Journal of Health and Rehabilitation Research 2791-156X JHRR

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Narrative Review

Classification of Oral Ulcers and its Treatment by focusing on Exosome Loaded Hydrogel: A Comprehensive Review

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Conflict of Interest: None.

Shahid F., et al. (2024). 4(2): DOI: https://doi.org/10.61919/jhrr.v4i2.867

ABSTRACT

Background: Oral ulcers significantly impact patient quality of life, manifesting as acute or chronic lesions that can cause considerable discomfort and pain. These ulcers arise from a variety of etiological factors and disrupt daily activities due to the painful loss of mucosal tissue.

Objective: This review aims to elucidate the etiology and management of oral ulcers, with a focus on innovative treatment modalities involving hydrogels and exosomes.

Methods: We reviewed current literature on the pathology and treatment of oral ulcers. Special attention was given to the properties of hydrogels and exosomes, their biomedical applications, and their roles in new therapeutic strategies for oral ulcers.

Results: Hydrogels, due to their biocompatibility, biodegradation, and controlled release properties, have emerged as effective drug delivery systems. Exosomes, loaded within these hydrogels, enhance treatment outcomes due to their high cellular communication capacity and anti-inflammatory properties.

Conclusion: Innovative treatments utilizing hydrogels and exosomes offer promising alternatives for the management of oral ulcers, potentially improving drug delivery efficiency and patient compliance.

Keywords: Drug-Delivery; Exosomes; Hydrogels; Oral Ulcers; Treatment.

INTRODUCTION

Oral ulcers, characterized as painful lesions within the oral cavity, significantly diminish the quality of life for affected individuals. Commonly, topical drugs serve as the primary treatment for these ulcers (1). However, the moist environment of the oral cavity poses challenges for ointment retention due to dynamic conditions such as swallowing, chewing, and speaking. Consequently, various strategies have been developed to improve treatment efficacy (7, 8). Among these, hydrogels have emerged as an effective drug delivery system, offering properties such as swelling, biodegradation, biocompatibility, and controlled release (3). Additionally, exosomes—vesicles secreted by numerous cell types, including mesenchymal stem cells (MSCs)—are under investigation for their potential in medical applications due to their enhanced cellular communication, biocompatibility, and anti-inflammatory activities (4, 5). This review discusses the various types of oral ulcers and explores the management of these lesions, particularly through the innovative use of hydrogel as a drug delivery vehicle and the promising role of exosomes in treating oral ulceration.

1. Oral Ulcers

Oral ulcers, often indicative of underlying conditions, pose diagnostic challenges for clinicians (9). These lesions, affecting nearly 25% of the global population, are recurrent and impact daily activities significantly (2). The primary feature of an oral ulcer is the disruption of the underlying epithelial integrity. Expert opinion is crucial for the accurate diagnosis and management of these lesions, as their morphologies can vary, with some displaying distinct features and others lacking specificity (10).

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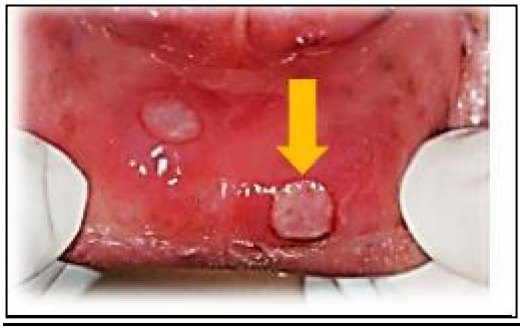
Figure 1 Ulceration in the Oral Cavity (10).



1.1. Etiology of Oral Ulceration

The primary causes of oral ulceration include infections and physical trauma, such as cheek biting or chemical burns from oral care products. Long-term exposure to medications like aspirin and immune reactions also contribute to ulcer development. Although less common, microbial infections from Herpes simplex virus I and II and autoimmune diseases like Behçet's disease are known etiological factors (11, 12).

2. Types of Oral Ulcers

Oral ulcers are classified based on duration as either acute, lasting less than two weeks, or chronic, persisting for more than two weeks. Solitary ulcers refer to a single lesion, whereas multiple ulcers describe numerous lesions within the oral cavity. Recurrent oral ulcers reappear after healing and require management strategies aimed at reducing pain and preventing secondary infections (13).

3.1. Acute Oral Ulceration

Acute oral ulcers typically resolve within two to three weeks (14). These include:

3.1.1. Traumatic Ulcers

Traumatic ulcers result from mechanical trauma or thermal burns, commonly occurring on the buccal mucosa, lips, and tongue. They appear as isolated red lesions with raised borders and a whitish-yellow membrane (13).

