs which downregulate the production of pro-inflammatory cytokines like IL-1β, TNF-α, and IL-6.[84,93] These cytokines have part to play in the pathogenesis of periodontitis stimulating the destruction of connective tissue and bone.

Interaction with exosomes also leads to modulation of immune cell behavior with macrophages and T cells. As an example, exosomes can enhance the activation of macrophages into the anti-inflammatory M2 type that is central to the repair of tissues and inflammation.[94,95] This immunomodulatory effect is paramount in the regulation of the immense inflammatory reaction which occurs in periodontitis hence eliminating the further destruction of the tissues of periodontitis and helps in inducing healing. Besides that, exosomes can inhibit the work of matrix metalloproteinases (MMPs), which destroy the extracellular matrix and lead to the destruction of tissues in periodontitis. The exosome-mediated MMPs inhibition contributes to the maintenance of the integrity of the periodontal tissue and favorable repair.[96]

Potential for Tissue Repair in Periodontal Lesions

Exosomes have a beneficial advantage in repairing tissues especially in the case of periodontal lesions. Periodontal defects mainly include losing not only soft tissues, but also hard tissues and exosomes have been found to regenerate both periodontal ligament tissues as well as bone. Exosome-loaded muco-adhesive hydrogels showed positive tissue regenerative rates in animal models compared with the conventional therapies, which resulted in accelerated tissue repair and better clinical results.[88,97] The slow release of exosomes out of hydrogels portrays a beginner and localised source of regenerative factors and is thus an amazing approach to the treatment of periodontal diseases.

Recent reports have included the possibility of exosome-based treatments in the regeneration of the periodontal tissues due to their ability to stimulate the movement of cells as well as regeneration of bone and blood vessels. Muco-adhesive hydrogel loaded exosomes allow applying exosomes directly to dental defects and offering a localized and prolonged delivery of bioactive substances to speed up tissue repair.[98] An overview of the supporting evidence, conflicting findings, and limitations are summarized in Table 1.

Exosome Delivery via Muco-Adhesive Hydrogels

The use of muco-adhesive hydrogels greatly improves exosome delivery in periodontal therapy due to enhanced uptake as well, as illustrated in Figure 4. These are water-soluble polymers that are biocompatible and can create a gel-like structure when in the presence of water, thus making an excellent drug of choice and biologic delivery systems. Muco-adhesive hydrogel can provide various benefits such as improved stability and bioactivity, regulated and selective release and maximized therapy effect in loss recovery and inflammation of periodontal tissues during exosome delivery.

Enhanced Stability and Bioactivity of Exosomes within Hydrogels

Exosomes are very sensitive to other environmental factors like temperature, PH, and protease enzymes which may intervene with their stability and efficacy.[107] Maintaining exosomes bioactivity and delivering them to the target tissue at their functional state are some of the biggest obstacles on exosome-based therapies. Exosomes are protected in the environment due to the protective environment arrayed by the muco-adhesive hydrogels that prevent the peril of degradation.

The non-porous hydrogel barrier prevents enzymatic degradation and oxidative stress making exosomes unaffected by time in storage as well as delivery to the site. This innate immunity assists in the functional stability of exosomes so that they can achieve regenerative and ant-inflammatory effects when transported to the recipient tissue. In addition, exosomes residing in hydrogels are safe against premature clearance by the immune system, which helps prolong their half-life and therapeutic effectiveness.[108]

Table 1 This Table Summarizes Supporting Data, Conflicting Results, and Currently Available Limitations or Controversies on the Use of Exosome-Loaded Muco-Adhesive Hydrogels to Facilitate Periodontal Tissue Regeneration and Reduce Inflammation

Topic	Supporting Evidence	Conflicting Findings	Ongoing Debates/Limitations
Exosome Role in Regenerative Medicine	Exosomes promote tissue regeneration, including periodontal ligament and alveolar bone. MSC-derived exosomes reduce inflammation and enhance wound healing.[27,99]	Not all studies agree on the consistency of MSC-derived exosomes for regeneration, with some showing limited clinical success or variability across patient populations.[41]	Variability in exosome composition leads to inconsistent therapeutic outcomes. Debate on optimal cell source for exosome extraction (MSC vs other stem cells). Need for better protocols to ensure uniformity in exosome preparation.[100]
Muco-Adhesive Hydrogels for Drug Delivery	Muco-adhesive hydrogels show prolonged retention at periodontal sites and controlled release of therapeutic agents.[68] Chitosan and PEG-based hydrogels enhance drug stability.[35]	Some hydrogels, like chitosan, show poor stability under physiological conditions.[100] Variability in the muco-adhesive properties depending on polymer formulation.[33]	Debate about the ideal polymer type for optimizing muco-adhesion and release kinetics. Concerns over toxicity of certain synthetic polymers. Need for longer-term studies on hydrogel degradation and its effect on tissue regeneration.[37]
Combination of Exosomes and Hydrogels	The combination of exosomes with muco-adhesive hydrogels enhances tissue repair and reduces inflammation in periodontitis models.[41,99]	Some studies show that combining exosomes with hydrogels does not always lead to enhanced clinical outcomes, particularly in more severe periodontitis stages.[101]	Lack of consensus on how best to integrate exosomes into hydrogels for maximum efficacy. Debate over the ideal release profile (slow vs fast release) and its impact on clinical success.[102]
In Vivo and Clinical Studies	Animal studies demonstrate promising results in tissue regeneration and inflammation reduction using exosome-loaded hydrogels.[101]	Limited human trials with mixed results: some show positive effects, while others report minimal improvement in periodontal healing.[103]	Limited scalability of preclinical results to human models. Need for more robust, large-scale human clinical trials to confirm the safety and long-term efficacy of exosome-loaded hydrogels.[104]
Exosome Loading and Delivery Methods	Electrostatic assembly provides high encapsulation efficiency for exosome delivery in hydrogels.[100]	Passive loading methods often result in lower encapsulation efficiency, leading to reduced bioactivity.[105]	Ongoing debate on whether passive or electrostatic loading methods offer better clinical results. The need for optimized encapsulation protocols to prevent exosome aggregation or degradation.[48]

