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Modified Drug Delivery of Steroids in Oral Lesions

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KEYWORDS

Drug Delivery Systems, Oral Administration, Bioadhesive Drug Delivery Systems, Mucoadhesive Agents, Nanoparticles, Pharmacokinetics , Therapeutics

ABSTRACT:

This Narrative Review investigates the advancements in steroid therapy for managing oral lesions through innovative drug delivery systems. Oral lesions, such as aphthous ulcers, oral lichen planus, and pemphigus vulgaris, pose significant therapeutic challenges due to their chronic nature and the potential systemic side effects of conventional steroid treatments. This review comprehensively examines current and emerging modified drug delivery methods designed to optimize the local administration of steroids, enhancing therapeutic efficacy while minimizing systemic exposure and side effects.

The review explores into various innovative delivery systems, including bioadhesive formulations, mucoadhesive patches, and nanoparticle-based carriers, each offering unique advantages in targeting and sustained release of steroids within the oral cavity by enhancing local drug concentration and prolonging drug action at the lesion site, these technologies aim to improve clinical outcomes and patient adherence to treatment protocols.

It also highlights the pharmacokinetics, clinical efficacy, and safety profiles of these advanced delivery systems and also discusses the practical implications of these findings and outlines potential future directions for research and development in this area.

Overall, this narrative review emphasizes the critical role of innovative drug delivery systems in the effective management of oral lesions with steroids, advocating for continued exploration and refinement of these approaches to enhance patient care in dentistry

1. Introduction

The realm of dental medicine frequently intersects with the complex management of various oral lesions, which can profoundly affect patients' oral health and overall well-being. Oral lesions are painful, debilitating and pose significant treatment challenges.[1] Traditionally, the therapeutic arsenal against these inflammatory and autoimmune conditions has heavily relied on corticosteroids due to their potent anti-inflammatory and immunosuppressive properties.[2] Moreover, the systemic administration of steroids is fraught with potential side effects, ranging from gastrointestinal disturbances to more severe complications like adrenal suppression and osteoporosis, making the risk-benefit ratio a critical consideration in their use.[3]

In light of these challenges, the development of modified drug delivery systems for oral steroids presents a promising avenue to enhance treatment efficacy while minimizing adverse effects. This evolution in pharmacotherapy is geared towards optimizing the therapeutic index of steroids through localized delivery mechanisms, which concentrate the drug's effects on the lesion site.[4] The concept and the primary goal of modified drug delivery in dentistry is to improve the bioavailability, stability, and patient compliance of steroid treatments by maximizing therapeutic outcomes while minimizing the adverse effects associated with systemic steroid administration.[5]

The novel delivery systems provide a sustained and controlled release of the steroid directly at the site of the lesion, ensuring a high local concentration of the drug while minimizing systemic exposure. This can be achieved through several innovative approaches, including bioadhesive gels, mucoadhesive tablets, liposomal formulations, nano-carriers, etc. Each method offers distinct advantages in terms of drug retention, absorption, and patient comfort, thereby enhancing the overall therapeutic outcomes.[6]

The modified drug delivery of oral steroids represents a significant leap forward in the treatment of oral lesions.

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So Here, we delve into the mechanisms, advantages, clinical applications, and innovations of the prominent methods in use today in the treatment of oral lesions.

BIOADHESIVE GELS

Bioadhesive gels represent a significant advancement in the localized delivery of steroids for treating various oral lesions.[7,8]

Key Components:

Polymers: These include cellulose derivatives (e.g., hydroxypropyl methylcellulose), carbomers, polycarbophil, and chitosan. These polymers swell upon contact with saliva, forming a gel matrix that adheres to the mucosa.

Steroids: Commonly used steroids in bioadhesive gels include triamcinolone acetonide, hydrocortisone, and clobetasol propionate.[7]

Mechanism of Action

These gels are designed to adhere to the mucosal surfaces within the oral cavity, providing sustained release of the active pharmaceutical ingredient (API) directly at the site of the lesion.[7,8]

Advantages:

Gels are easy to apply and can cover irregular lesion surfaces effectively. The gel matrix allows for a slow and steady release of the steroid, maintaining therapeutic drug levels at the lesion site for extended periods. The adhesive nature of the gel ensures that the steroid is concentrated at the site of the lesion, reducing systemic exposure.[8,9]

Current Formulations and Innovations

Kenalog in Orabase: This formulation contains triamcinolone acetonide in a bioadhesive paste, commonly used for inflammatory oral lesions.