3.1.2. Necrotizing Sialometaplasia

This condition involves the salivary glands and is thought to be caused by blood flow obstruction to the salivary gland lobules. Other factors include trauma, smoking, and eating disorders. Often misdiagnosed, it mimics malignant conditions like squamous cell carcinoma and typically heals within two to twelve weeks (15).

3.1.3. Primary Herpetic Gingivostomatitis

Caused predominantly by Herpes simplex virus type I, this condition manifests with general malaise, fever, and nausea, followed by fluid-filled blisters that rupture to form painful ulcers. Treatment includes fever reduction, a soft diet, and in severe cases, antiviral therapy (16, 17).

3.1.4. Erythema Multiforme

Triggered mainly by an immune reaction to HSV type I, erythema multiforme lesions are distinguished by their target-like appearance. Management aligns with the etiological factors, often involving antiviral therapy and topical corticosteroids (19).

3.1.5. Oral Hypersensitivity Reactions

These reactions are rare and challenging to diagnose, often manifesting as white or red ulcers similar to lichenoid reactions. Common causes include dental restoration materials like nickel alloys and components in toothpastes. Management involves ceasing the use of suspected materials and applying topical drugs such as triamcinolone if the cause remains unidentified (20).

3.2. Chronic Oral Ulceration

Chronic oral ulcers, which do not resolve within two weeks, may indicate severe conditions such as squamous cell carcinoma or tuberculosis (18). Various diseases associated with chronic ulceration include:

3.2.1. Lichen Planus

This autoimmune disease presents as lacey white lesions with erosive areas, causing a burning sensation and soreness. Treatment may involve topical steroids, and in more severe cases, systemic therapies such as cyclosporine or methotrexate (23).