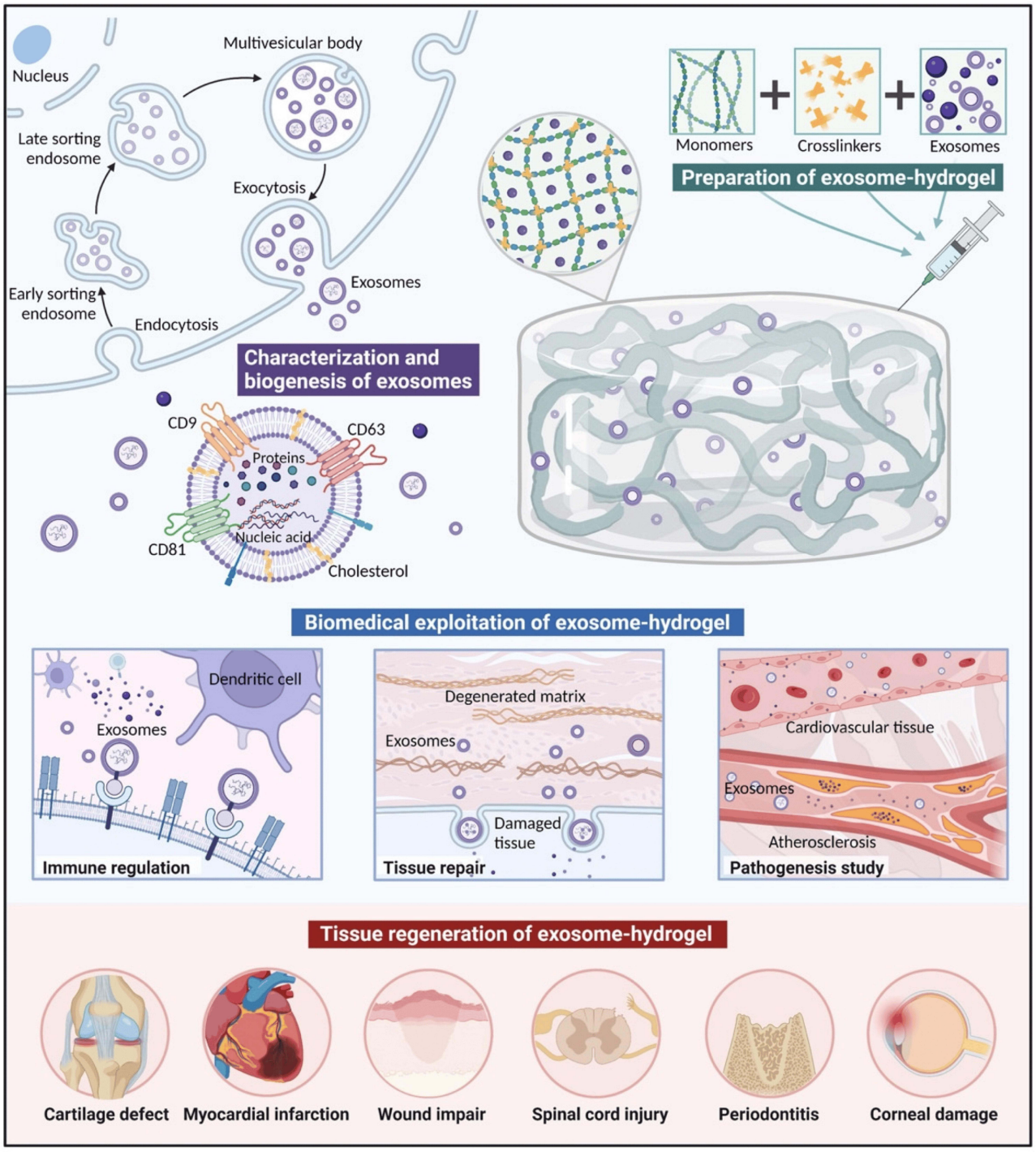

Figure 4 Biomedical applications exosome delivery via hydrogels. Endosomes are formed by inward budding of the plasma membrane of the cell, and multivesicular bodies (MVBs) by inward invagination of the limiting membrane, and inward budding. Vesicles are then released into the extracellular space to become exosomes as the MVBs fuse with the lysosome or plasma membrane. Exosomes secreted are primarily proteins, nucleic acids and lipids. Proteins found inside the exosomes may be categorized into two: the first category consists of the proteins that are frequently expressed on exosomes that can be utilized as markers (CD9, CD63, and CD81); and the second category the unique proteins of the parent cells. Hydrophilic polymer networks (hydrogels) can trap exosomes and mediate the problem of poor retention in tissues by providing a controlled-release scaffold that fixes them into a specific area of activity. Composite hydrogel-exosome systems have been utilized in such areas as tissue engineering and pathogenesis investigation. Adapted from refernce[106] under a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