Oracort E: A bioadhesive gel containing triamcinolone acetonide, designed for prolonged mucosal adhesion and sustained release.[10]

Experimental Formulations:

Hydrocortisone Gels: Research continues into optimizing hydrocortisone-containing gels for better adhesion and drug release profiles.

Combination Therapies: Gels combine steroids with other agents, such as antimicrobial or analgesic agents, to address multiple symptoms and complications of oral lesions.

Mucoadhesive Nanofiber Gels: Utilizing nanotechnology to enhance the adhesion and controlled release properties.

Thermo-responsive Gels: These gels remain liquid at room temperature but transform into a gel upon contact with the warmer temperatures of the oral cavity, improving application and retention.[10,11]

MUCOADHESIVE TABLETS

Mucoadhesive tablets represent a cutting-edge approach to the localized delivery of steroids for treating oral lesions.[11, 12]

Mechanism of Action

Mucoadhesive tablets leverage the adhesive properties of specific polymers to stick to the oral mucosa. The tablet gradually hydrates and swells, forming a gel-like layer that releases the steroid in a controlled manner ensuring prolonged contact time and localized drug release ensuring high drug concentration at the lesion site while minimizing systemic exposure.[13]

Key Components:

Polymers: Commonly used mucoadhesive polymers include hydroxypropyl methylcellulose (HPMC), carbomers, polyvinyl alcohol (PVA), and chitosan. These polymers interact with the mucosal surface through hydrogen bonding, van der Waals forces, and electrostatic interactions.

Steroids: Steroids commonly incorporated into these tablets include hydrocortisone, triamcinolone acetonide, and dexamethasone.[12,13]

Advantages:

The adhesive properties allow for sustained release, reducing the need for frequent reapplication, and are concentrated at the lesion site, enhancing efficacy and reducing systemic side effects. Ease of use and reduced dosing frequency improve patient adherence.[14]

Current Formulations and Innovations

Oracort E: This drug is also available in mucoadhesive tablet form. A widely used formulation containing triamcinolone acetonide, designed to adhere to the mucosal tissues and provide sustained drug release.

Experimental Formulations:

Hydrocortisone Mucoadhesive Tablets: Research continues to optimize these tablets for better adhesion and controlled release profiles.

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Combination Therapies: Tablets combine steroids with other therapeutic agents, such as antimicrobials or analgesics, to address multiple symptoms and complications of oral lesions.

Layered Tablets: Utilizing multi-layer designs to control the release rate and sequence of the drug.

Biodegradable Polymers: Developing tablets with biodegradable polymers that gradually dissolve, releasing the drug and leaving no residue.[15]

LIPOSOMAL

Liposomal formulations represent a sophisticated and highly effective approach to delivering oral steroids for the treatment of various oral lesions.[16]

Mechanism of Action

Steroids are encapsulated within the aqueous core or lipid bilayer of the liposomes. Upon application, the liposomes fuse with the mucosal membranes, facilitating the release of the steroid directly at the site of the lesion. The lipid bilayer protects the steroid from immediate degradation, allowing for a controlled and sustained release.[16,17]

.**Key Components:**

Lipids: Common lipids used in liposome formulations include phosphatidylcholine, cholesterol, and other phospholipids. These lipids form bilayers that encapsulate the drug.

Steroids: Steroids commonly used in liposomal formulations for oral lesions include dexamethasone, hydrocortisone, and triamcinolone acetonide.

Advantages:

Liposomes enhance the localization of steroids at the lesion site, increasing therapeutic efficacy. Encapsulation minimizes systemic absorption, reducing the risk of side effects. Liposomes protect the encapsulated steroid from degradation, improving its stability and bioavailability.[17]

Current Formulations and Innovations

Dexamethasone Liposomal Gel: This formulation provides sustained release and enhanced penetration of dexamethasone for treating inflammatory oral lesions.

Hydrocortisone Liposomes: Research continues into optimizing liposomal hydrocortisone for better adhesion, controlled release, and improved patient outcomes.

Combination Therapies: Liposomal formulations combining steroids with other therapeutic agents, such as antifungals or antimicrobials, to address multiple symptoms and complications of oral lesions.