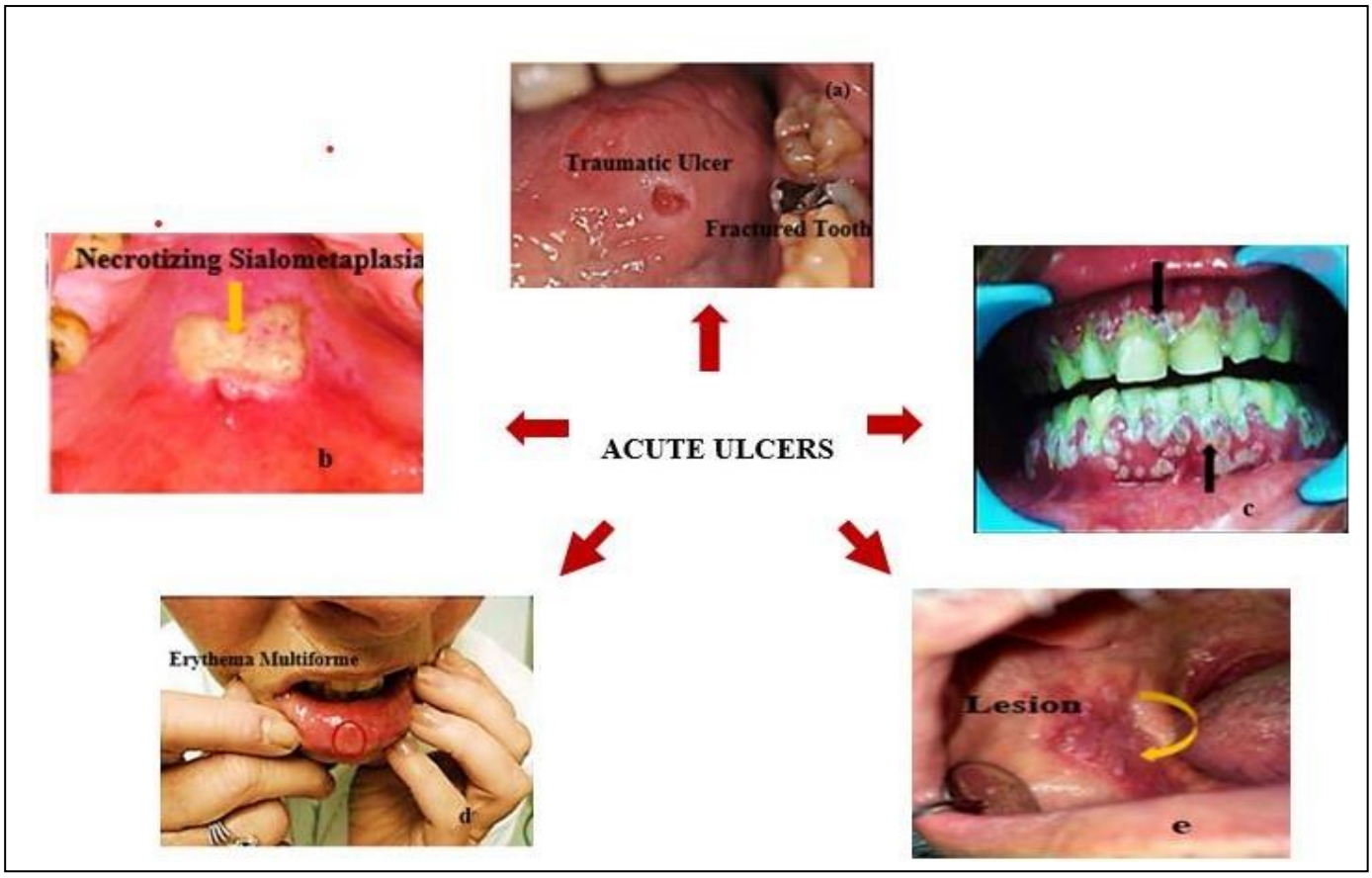


Figure 2 Acute Ulcers: (a) Traumatic Ulcer (21). (b) Necrotizing Sialometaplasia (15). (c) Primary Herpetic Gingivostomatitis (22) (d) Erythema Multiforme(19). (e) Oral Hypersensitivity Reactions (18).

3.2.2. Mucous Membrane Pemphigoid

Primarily affecting the mucosal lining of the oral cavity, this condition presents as erythematous patches or blisters. Treatment strategies vary based on the severity, ranging from topical corticosteroids to systemic immunosuppressants like azathioprine (24).

3.2.3. Pemphigus Vulgaris

Characterized by superficial blisters that rupture to form irregular, painful lesions, treatment for pemphigus vulgaris includes systemic corticosteroids and newer biologic therapies such as rituximab (25).

3.2.4. Deep Fungal Infections

Infections like oral candidiasis, histoplasmosis, and blastomycosis present with lesions that may resemble malignancies. Management involves antifungal therapies such as itraconazole, supplemented by amphotericin B in severe cases (26, 27).

3.2.5. Squamous Cell Carcinoma

This malignant condition often manifests as crater-like lesions with a velvety base, primarily affecting the tongue and floor of the mouth. Treatment approaches include targeted therapies such as cetuximab and tyrosine kinase inhibitors like gefitinib (28, 29).

This comprehensive review highlights the classification of oral ulcers based on duration and appearance, discusses their etiologies, and examines innovative treatments such as exosome-loaded hydrogels, offering promising directions for enhancing therapeutic outcomes in oral ulcer management.