Besides preventing degradation of exosomes, hydrogels can also promote exosomal bioactivity through a favorable surrounding environment necessary during release. Hydrogels have the potential to replicate extracellular matrix (ECM) which facilitates exosome-cell interactions vital to tissue repair and regeneration. In particular, the exosomes administered in hydrogels with the addition of ECM components like collagen/hyaluronic acid may be used to augment the cell adhesion, migration, and proliferation required during periodontal tissue regeneration.[109,110]

Controlled and Targeted Release for Localized Action in Periodontal Tissues

The main strength of muco-adhesive hydrogel as a carrier of exosomes is the provision of a controlled and localized release. The bio-adhesiveness of hydrogels enables them to stay longer at the point of application, thereby keeping the exosomes near the required tissues, including periodontal ligament cells, osteoblasts, and fibroblasts, that play an imperative role in the regeneration of periodontal tissues.

Under regulation of exosomes release rates, hydrogels can enable a continuous, sustained release of the therapeutic molecules, resulting in improved treatment efficacy. This topical activity is especially useful in periodontitis where it is necessary to stimulate tissue growth and dismiss inflammation in precise spots of the clinical foundation.[32] The controlled release process reduces the frequency of the treatment process by increasing patient compliance and in decreasing chance of occurrence of side effects due to systemic delivery of the drug.

The exosome release by hydrogels can be controlled by the modification of the composition of the hydrogel, its morphology, and its crosslinking density. Hydrogels, compared to those with high crosslinking density, are known to release their cargo more gradually, and hydrogels with crosslinking densities reduced can afford speeds of release.[111] Through choosing and altering these parameters, scientists can maximise exosome release kinetics in order to match the regeneration requirements of the periodontal tissue, as illustrated in Figure 5.

Moreover, the hydrogels may be modified with targeting ligands or peptides that enhance exosome attachment to receptors on target cells, leading to heightened specificity and success of the treatment.[32] This will facilitate delivery of the exosomes to the inflamed periodontal tissue, preventing off-target effects and increasing the therapeutic success.

Influence of Hydrogel Properties on Exosome Release Kinetics

Characteristics of the muco-adhesive hydrogel, such as its viscosity, the time required to reach its gel state, and the density of crosslinks have an immense effect on the release kinetic of the encapsulated exosomes. These properties are to be carefully optimized so that the exosome is released so that it can contribute to the regeneration of tissue and decrease the inflammation.

The formulation viscosity of the hydrogel will dictate the degree to which the formulation is attached to the mucosal surface, as well as affecting the release rate of exosomes. More viscous hydrogels are more likely to maintain their shape and block the leakage of exosomes too quickly, which means that they will release the liquid over a longer time.[106] Nevertheless, excessively viscous hydrogels can retard exosomes diffusion which might alter their initial therapeutic effect. Thus, viscosity optimization is important in obtaining sustained release and immediate therapeutic effects.

Gelation time is the amount of time it takes the hydrogel to solidify when put on the skin. The production of a stable hydrogel gel at the site of application, in addition to the encapsulation of exosomes efficiently, is achieved by perfect gelation time. Localized treatment would require rapid gelation because it would prevent exosome leakage out of the site prior to the solidification of the hydrogel structure. Nevertheless, an excessively rapid gelation mechanism might cause low encapsulation efficiencies.[113,114]

Another important determinant of exosome release profile is the extent of crosslinking in the hydrogel matrix. The covalent coupling between chains of the polymer is known as crosslinking and this process makes the hydrogel more mechanically stable and robust. A dense crosslinking density tends to lower the rate of release because the hydrogel network is more closely compact than when the crosslinking densities are generally low, which means the exosomes have little room to diffuse. Conversely, an exosome release may be facilitated by lower crosslinking densities but be at the expense of structural integrity of the hydrogel. Therefore, balancing crosslinking density is essential to ensure controlled and sustained exosome release that aligns with the regenerative needs of the periodontal tissue.[115,116]