Novel Lipid Compositions: Innovations in lipid compositions to enhance the stability and bioavailability of the encapsulated steroid.

Stealth Liposomes: Incorporating polyethylene glycol (PEG) to create PEGylated liposomes, which can evade the immune system, prolong circulation time, and enhance drug delivery to the target site.[17,18]

NANOCARRIERS

These Nano-sized delivery systems are designed to enhance the solubility, stability, and bioavailability of steroids, ensuring targeted delivery and controlled release at the lesion site.[20]

Mechanism of Action

Nano-carriers, including nanoparticles, nanofibers, and nanogels, are engineered to deliver steroids in a highly controlled and targeted manner. Steroids are encapsulated within or bound to the surface of nanoparticles, ensuring stability and protection from degradation. It is designed to target specific cells or tissues within the oral cavity, ensuring that the drug is delivered precisely where it is needed. The nano-carrier matrix allows for a sustained and controlled release of the steroid, maintaining therapeutic levels over extended periods.[20,21]

Key Components:

Polymers and Materials: Common materials used for nano-carriers include biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA), chitosan, and polyethylene glycol (PEG). These materials are chosen for their biocompatibility and ability to protect the drug.

Steroids: Steroids commonly delivered via nano-carriers include dexamethasone, hydrocortisone, and betamethasone.

Advantages:

It improves the solubility and stability of steroids, enhancing their bioavailability. The targeted approach minimizes systemic absorption, reducing the risk of side effects. Controlled release mechanisms maintain consistent drug levels at the lesion site, reducing the need for frequent administration.[21]

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Current Formulations and Innovations

PLGA Nanoparticles: These biodegradable nanoparticles are widely researched for encapsulating steroids like dexamethasone and hydrocortisone. They offer controlled release and targeted delivery, enhancing therapeutic outcomes.[21]

Chitosan Nanoparticles: Chitosan is used for its mucoadhesive properties, which help the nanoparticles adhere to the mucosal surface, providing localized and sustained drug release.

Nanofibers: Electrospun nanofibers loaded with steroids like budesonide offer a high surface area for drug loading and controlled release, making them suitable for direct application to oral lesions.

Nanogels: Hydrophilic nanogels can encapsulate steroids and provide a moist environment, promoting healing while releasing the drug in a controlled manner.

Functionalized Nano-Carriers: Nano-carriers can be functionalized with ligands or antibodies to target specific cells or receptors within the oral cavity, enhancing the precision of drug delivery.

Hybrid Nano-Systems: Combining nanoparticles with other delivery systems, such as liposomes or hydrogels, to create hybrid systems that offer multiple mechanisms for controlled and targeted drug release.[23,24]

IN SITU GELS

In situ gels represent a novel and highly effective approach for the localized delivery of oral steroids to treat various oral lesions. These systems undergo a sol-to-gel transition upon contact with physiological conditions in the oral cavity, allowing for the sustained and targeted release of steroids directly at the lesion site.[25,26]

Mechanism of Action

In situ gels are designed to be applied in a liquid or semi-liquid form. The in situ gel remains in a liquid state at room temperature but transforms into a gel upon contact with warmer temperatures, pH changes, or ionic conditions in the oral cavity. The gel adheres to the mucosal surface, providing a controlled and sustained release of the steroid at the site of the lesion.[26]

Key Components:

Polymers: Common polymers used in in situ gel formulations include poloxamers, chitosan, gellan gum, and alginates. These polymers are chosen for their biocompatibility and responsiveness to environmental triggers.

Steroids: Steroids frequently used in these formulations include dexamethasone, triamcinolone acetonide, and hydrocortisone.[25,26]

Advantages:

The gel's adhesion properties ensure prolonged contact time with the mucosal surface, allowing for sustained drug release. The drug is concentrated at the lesion site, enhancing therapeutic efficacy and reducing systemic side effects. The liquid form allows for easy application, and the subsequent gel formation ensures it stays in place.[27]

Current Formulations and Innovations

Poloxamer-Based Gels: These gels use poloxamers (e.g., Pluronic F127) that remain liquid at lower temperatures and gel upon warming to body temperature. They are used for the sustained release of steroids like dexamethasone.[27]

Chitosan-Based Gels: Chitosan gels, which gel in response to the acidic environment of the oral cavity, are utilized for their mucoadhesive properties and controlled release of steroids.