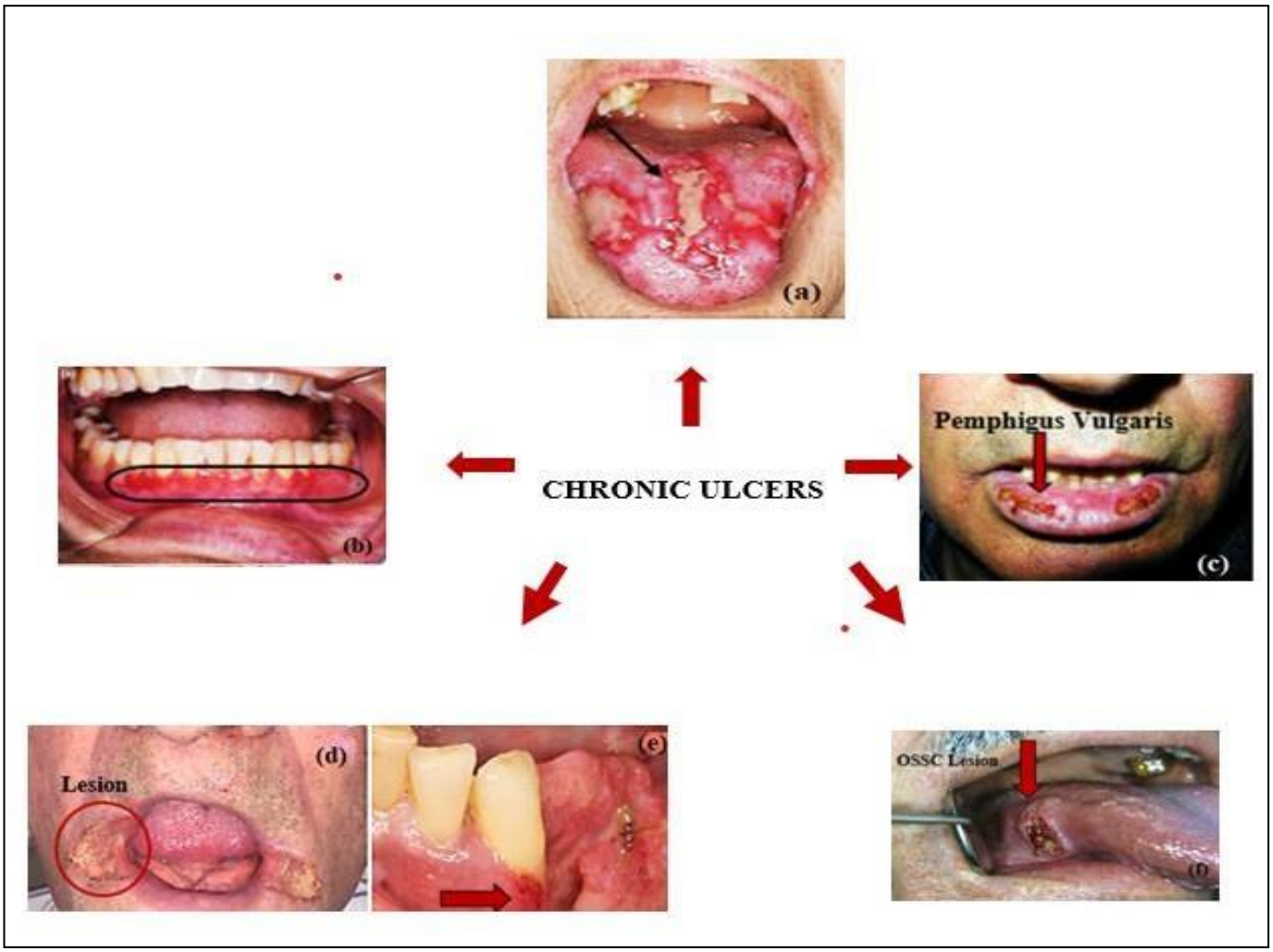


Figure 3 Chronic Ulcers: (a) Lichen Planus (30). (b) Mucous Membrane Pemphigoid (24).(c) Pemphigus Vulgaris(25).(d)&(e) Deep Fungal Infections (26). (f) Squamous Cell Carcinoma (13).

3.3. Recurrent Oral Ulceration

Recurrent ulcers consistently reemerge following periods of healing (13). Various forms of ulcers in the oral cavity exhibit this recurring pattern.

3.3.1. Recurrent Aphthous Stomatitis (RAS)

Recurrent aphthous stomatitis represents one of the most prevalent disorders affecting the oral mucosa, afflicting approximately 20% of the population, with a higher incidence observed in women (31). These lesions, typically small—around 1 cm in diameter—and round, are characterized by a red halo surrounding a gray-colored membrane. The standard therapy for mild cases of RAS employs topical corticosteroids such as dexamethasone, triamcinolone, and fluocinonide, alongside antimicrobial agents like tetracycline and chlorhexidine gluconate. Topical anesthetics, including lidocaine and benzocaine, are also used to alleviate pain (32).

3.3.2. Behçet's Disease

Behçet's disease, a chronic condition marked by inflammation of blood vessels, frequently manifests with recurrent oral ulcers, genital ulcers, and skin lesions (33). These lesions can appear anywhere on the mucosal lining of the oral cavity or the pharynx (13). The management of oral ulcers in Behçet's disease typically involves topical treatments such as corticosteroids, sucralfate, and pentoxifylline, complemented by diligent oral hygiene. In severe cases, systemic corticosteroids are prescribed (34).

4. Treatment of Oral Ulcers

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Ulcers are predominantly managed through the administration of topical medications, such as corticosteroids and analgesics. In cases of severe ulceration, immunosuppressive drugs are employed, although this approach carries risks such as drug resistance (1). The initial treatment regimen for oral ulcers includes topical agents. Antiseptics and anti-inflammatory drugs are also utilized, with 0.2% chlorhexidine gel being applied directly to the ulcers. Diclofenac and hyaluronic acid are used to reduce pain. Amlexanox, an anti-inflammatory agent, is another topical medication employed in ulcer treatment (36).

Topical antibiotics serve to inhibit collagenases and metalloproteinases, crucial in ulcer management. Tetracycline and its derivatives, doxycycline and minocycline, are administered in tablet form. Triamcinolone acetonide is specifically used for treating erosive lesions in the oral cavity (36). In chronic ulcerations, corticosteroids and immunosuppressive drugs such as oral prednisone, thalidomide, and clofazimine are utilized (36). Recent research has explored natural extracts for treating oral ulcerations, with compounds from Salvadora persica, Jasminum grandiflorum, Bixina orellana, and curcumin showing efficacy in accelerating the healing process (1).