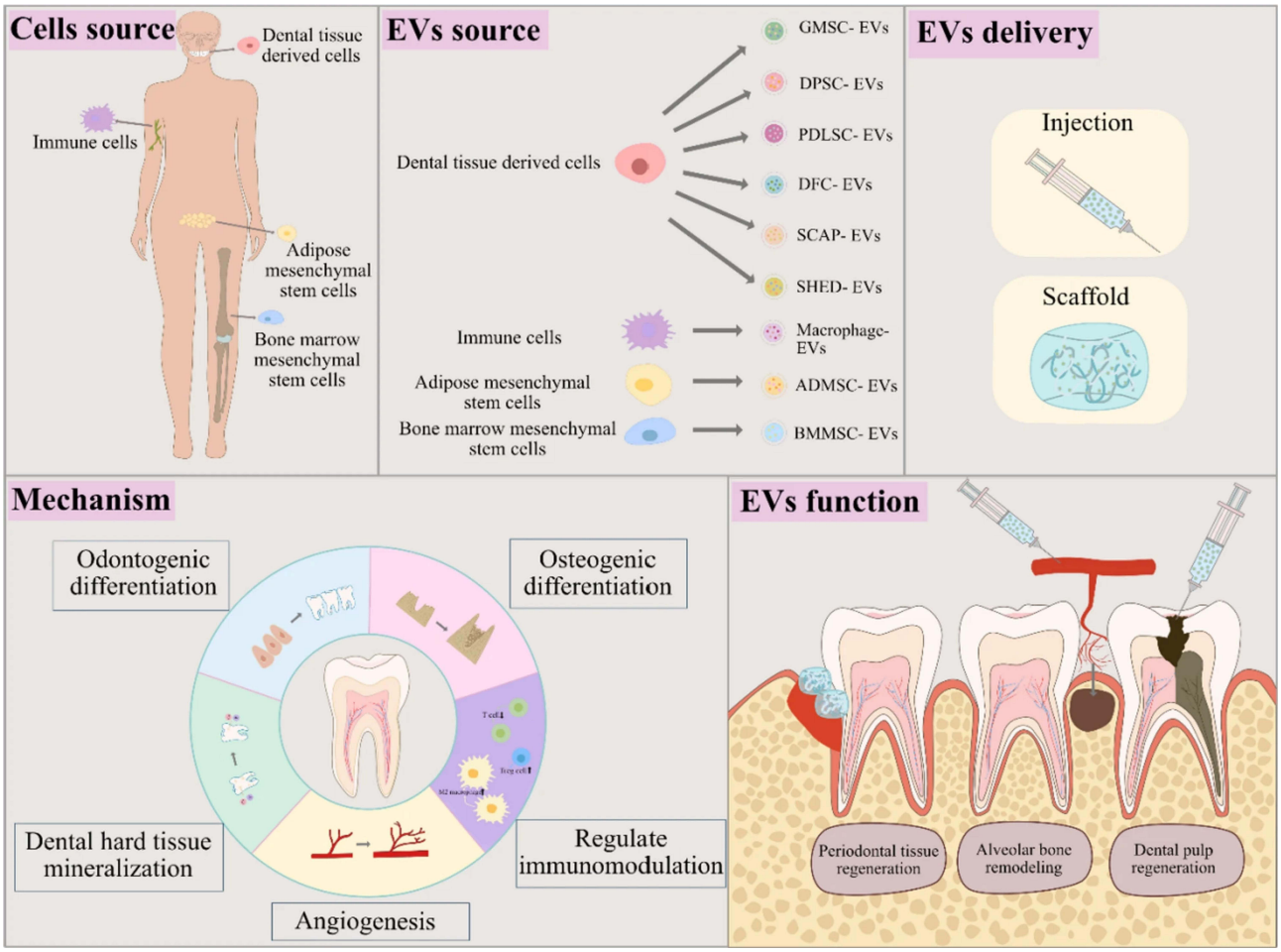

Figure 5 The figure provides a detailed representation of the role of EVs in the regeneration of periodontium. It describes the differing cellular sources and EV sources that are suitable for this purpose, which include dental tissue-derived cells, immune cells, and mesenchymal stem cells that originate from adipose tissue and bone marrow. Moreover, it depicts the modalities of EV administration, this involves direct injection as well as scaffold-mediated delivery. The figure highlights a mechanistic role EVs play in Periodontal regeneration including enhancing odontogenic, osteogenic differentiation, enabling dental hard tissue mineralization, promoting angiogenesis and modulating immune responses. Ultimately, it emphasizes the functional importance of EVs for regeneration of periodontal tissues, remodeling of alveolar bone, and dental pulp regeneration. Adapted from reference[112] under a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

Strategies for Designing Exosome-Loaded Muco-Adhesive Hydrogels

Exosome-loaded muco-adhesive hydrogel design plays a key role in advancing new therapeutic techniques in tissue restoration and inflammation management, especially in situations with periodontitis, some of which are mentioned in Table 2. Muco-adhesive hydrogels are very useful in delivering exosome to the periodontal tissues in a local and cumulative manner and this provides means to improve the stability of exosome, its controlled release, and its bioactivity.

Exosome Encapsulation Methods

The optimal delivery of such vesicles to the target tissues depends on exosome encapsulation that would safeguard their biological activity. Different methods of filling the exosome into muco-adhesive hydrogels exist and offer different benefits and difficulties. One of the most applicable ways of loading is the passive method in which the exosomes are incorporated into the precursors of hydrogel prior to its crosslinking. It is a very straightforward method that is based on the ability of exosomes to bind with hydrogel matrix naturally.[114] It is economical with low material costs and capable of using exosomes without denaturing their bioactivity under harsh conditions, thus, it is applicable to formulations that need non-aggressive encapsulation.[118] Low encapsulation efficiency with passive loading is however possible because

Table 2 Summary of Key Strategies, Mechanisms, and Materials Involved in Exosome-Loaded Muco-Adhesive Hydrogel Systems for Periodontal Therapy