Alginate-Based Gels: Alginate gels, which gel in response to calcium ions present in saliva, provide a sustained release mechanism for steroids such as hydrocortisone.

Combination Gels: Formulations combining multiple responsive polymers to create a gel that responds to more than one environmental trigger, enhancing control over the release profile.

Biodegradable In Situ Gels: Using biodegradable polymers that gradually break down, providing a sustained release of the steroid and reducing the need for removal.[26,27,28]

MICRCO EMULSIONS

Microemulsions are isotropic, thermodynamically stable mixtures of oil, water, surfactants, and co-surfactants, capable of encapsulating both hydrophilic and lipophilic drugs. Microemulsions enhance the solubility, stability, and bioavailability of steroids, providing targeted and controlled release directly at the lesion site.[29,30]

Mechanism of Action

Microemulsions utilize a unique composition to deliver steroids efficiently and effectively to the site of oral

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lesions. Steroids are dissolved in the oil phase and dispersed uniformly within the microemulsion. The small droplet size of the microemulsion facilitates the penetration of steroids through the mucosal barrier, ensuring localized delivery. The microemulsion structure allows for a controlled release of the steroid, maintaining therapeutic levels at the lesion site over an extended period.[31]

Key Components:

Oil Phase: Common oils used include medium-chain triglycerides (MCTs), isopropyl myristate, and oleic acid. These oils dissolve the lipophilic steroid and enhance its penetration through the mucosal barrier.

Aqueous Phase: Water or aqueous buffers in which hydrophilic components are dissolved.

Surfactants and Co-surfactants: Surfactants such as polysorbates (e.g., Tween 80), and co-surfactants like ethanol or propylene glycol, stabilize the microemulsion and reduce surface tension.

Advantages:

Microemulsions can solubilize lipophilic steroids, improving their bioavailability. The system targets the drug to the lesion site, reducing systemic absorption and side effects. Microemulsions are thermodynamically stable, ensuring consistent performance and prolonged shelf life. Their liquid form allows for easy application and spreading over the mucosal surfaces.[30,31]

Current Formulations and Innovations

Microemulsion Gels: Combining the benefits of microemulsions and gels, these formulations offer enhanced stability and prolonged contact time at the lesion site.

Dexamethasone Microemulsion Gel: A formulation that provides sustained release and enhanced penetration of dexamethasone for treating inflammatory oral lesions.

Nanoemulsions: These are similar to microemulsions but with even smaller droplet sizes, offering improved stability and drug delivery properties.

Hydrocortisone Nanoemulsion: Research into optimizing nanoemulsions for better adhesion and controlled release profiles.

Incorporation of Penetration Enhancers: Adding compounds such as essential oils or permeation enhancers to further improve the penetration of steroids through the oral mucosa.

Hybrid Systems: Combining microemulsions with other delivery systems, such as liposomes or nanoparticles, to create hybrid systems that offer multiple mechanisms for controlled and targeted drug release.

Customized Microemulsions: Tailoring the composition of microemulsions to individual patient needs and specific lesion characteristics for personalized treatment approaches.[31]

HYDROGELS

Hydrogels are polymeric networks that can retain a significant amount of water while maintaining a gel-like structure, making them ideal for sustained and targeted drug release in the moist environment of the oral cavity.[32]

Mechanism of Action

Steroids are incorporated into the hydrogel matrix during the preparation process.The hydrogel adheres to the mucosal surface, forming an intimate contact that facilitates localized drug delivery. The hydrated polymer network allows for a gradual and sustained release of the steroid, maintaining therapeutic levels at the lesion site over time.

Key Components:

Polymers: Common polymers used in hydrogel formulations include natural polymers like chitosan, alginate, and gelatin, as well as synthetic polymers like polyvinyl alcohol (PVA) and polyethylene glycol (PEG).

Steroids: Steroids commonly delivered via hydrogels include dexamethasone, triamcinolone acetonide, and hydrocortisone.[33]

Advantages:

It provides a prolonged release of the drug, reducing the frequency of administration. Targeted delivery minimizes systemic absorption and associated side effects. Hydrogels are typically biocompatible and well-tolerated by the oral tissues. Their gel-like consistency allows for easy application and retention at the lesion site.

Current Formulations and Innovations

Pluronic F127 Gels: These hydrogels remain in a liquid state at lower temperatures and gel upon warming to body temperature, allowing for easy application and sustained release of steroids like dexamethasone.