4.1. Problems Associated with Treatment of Oral Ulceration

The systemic therapy for oral ulcers can lead to adverse effects. Thalidomide, for instance, is teratogenic and can also cause drowsiness and constipation. Oral prednisone may result in prolonged adverse effects such as oral thrush (36). Resistance to medications, disruption of the oral cavity's flora, and secondary infections have also been documented (1).

4.1.1. Dynamic Environment of the Oral Cavity

The oral cavity's dynamic environment, characterized by continuous exposure to saliva and the impact of eating and speaking, complicates the treatment of ulcers using topical drugs. The retention time of topical ointments and gels is limited, often being cleared by saliva within less than an hour, whereas oral lesions require at least 12-24 hours for optimal healing (37).

5. Newer Strategies to Treat Oral Ulcers

Beyond conventional topical therapy, innovative approaches involving tissue engineering have been adopted to enhance the treatment of oral ulcers.

5.1. Tissue Engineering

Tissue engineering, as defined by Langer and Vacanti, is an interdisciplinary field that applies engineering and life sciences principles to develop biological substitutes that restore, maintain, or improve tissue or organ function (39). This field typically involves three fundamental components: cells, signaling molecules, and scaffolds. Scaffolds, constructed from polymers, ceramics, or their composites, can be designed in various three-dimensional configurations. Cells may be embedded within these scaffolds or the implanted scaffolds may facilitate cellular proliferation (38).

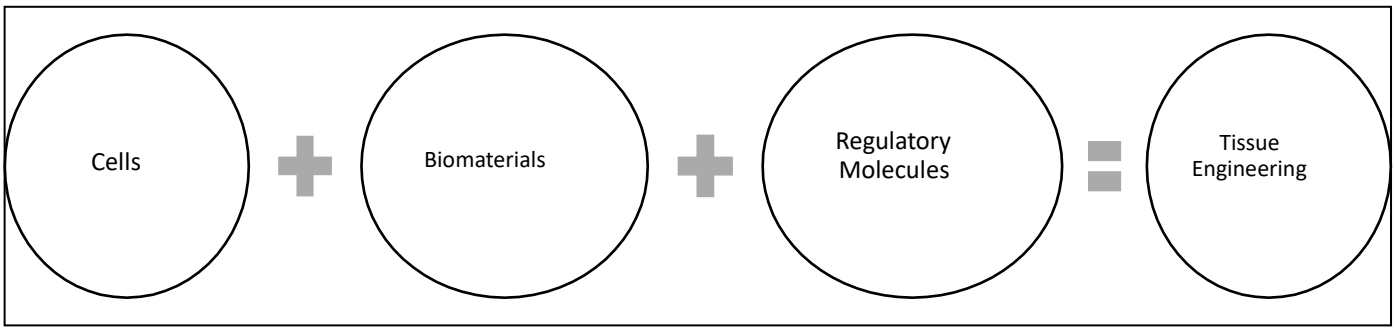

Figure 5: Components of Tissue Engineering.

5.2. Hydrogels

Hydrogels, hydrophilic polymer networks capable of absorbing substantial amounts of water or bodily fluids, mimic the structure and properties of bodily tissues due to their high water content, porous structure, and flexibility (41, 42). Their biocompatibility makes them suitable for various medical applications, including drug delivery, contact lenses, and wound dressing materials (43).

5.2.1. Classification of Hydrogels

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Hydrogels are classified based on their origin as natural, synthetic, or hybrid, incorporating properties of both types. These polymers may be homopolymers or copolymers, and their networks can be cross-linked either physically through temporary junctions or chemically via permanent bonds. Cross-linking methods include free-radical polymerization, simple mixing, and bulk polymerization (44).

5.2.2. Biomedical Applications of Hydrogels

The biocompatibility of hydrogels facilitates their use in various biomedical applications. These applications include drug delivery, contact lenses, and wound dressing. Hydrogels in tissue engineering are particularly promising, used in constructing scaffolds for regenerative medicine, including bone, nerve, and cardiac tissue engineering (46).

This section has been revised to ensure high-quality, medically researched content, interconnected paragraphs, and clarity in English language usage, maintaining the same headings and subheadings, and preserving in-text references appropriately.