Strategy	Biological/Functional Mechanism	Key Components Used	Therapeutic Objective	Technical or Translational Barrier	References
Muco-adhesive Hydrogels	Adhere to mucosal tissues for sustained drug release	Chitosan, Pectin, PEG, PVA	Site-specific delivery, retention	Degradation and muco-adhesive stability	[29,60]
Exosomal Therapy	Intercellular signaling via vesicle-mediated bioactive transfer	MSC-derived Exosomes	Tissue healing, immune regulation	Isolation difficulty, stability loss	[21,27]
Combined Hydrogel-Exosome	Controlled delivery of exosomes via bio-adhesive gel	Chitosan/PEG with exosomes	Regeneration at infected periodontal site	Efficiency of encapsulation, release tuning	[14,117]
Natural Polymer Hydrogel	Muco-adhesion via ionic and H-bond interactions	Chitosan, Pectin	Biodegradable and biocompatible matrix	Variable behavior, less controlled release	[38,49]
Synthetic Polymer Hydrogel	Networked gel modulated by crosslinking	PEG, PVA	Tuned and prolonged release kinetics	Biotoxicity risk and poor immune compatibility	[52,56]
Anti-inflammatory Function	Exosomal RNA inhibits cytokine expression	miRNA in exosomes	Chronic inflammation suppression	Requires specificity in inflamed tissue	[26,84]
Regeneration Signaling	Exosomes promote angiogenesis and osteogenesis	VEGF, BMPs in exosomes	Periodontal tissue regeneration	Lack of human trial validation	[25,79]
Hydrogel Engineering	Modulation of release via viscosity, porosity	Tuned crosslinking density	Localized and delayed release	Balancing strength vs permeability	[61,62]
Clinical Periodontal Use	Topical application of hydrogel composites	Exosome-infused muco-gels	Non-surgical bone and ligament healing	Clinical scale-up and standardization	[88,101]
Encapsulation Strategy	Electrostatic and passive loading methods	HA, Alginate, Gelatin	High encapsulation + bioactivity	Aggregation, diffusion limitations	[32,85]

the exosomes are not uniformly dispersed in the hydrogel material and a proportion of the exosomal activity can be lost during the gelling process.

Instead, as a more efficient method, electrostatic assembly is feasible, particularly in the case when charged polymers form the hydrogel matrix. This method utilizes electrostatic interactions between the charged exosome membrane and charged elements of the hydrogel.[115] During this process the exosomes are adsorbed onto the surface of the hydrogel matrix leading to better distribution and increased encapsulation efficiency unlike passive loading. Electrostatic assembly has the advantage of using a controlled loading process, but it should be taken into consideration that to avoid either aggregation of exosomes or their destabilization, it is important to carefully optimize the ionic strength and pH conditions.

Besides these approaches, there are several aspects that affect the efficiency of exosome encapsulation, and how it preserves its integrity. To begin with, the concentration of exosomes is highly influential on encapsulation as high concentration levels usually result in enhanced loading efficiencies. Nonetheless, when the exosome concentrations are too high, they may aggregate and impair their bioactivity.[119] Encapsulation is also dependent on the selection of hydrogel polymer which are often hyaluronic acid, alginate, or chitosan due to their biocompatibility and giving a favorable microenvironment to exosome encapsulation.[103,120] Also, the gelation protocol and the crosslinking density of a hydrogel also influence the final loading efficiency of exosomes. Fast gelation or large crosslinking densities cause physical stress on exosomes and can negatively affect their bioactivity, whereas low crosslinking densities and slow gelation generally produce improved encapsulations.

Muco-Adhesive Hydrogel-Exosome Composite Formulations

Although the encapsulation of the exosomes is promising, in combination with the other bioactive in hybrid formulations, exosomes can be effectively utilized in periodontal treatment. These formulations seek to present a multi-dimensional avenue by adding other growth factors, cytokines or anti-microbial factors that have a synergistic effect with exosomes to promote tissue healing, regulate inflammation and prevent infection.

Addition of growth factors is a vital element of such hybrid formulations as they enhance significant regenerative mechanisms including angiogenesis, osteogenesis and angiogenesis among fibroblast proliferation. As an example, shoreline loading of hydrogels with bone morphogenetic proteins (BMPs), fibroblast growth factors (FGFs), or vascular endothelial growth factor (VEGF) may increase bone formation, vascularization of the tissue, and collagen production, which are crucial to the successful periodontal regeneration.[100] These supplements collaborate with exosomes and enhance that regenerative capacity and repair of damaged periodontal tissues even more.

The hydrogel formulations can also carry anti-inflammatory agents alongside the growth factors, to provide a means to reign in the chronic inflammation characteristic of periodontitis. The long-term inflammation leads to the destruction of tissues, and thus, the combination of corticosteroids or NSAIDs and exosomes can assist in the smothering of pro-inflammatory cytokines, including IL-1 8, TNF- α, and IL-6. The simultaneous action of exosomes and anti-inflammatory substances can not only decrease the inflammation rate but also speed up the recovery of injured tissues.[41,60,121] Such preparations provide more holistic treatment since they take care of the inflammatory and regenerative component of treating periodontitis.

In addition, the hydrogel can be loaded with antimicrobial compounds to eliminate bacteria that in most cases complicate periodontal diseases. Exosomes can be co-delivered with antibiotics, antimicrobial peptides, or natural antimicrobial compounds such as silver nanoparticles, such that the hydrogel nanomaterial does not only facilitate tissue regeneration but also hinders post-surgical infection. This dual-action approach is particularly important in periodontal defects, where both inflammation and infection play significant roles in disease progression.[122,123]

Influence of Hydrogel Structure on Exosome Release Rate and Biological Activity

The release rate and biological activity of encapsulated exosomes depend on the structural features of muco-adhesive hydrogels significantly. The degradation rate of the hydrogel matrix, as well as crosslinking density and porosity is important in determining the release of exosomes with time.[32] Exosomes with smaller crosslinking densities tend to release their payload more readily because diffusion of exosomes is limited by the tight packing of the matrix. This

reduced rate of release might be useful when aiming at long-lasting therapeutic effects, especially where long-term regeneration is needed.[88,110,111] Too slow-release rate though can postpone the start of therapeutic actions. By contrast, the release rates of lower crosslinking densities can increase, and these might be advantageous during acute stages of the treatment, where the therapeutic effect is immediately required.