Chitosan Gels: Chitosan-based hydrogels gel in response to the acidic environment of the oral cavity,

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providing mucoadhesive properties and controlled release of steroids.

Alginate Gels: Alginate hydrogels gel in response to calcium ions present in saliva, providing a sustained release mechanism for steroids such as hydrocortisone.

Hybrid Systems: Combining hydrogels with other delivery systems, such as nanoparticles or liposomes, to create hybrid systems that offer multiple mechanisms for controlled and targeted drug release.

PEGylated Hydrogels: Incorporating PEG to enhance the biocompatibility, stability, and controlled release properties of the hydrogel.[34,35,36]

ELECTROSPUN FIBERS

Electrospun fibers are nanofibrous matrices that offer a high surface area-to-volume ratio and tunable properties, allowing for controlled drug release and enhanced therapeutic outcomes. Electrospun fibers can be engineered to encapsulate steroids and deliver them directly to the lesion site in a sustained manner, minimizing systemic exposure and associated side effects.[37]

Mechanism of Action

The polymer solution containing the steroid is ejected through a fine needle or nozzle and subjected to an electric field, resulting in the formation of nanofibers. The steroid is incorporated into the polymer matrix during the electrospinning process, ensuring uniform distribution throughout the fibers. The porous structure of the electrospun fibers allows for the sustained release of the steroid, providing prolonged therapeutic effects at the lesion site.[37,38]

Key Components:

Polymers: Common polymers used in electrospun fiber formulations include biocompatible and biodegradable materials such as poly(lactic-co-glycolic acid) (PLGA), polyethylene glycol (PEG), and chitosan.

Steroids: Steroids like dexamethasone, triamcinolone acetonide, and hydrocortisone are encapsulated within the electrospun fibers.

Advantages:

It has a high surface area-to-volume ratio, enhancing drug loading capacity and facilitating efficient drug release. The properties such as fiber diameter, porosity, and degradation rate, can be tailored to meet specific therapeutic requirements. Targeted delivery minimizes systemic exposure, reducing the risk of systemic side effects. Many polymers used in electrospun fiber formulations are biocompatible and well-tolerated by oral tissues.[38]

Current Formulations and Innovations

Dexamethasone-Loaded PLGA Fibers: PLGA is a commonly used polymer for electrospun fibers, providing sustained release of dexamethasone for the treatment of oral lesions.

Triamcinolone-Loaded Chitosan Fibers: Chitosan offers mucoadhesive properties and controlled release of triamcinolone acetonide, enhancing its retention and therapeutic efficacy in the oral cavity.

Combination of Polymers: Formulations combining different polymers to create hybrid fibers with synergistic properties, such as improved mechanical strength or enhanced drug release kinetics.

Surface Modification: Surface modification techniques to introduce functional groups or ligands that enhance cellular adhesion or target specific receptors within the oral cavity.

Polymeric Blends: Blending biodegradable polymers with different degradation rates to tailor the release profile and duration of steroid delivery.[37,39]

CHALLENGES

The persistent challenge could be developing drug delivery systems that specifically target oral lesions while minimizing off-target effects on healthy tissues and developing formulations that are easy to use, palatable, and convenient for patients to maximize treatment adherence. The materials used in drug delivery systems must be biocompatible and safe for oral use.[19] Some materials may cause irritation or adverse reactions in oral tissues, limiting their clinical applicability. Patient compliance with oral steroid therapy can be challenging, particularly for formulations that require frequent administration or have unpleasant taste or texture. Optimal drug loading and release kinetics are essential to ensure the sustained and controlled delivery of steroids to oral lesions.[3] Fine-tuning these parameters requires a thorough understanding of the interactions between the drug, delivery system, and target tissue.[24] Tissue specificity often requires the incorporation of targeting ligands or the use of stimuli-responsive systems that respond to specific physiological clues in the oral cavity. Cost-effective drug delivery systems that can be manufactured at scale are crucial for widespread clinical adoption.[4]

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CONCLUSION

In conclusion, the current landscape of modified drug delivery of oral steroids for oral lesions presents a promising array of advancements and challenges. The tailored delivery systems offer the potential to mitigate systemic side effects while maximizing therapeutic outcomes through sustained and localized drug release at the lesion site.

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