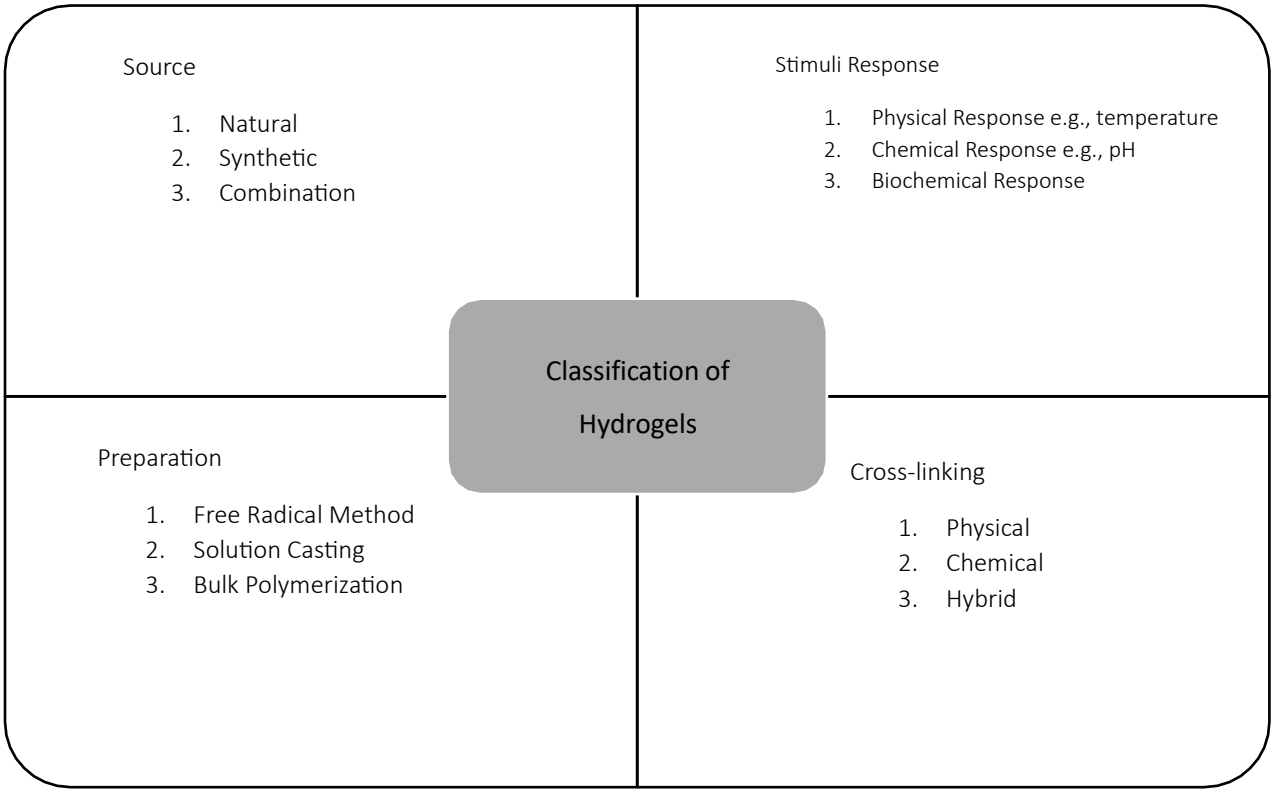

Figure 6 Classifications of Hydrogels.

5.2.2.1 Contact Lenses

Contact lenses, utilized for vision correction, drug delivery, and aesthetic enhancement, are directly associated with the eye. These lenses are often fabricated from hydrogels composed of Poly (2-hydroxyethyl methacrylate) (pHEMA), polyacrylonitrile, polyvinyl alcohol, and other hydrophilic polymers. Silicone hydrogels and hydrogels based on fluorine are also prevalent due to their enhanced biocompatibility, superior oxygen permeation, and suitability for drug delivery (46, 47). Commercially available hydrogel-based contact lenses include brands such as Airsoft™, Gentle 59, and everclear™ ELITE (47).

5.2.2.2 Wound Dressing

Hydrogels are employed in wound dressings for burns or injuries affecting all skin layers. These hydrogels, available as gels, gauzes soaked in gels, or sheets, are designed to be biocompatible, non-toxic, and biodegradable. They also must possess sufficient mechanical strength and maintain a moist healing environment (48). Examples of commercially available hydrogel wound dressing materials include ActivHeal®, DermaSyn®, NU-GEL™, INTRASITE◊ Gel, SOLOSITE◊ Gel, Purilon®, and Woun'Dres® (47).

5.2.2.3 Hydrogels in Tissue Engineering

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Due to their resemblance to living tissues, hydrogels demonstrate significant potential in regenerative medicine (49). They are utilized to construct scaffolds for heart, bone, and cartilage tissues. For instance, hydroxyapatite nanoparticles incorporated into hydrogels have shown promising osteoinductive behavior in bone tissue engineering. Similarly, in nerve and cardiac tissue engineering, hydrogels aid in nerve regeneration and cardiac muscle repair, respectively. Studies by Ayesha et al. have indicated that hydrogels containing nano-cellulose, sodium alginate, and calcium chloride can serve as effective tools in cardiac tissue engineering (47, 51). Another study demonstrated that hydrogels containing gelatin and eggshell particles could promote osteoblastic differentiation (47, 52).