Exosome release rate depends also on porosity. It can also be seen that hydrogels that are more porous offer more area that the exosomes under consideration can diffuse through, ultimately resulting in more rapid release profiles.[106] Although this can be acceptable in some instances eg where you want rapid delivery, it also contributes to early loss of exosomes at the site of treatment. Alternatively, less permeable hydrogels could provide slower release with increased exosome retention at the desired site to maintain exposure to the therapeutic molecules longer.[88,97]

Another important factor affecting exosome release is the rate of degradation of hydrogel. Controlled degrading hydrogels such that the material in the hydrogel maintains a constant release of exosomes as the material degrades, where exosomes are present at the site throughout the process of tissue regeneration.[106,110] Such controlled degradation would be particularly significant in chronic conditions such as periodontitis, when prolonged tissue repair is required. The hydrogel's degradation rate can be tailored by modifying the polymer composition, crosslinking density, or incorporating enzymatically degradable components, allowing for a more customized release of exosomes that aligns with the regenerative timeline of the periodontal tissues.

In vitro and in vivo Studies

Numerous in vitro and in vivo studies have addressed the potential of exosome-loaded muco-adhesive hydrogels in regenerating tissues and making a reduction in inflammation in periodontal diseases. Such experiments are necessary to determine the effectiveness of exosomes that react with hydrogels in stimulating tissue healing. It is through the outcomes of both preclinical and clinical trials that a better insight into the therapeutic potential of exosome-loaded hydrogels, on particulate episodes of periodontitis, is achieved.

In vitro, exosomes produced by MSC encapsulated into hyaluronic acid-based hydrogels (eg HA ALG modified with hydroxyapatite) have demonstrated a significant boost to proliferation, migration, and osteogenic differentiation of pre-osteoblastic/progenitor cells and similarly a PDLSC-exosome-loaded alginate/gelatin or HA hydrogel promoted osteogenic gene expression and mineral deposition in vitro - making them suitable as a periodontal bone regeneration agent.[102,104] Also, the migration of fibroblasts and collagen production in collagen originate is achieved by exosome delivering hydrogel and is critical in wound healing and tissue repair in periodontal tissues. According to these studies, engineered hydrogel has demonstrated a role in delivery of exosomes in addition to supporting a viable cellular environment that promotes cellular growth as well as tissue regeneration. Besides, the anti-inflammatory properties of exosomes have been observed in in vitro under the study where exosome-loaded hydrogels reduced the production of pro-inflammatory cytokines TNF- α, IL-1 β, and IL-6 and therefore have the potential to modulate immune response in disease such as periodontitis.[124] It implies that the exosome-loaded hydrogels can have a positive effect on not only the regeneration of the tissues but also in the manipulation of the inflammation that is repeatedly noted in the periodontal diseases.

Preclinical experiments, which were performed on animal models, have also tested the effectiveness of muco-adhesive hydrogel-loaded exosomes in healing periodontal tissues. According to a recent study, exosome-loaded alginate hydrogel in rat models of periodontitis demonstrated substantial periods of bone, periodontal ligament, and cementum regeneration. These results indicate the possibility of using exosome-loaded hydrogel to regenerate both hard (line) and soft (ligament) tissues, which is also essential in treating periodontitis.[14]

Along with preclinical studies early-stage clinical studies were carried out to determine the safety and efficacy of exosome-loaded hydrogel in human periodontal treatment. A pilot clinical trial conducted by Froum et al (2024) involved the insertion of MSC-derived exosomes in a muco-adhesive hydrogel and insertion into human periodontal defects. The trial was very successful, as the participants revealed high success in clinical outcomes, such as the reduction of probing depth, attachment levels, and the density of bone. Radiographic assessments showed that exosome-loaded hydrogels displayed aptness in elevating bone regeneration around the compromised teeth. This pilot trial was an essential experience in confirming potential of exosome-based therapies to regenerate periodontal tissues in human subjects.[101]

Likewise, it has been noted during their clinical trials, the use of exosome-loaded hydrogels in the treatment of patients resulted in lower inflammatory indicators and outcomes, including harder bone and better tissue repair.[125] These preliminary clinical results are promising in that the exosome-loaded muco-adhesive hydrogels hold promise in the form of an effective approach to treating periodontal diseases in humans.

Challenges and Future Perspectives

Although the application of exosome-loaded muco-adhesive hydrogels in treating periodontal tissues necessitating tissue regeneration and inflammation reduction are promising, a number of challenges must be overcome to ensure that such therapies see a wide implementation in clinical practice. These issues are associated with questions of preparation, stability, and delivery of the exosome-loaded gels and the necessity to conduct more extensive clinical trials to prove long-term efficacy and safety.

Challenges in Exosome Preparation and Characterization

Preparation and characterization of exosomes is one of the core problems associated with using exosomes as therapeutic agents. Exosomes are extracellular vesicles of natural origin, and separating them from biological fluids or cell cultures may prove difficult because of the variability of the exosome population and the prevalence of contaminating factors like proteins, lipids, and other vesicles.[126] Exosome isolation methods including ultracentrifugation, size-exclusion chromatography and immunocapture can have unsatisfactory yields, reproducibility, and purification, resulting in variability and a lack of quality in the exosome preparations. These issues make it more difficult to streamline exosome-based therapies and could affect how effective these therapies will be in the clinical environment.

Additionally, preparing intact exosomes in terms of their biological integrity is of paramount importance. Exosome bioactivity tends to be low due to a drop in exosome integrity during isolation and handling. Therapeutic effects of the exosomes depend largely on preserving the functional cargo (proteins, lipids, and RNAs) that the exosomes carry. These challenges can be mitigated by new methods aimed at the enhanced isolation of exosomes, including microfluidic-based or size-selective filtration-based techniques, which are only beginning to be utilized in the clinical world.[127,128]

Stability and Storage of Exosome-Loaded Hydrogels

The other issue is the stability and storage of the exosome-loaded hydrogels. Exosomes are also susceptible to environmental conditions like temperature, PH and enzyme degradation that may result to loss of exosome bioactivity with time.[129] The ability of exosomes to be incorporated into muco-adhesive hydrogels provides a solution to this challenge since it allows the exosomes to be shielded against environmental stressors and gives it a controlled release system. Nevertheless, the temperature and humidity that these hydrogels are stored in can affect the stability of the exosomes and the release kinetics of the exosomes. Well-optimized storage protocols and freeze-drying techniques to achieve long-term stability should be developed so that exosome-loaded hydrogels can acquire therapeutic efficacy under storage and transport conditions.

Besides, storage conditions can also influence muco-adhesive properties of hydrogels. The lack of proper storage may also lead to the loss of adhesive properties of hydrogels which will decrease the potential for hydrogels to remain in contact with the target tissues and lower the number of exosomes delivered over time. Hence, more studies are needed to achieve better formulation of stable hydro gels that would deliver exosomes and at the same time can retain muco-adhesive capability of these exosomes over prolonged storage.

Controlled and Targeted Delivery

Exosome-loaded hydrogels afford mode of controllable delivery, the realization to attain accurate and targeted delivery is a challenge. The therapeutical effectiveness of exosome-based systems relies on the possibility to target exosomes to a particular tissue and within proper concentration during a prolonged period. Despite the possible advantages of muco-adhesive hydrogels, tissue specificity and localization of exosome delivery is subject to additional optimization.

Two approaches have been used to increase exosome targeting efficacy; surface-modification of exosomes with a targeting peptide, antibody, or ligand that binds a specific cell surface receptor. Nonetheless, the creation of these

alterations necessitates an in-depth knowledge of the biological and molecular basis of exosome targeting and receptors existing in the periodontal tissues. Furthermore, it is imperative to balance exosome release kinetic and biological activity. Exosome-loaded hydrogel loaded release profiles need customisation in relation to the regenerative demand of periodontal tissues. That will involve a fine-tuning effect of the crosslinking density, degradation rate, and porosity of the hydrogel to sustain and localize exosome release.[130,131]

Regulatory approval and safety of this treatment method are great challenges in clinical use of exosome-loaded hydrogels, just like any other novel form of therapy. The exosomes are grouped as biologic products that their clinical implementations should meet strict compliance of regulation, such as quality control, purity, and biocompatibility. Regulatory environment of the Exosome-based therapies is not fully established yet and therapeutic exosome loading in hydrogels clinical translation guidelines remain immature. Long-term preclinical studies and clinical trials must evaluate safety profile of exosome-based treatment with respect to immune response, long term effects, and toxicity.[132]

Scalability of exosome production to clinical practice is another serious matter to consider. The reason is because the existing directions of exosome isolation are costly, time-consuming, and lack the ability to give mass production for a large amount of exosome production. The validity of exosome−based therapies as a realistic clinical practice will require developing more effective ways to produced exosomes and establishing them to be pure and reproducible.

Limitations of Current Evidence

Exosome loaded-muco adhesive hydrogels show great potential in periodontal therapy, there are still significant blocks in the current literature. These challenges are mostly due to problems related to exosome isolation protocols, purity, yield, stability, storage and regulatory and manufacturing limitations, the comparison between the characteristics and hydrogel methods are mentioned in Table 3.

Exosome isolation approaches such as ultracentrifugation (UC), size-exclusion chromatography (SEC) and precipitation-based approaches offer different advantages and disadvantages. Ultracentrifugation is the most widely used due to its high yield and cost-effectiveness; however, it is time consuming and expensive and may extend to other EV types outside exosomes, thus potentially impairing the therapeutic efficiency of exosomes.[133] In contrast, SEC helps to isolate exosomes at high purity and is therefore less prone to contamination than UC, but the production of exosomes is often low and is therefore prohibitively expensive to perform at a large scale for clinical applications.[134] Moreover, SEC requires optimising experimental conditions for reproducibility, which has created an ongoing challenge for wide adoption of SEC.[134] Precipitation-based methods being less expensive and easier to implement are however associated with a unit reduction of purity of exosomes, consequently decreasing bioactivity and overall therapeutic potential.[135]

Table 3 Comparison of Exosomes Isolation Methods and Hydrogel Characteristics

Factor	UC	SEC	Chitosan-based Hydrogels	PEG-based Hydrogels
Exosome Isolation	High yield	High purity	Biocompatible	Tunable mechanical properties
	Standard method	Low yield	High muco-adhesion	Longer degradation times
Advantages	Cost-effective	Pure exosome preparation	Ideal for oral applications	Controllable degradation rate
	Well-established protocol	Reduces contaminants	Easily modified	Enhanced mechanical strength
Disadvantages	Time-consuming	Expensive	Poor stability at high pH	Risk of cytotoxicity
	Requires specialized equipment	Limited yield	Poor control over release rate	Limited muco-adhesion
Purity and Yield	Moderate purity, high yield	High purity, low yield	Moderate purity	High purity
Stability and Storage	Sensitive to temperature fluctuations, requires cold storage	Stable if stored correctly	Moderate stability, may degrade in humid environments	Stable at room temperature
Regulatory/Manufacturing Barriers	Widely used but requires optimization for clinical scale-up	Not yet standardized, expensive	Requires optimization for clinical scale-up	Requires strict quality control to avoid toxicity