5.2.2.4 Hydrogels for Drug Delivery

Hydrogels have attracted significant attention as drug delivery devices due to their porous structure, which facilitates the efficient loading and release of drugs. Drug release from hydrogels can be controlled through mechanisms such as diffusion, chemical reactions, environmental factors, and swelling. This capability, coupled with their biocompatible nature, allows hydrogels to protect the drug from the surrounding environment and provide controlled release (Caló and Khutoryanskiy, 2015). When crafted from degradable polymers, these hydrogels enable the gradual release of drugs as they degrade within the body (53).

5.3 Mucoadhesive Hydrogels

In the context of hydrogels, mucoadhesion refers to the ability of hydrogel particles to adhere to the mucosal lining, a process that relies on the interactions between the hydrogel and its environment, resulting in swelling and expansion (54). Polymers exhibiting inherent cationic properties, such as chitosan, enhance the mucoadhesive properties of hydrogels due to the anionic nature of glycoproteins in mucin. Conversely, anionic materials with carboxyl functional groups and thiol groups also contribute to mucoadhesion through the formation of disulfide bonds (55).

6 Exosomes: An Innovation

Exosomes are membranous vesicles excreted into the extracellular space by nearly all cell types, facilitating numerous cellular functions such as intercellular communication and responses to trauma and infections. They carry essential cellular information, containing a mix of proteins, nucleic acids, and lipids (4).

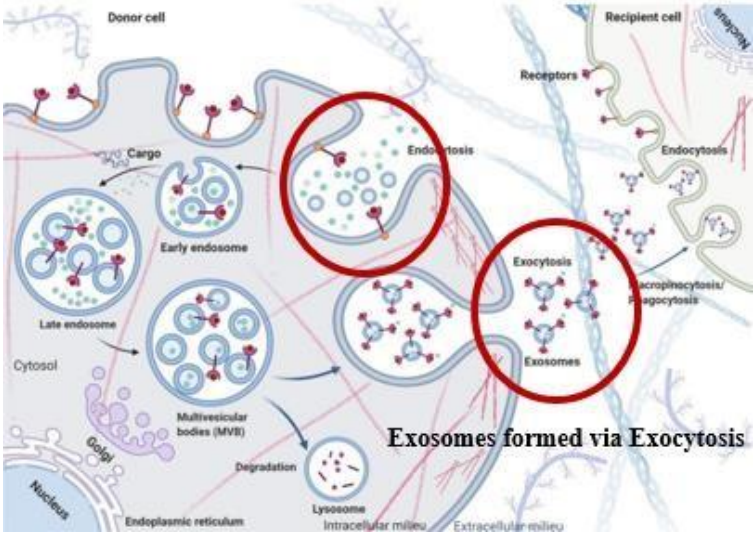
6.1 Architecture of Exosomes

Exosomes comprise various biologically active molecules crucial for cellular communication. Their composition includes proteins, DNA, RNA, and lipids. The protein content includes surface proteins like immunomodulatory proteins and integrins, and other components such as endosomal sorting complexes required for transport (ESCRT). Exosomes also contain significant biomarkers like CD8, CD9, CD63, CD81, Flotillin, Ceramide, and Alix (56).

6.2 Biogenesis of Exosomes

Exosome formation occurs through exocytosis (4). This process starts in the endosomal system where early endosomes evolve into multi-vesicular bodies (MVBs). These MVBs eventually integrate with the plasma membrane, releasing intraluminal vesicles (ILVs) into the extracellular space (57).

Figure 7 Exosome Biogenesis (4).



6.3 Isolation of Exosomes

Isolating exosomes is challenging due to their low density and similarity to other bodily components (58). Techniques such as ultracentrifugation, ultrafiltration, and size exclusion chromatography (SEC) are employed. Ultracentrifugation, based on size and density differences, is the most commonly used method. Ultrafiltration relies on molecular size or weight, while SEC utilizes a column with porous beads to separate exosomes based on size (4, 58).

This revision preserves the high standards of medical research, interconnectedness of paragraphs, clarity in the English language, and accurate citation of references, ensuring a cohesive and technically correct presentation.

6.4. Therapeutic Applications of Exosomes

Exosomes have garnered significant attention for their multifaceted applications in biomedicine. These vesicles have demonstrated the capability to facilitate wound healing by activating various biological pathways and have shown potential in traversing the blood-brain barrier. Research has also explored their utility in treating cardiovascular and hepatic diseases, as well as in bone regeneration. The focus of many studies has been on their capacity to be loaded with therapeutic agents, maintain drug stability, and deliver these drugs effectively to targeted sites. Conventional drug delivery systems often face challenges related to targeted delivery and biocompatibility, issues which exosome-based systems promise to address (4, 5).

6.4.1. Wound Healing

Studies have indicated that exosomes derived from mesenchymal stem cells significantly promote the healing of wounds. They enhance epithelial cell proliferation and stimulate fibroblasts to secrete collagen, aiding in epithelialization. Furthermore, exosomes contain microRNA that could potentially serve as a treatment for chronic ulcers. The beneficial effects of exosomes in wound healing are attributed to the activation of pathways such as phosphoinositide 3-kinase (PI3K)/AKT, ERK, and STAT-3. They also have the potential to mitigate chronic inflammation, which is particularly beneficial in diabetic conditions where it can prevent wound formation (4).

6.4.2. Cardiovascular Diseases

Exosomes are composed of a complex array of molecules, including lipids, proteins, DNA, and RNA. The microRNA (miRNA) within exosomes has been recognized for its role in the post-transcriptional regulation of gene expression. In the context of atherosclerosis, miRNA facilitates cellular communication, which is thought to reduce the formation of atherosclerotic plaques. For patients experiencing acute coronary syndrome (ACS), miRNA levels are significantly higher compared to those in healthy individuals, suggesting its potential as a diagnostic biomarker. Additionally, miRNA is implicated in the myocardial remodeling observed in heart failure patients (60).

6.4.3. Brain Injury

Exosomes have shown promise in the treatment of traumatic brain injuries, which can significantly reduce life expectancy and lead to long-term disabilities. Their ability to cross the blood-brain barrier makes them a viable option for treating inflammatory conditions and promoting healing processes in the brain. In stroke patients, elevated levels of miRNA have been observed, which may serve as a diagnostic biomarker. Exosomes from mesenchymal stem cells (MSCs) are noted for their enhanced ability to support neuron formation and neurovascular remodeling (4).

6.4.4. Cancer

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Exosomes play a crucial role in detecting physiological changes from their cells of origin and are being explored for their potential in liquid biopsies. They offer advantages in early diagnosis and monitoring when compared to circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA). For instance, in hepatocellular carcinoma and non-small cell lung cancer, specific proteins and PD-L1 levels have been identified at increased levels in exosomes, highlighting their potential as diagnostic biomarkers (61).

6.5. Usage of Exosomes in Dentistry

Exosomes, ubiquitous across all cell types, have captured interest as potential biomarkers for diagnosing various oral diseases. They can differentiate between normal and diseased states by analyzing specific molecules unique to their cell of origin. For example, elevated miRNA levels have been observed in the salivary exosomes of patients with periodontitis. Similarly, increased PD-L1 mRNA levels have been found in exosomes from the saliva of periodontitis patients. Although research is limited in diseases like Sjögren's syndrome, combining tear and salivary exosomal molecules could potentially lead to accurate diagnoses (62).

7. Hydrogels Encapsulating Exosomes for Drug Delivery

The delivery of exosomes to target sites has been enhanced by the use of hydrogels. These materials are biocompatible and can be engineered to maximize the effectiveness of exosome delivery. Chitosan-based hydrogels, for example, have been developed for effective wound healing. However, research into hydrogels loaded with exosomes is still in its early stages. Ongoing efforts aim to refine these systems to overcome challenges such as the presence of un-reacted cross-linking agents, which pose risks during the hydrogel processing. Thus, the selection of biocompatible materials for hydrogel fabrication is critical (63).

CONCLUSION

Oral ulcers manifest in a variety of forms, with treatment strategies tailored to the severity of each lesion. Topical steroids, commonly administered as gels or ointments, represent the initial therapeutic approach. However, due to the dynamic environment of the oral cavity, maintaining the retention of these treatments poses significant challenges. In response, hydrogels have emerged as a promising alternative for drug delivery. Ongoing research efforts are focused on developing an optimal hydrogel-based drug delivery system. Additionally, the potential of exosomes encapsulated in hydrogels to serve as effective drug delivery vehicles is being explored. Various strategies are currently under development to harness exosomes for the treatment of oral ulcers.

ACKNOWLEDGEMENT

Dr. Fahhem Ullah expresses deep gratitude to the National University of Medical Sciences (NUMS) for supporting this research through the Technology Innovation Fund project # NUMS-TIF-1/2022.

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