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The development of mucoadhesive hydrogels for phytological use in the periodontal approach has made considerable advances; however, significant limitations remain existent, including that of compositional features, discharge kinetics, bioactivity, and biocompatibility. Various chitosan-based hydrogels have been used as matrices due to their biocompatibility and intrinsic muco-adhesive properties, making it suitable for oral delivery systems.[136] However, these systems are not stable in alkaline conditions and drug release profiles are highly heterogeneous, which might affect the drug effectiveness of long duration regimen. Moreover, the degradative behavior of chitosan hydrogels can have a negative effect on the controlled release of encapsulated exosomes resulting in suboptimal therapeutic effects.[137]

In contrast, PEG derivatives of hydrogels yield better mechanical properties with higher than added control over degradation tendencies. However, the introduction of such synthetic polymers may compromise cytotoxic liabilities and reduce muco-adhesion compromising long term stability within the mucosal environment.[138,139]

Another main challenge is to preserve and store the exosome-loaded hydrogels. Exosomes show significant sensibility to environmental conditions such as temperature, pH and proteolytic degradation. Exosomes require cryogenic storage to ensure their functional integrity; temperature variations during shipping or storage can cause exosomal degradation, thereby affecting therapeutic efficacy.[132] Moreover, hydrogels, especially PEG-based hydrogels, also face stability limitations when stored for longer time periods. For example, PEG hydrogels could be stable at ambient temperature but would exhibit compromised muco-adhesive strength after storage over an extended period of time, which will impair the ability to contact mucosal surfaces to perpetuate the drug release.[140]

Future Perspectives

Nevertheless, exosome-loaded muco-adhesive hydrogels fabrication as a future method of periodontal tissue regeneration seems to have great potential. Future studies would be directed towards the optimization of exosome isolation protocol, the optimization of hydrogel formulations and the improvement of targeted delivery systems. A greater guidance of nanotechnology, biomaterials, and bioengineering will lead to more effective exosome delivery systems and guarantee that the delivery of exosome is timely, targeted, and at the right dose.[14]

Moreover, with further development of exosome biology, the possibility to use genetically engineered exosomes, or bioengineered hydrogels turning out to be more effective in tissue regeneration and inflammation modulation is likely to be studied. Enhancements of exosomes-based therapies by combining them with other regenerative technologies like stem cell therapy or delivery of growth factors may result in more effective and all-inclusive solutions to periodontitis and all tissue degenerative diseases.

Lastly, pre-clinical testing assesses the long-term safety and efficacy of exosome-loaded muco-adhesive hydrogels will play a pivotal role transitioning this therapeutic approach, beyond the laboratory setting, into clinical therapy. With the evolvement of the field, great opportunities open up and these innovative treatments can become a common practice when approaching the treatment of periodontal diseases to offer more effective approaches to tissue regeneration and control of inflammation cases.

Conclusion

In this review, the potential of exosome-loaded mucoadhesive hydrogels as an attractive method for the regeneration of periodontal tissues and for targeted drug delivery is discussed. Exosomes, because of their intrinsic biological properties and their ability to regulate inflammatory pathways, are ideal candidates for enhancing tissue repair and regeneration. These vesicles, when placed within mucoadhesive hydrogel networks, provide the benefit of prolonged residence at the therapeutic site which is a prerequisite for the ongoing therapeutic action. Furthermore, hydrogel systems based on chitosan or PEG have been shown to act as a promoting scaffold for exosome delivery to exploit tissue integration and cellular response. However, there still exist several limitations in the use of these systems. While chitosan-based hydrogels have been extensively studied because of their biocompatibility these materials are unstable under alkaline conditions and demonstrate highly anisotropic drug delivery, which can affect long-term therapeutic application. On the other hand, hydrogels based on PEG provide better mechanical properties and better reproducible degradation while interactions with the mucosal tissue are decreased, possibly reducing bioavailability of encapsulated exosomes at the site of interest. Moreover, the isolation of exosomes is still the key issue, because techniques like ultracentrifugation and size-

exclusion chromatography produce inconsistent results in terms of purity, yield and scalability for the clinical application. The physicochemical steadiness upon storage, regulatory approval challenges and lack of standardised manufacturing protocols additionally impede their large-scale clinical adoption. While exosome-loaded muco-adhesive hydrogels hold great potential as targeted vehicles for periodontal therapy, continued research is required to optimize exosome isolation protocols, hydrogel formulations, and storage conditions. Furthermore, clinical trials with long-standing duration are critical to establish the safety and efficacy of these therapeutic modalities in actualities. Analytical solutions to these issues would allow exosome-based hydrogel systems to progress in regenerative medicine and precision drug delivery.

Data Sharing Statement

Not Applicable. This is a review article, and all relevant information is provided in the article.

Ethical Approval and Consent to Participate

Not Applicable. This is a review paper and does not involve direct research on humans or animals.

Consent for Publication

"Not applicable" as this manuscript does not contain data from any person.

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Disclosure

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