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FOCUS ON EMERGING TRENDS IN POLYMERIC FORMULATIONS FOR GINGIVITIS TREATMENT

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ABSTRACT

Gingivitis, a prevalent and reversible form of periodontal disease, is characterized by inflammation of the gingival tissues primarily induced by microbial plaque accumulation. It represents the initial stage of periodontal pathology, marked by clinical symptoms such as bleeding gums, erythema, oedema, halitosis, and in some cases, discomfort during mastication. If left untreated, gingivitis may progress to periodontitis, leading to irreversible periodontal destruction. Conventional treatment modalities focus on mechanical plaque control and systemic antibiotics. However, systemic therapy often leads to undesirable side effects and limited drug concentration at the target site. As a result, localized drug delivery systems (LDDS) have emerged as a promising alternative to enhance therapeutic outcomes while minimizing systemic exposure. Matrix-type delivery systems including biodegradable fibers, mucoadhesive films, injectable formulations, microcapsules, and in situ gels allow sustained drug release directly into the gingival sulcus. Natural polymers such as chitosan, alginate, and guar gum offer biodegradability and muco-adhesiveness, while synthetic and semisynthetic polymers like Eudragit, HPMC, and Carbopol provide controlled release properties. Smart polymers responsive to stimuli such as temperature and pH have been explored to formulate advanced in situ gels. The review also compiles and critically analyses recent clinical studies evaluating the efficacy of polymer-

based films, fibres, and other localized formulations, as well as currently marketed products for gingivitis treatment. This comprehensive insight into polymer-based LDDS highlights their potential as an effective strategy for gingivitis management and future periodontal therapies.

KEYWORDS: Gingivitis, Local drug delivery systems, Mucoadhesive polymers, Matrix-Type drug delivery systems, In situ gel formulations.

INTRODUCTION

Gingivitis is a common, reversible inflammation of the gums caused primarily by bacterial plaque build-up. It affects the gingival tissue—part of the oral mucosa that surrounds and supports the teeth—without damaging the connective tissue attachment. The condition involves key structures such as the gingival margin, sulcus, free gingiva, and attached gingiva. Clinically, it presents with redness, swelling, and bleeding gums. If untreated, gingivitis can progress to periodontitis, a more severe form of gum disease. Emerging research also links untreated gum inflammation to systemic health issues, including heart disease, respiratory infections, and diabetes.[1,2] A mucoadhesive niosomal gel presents a novel and promising approach for the treatment of gingivitis, offering enhanced drug delivery, prolonged retention, and improved therapeutic efficacy. Niosomes are non-ionic surfactant-based vesicles that can encapsulate both hydrophilic and lipophilic drugs, providing controlled and sustained release at the target site. When formulated into a mucoadhesive gel, these vesicles adhere effectively to the gingival mucosa, ensuring localized drug delivery and reducing systemic side effects. This approach is particularly advantageous in gingivitis, where localized inflammation of the gingival tissue demands site-specific treatment. The mucoadhesive property ensures prolonged contact with the oral mucosa, enhancing drug absorption and maintaining therapeutic drug levels in the affected area. Studies have shown that niosomal gels loaded with antimicrobial agents, such as chlorhexidine or metronidazole, significantly reduce gingival inflammation, plaque accumulation, and microbial load compared to conventional formulations. [3-5] The use of niosomal drug delivery systems in mucoadhesive gels thus represents a promising strategy for effective, targeted, and patient-friendly management of gingivitis.

TREATMENT APPROACHES

LOCAL DRUG DELIVERY SYSTEM: This approach involves the direct application or administration of the drug to the specific site of infection or gingival inflammation, bypassing systemic routes such as oral or intravenous administration. It is classified into two types as Reservoir type drug delivery system and Matrix type drug delivery system. It offers several advantages, including avoiding gastrointestinal side effects, increasing drug concentration at the target site, and achieving high bactericidal concentrations at the site of action.[6,10]

A] Reservoir-Type Drug Delivery Systems: This widely used controlled drug delivery method involves encapsulating a drug core within a polymeric membrane. The drug release rate is influenced by factors such as the polymer's composition, molecular weight, and coating thickness, along with the drug's physicochemical properties like solubility, particle size, and molecular weight.[9,13] These systems offer significant advantages in two primary applications:

- **Targeted, Localized Drug Delivery for Mid- to Long-Term Use:** This approach is utilized when direct delivery to a specific site, such as an organ or body cavity, is required due to limitations of systemic administration. [11]
- **Long-Term Systemic Drug Release:** In this case, the drug is delivered through intramuscular or subcutaneous injection, or via an implantable depot system, to maintain sustained release and prolonged systemic circulation over time. [12]

Fibers: Fibers function as reservoir-based drug delivery systems by incorporating therapeutic agents and being strategically placed around the circumference of the periodontal pocket using a specialized applicator.[7] Natural polymers like chitosan, zein, and gelatin, as well as synthetic polymers such as poly (ε-caprolactone), polyurethane, polypropylene, cellulose acetate propionate, and ethyl vinyl acetate, have been studied for this purpose. These polymers are evaluated for their ability to enhance localized antibacterial treatment effectiveness.[8]

B] Matrix type drug delivery system: Matrix-based controlled drug delivery systems are designed to provide continuous drug release through a combination of dissolution and diffusion mechanisms. To manage the release of drugs with varying solubility, they are incorporated into different matrix types, such as swellable hydrophilic substances, insoluble hydrophobic materials, or plastic-based matrices. Hydrophilic polymer matrices are especially common for sustained drug release.[10] These systems consist of a uniform mixture

of one or more drugs with gelling agents, typically hydrophilic polymers. Sustained release formulations help maintain therapeutic drug levels over an extended period, enhancing treatment effectiveness and improving patient compliance. [14]

Films: Bioadhesive periodontal films have become a prominent method for local drug delivery. These thin, flexible films are formulated using a blend of bioadhesive polymers, binding agents, plasticizers, and drug release modulators. [16] They can be loaded with antibiotics, metal nanoparticles, metal oxide nanoparticles, or combinations of these therapeutic agents. After drying, the films are cut to suitable sizes and inserted directly into the periodontal pocket, enabling precise, localized drug delivery. This approach allows for lower dosages and significantly reduces the risk of systemic side effects. [17]

In situ gels: In situ drug delivery systems offer a promising solution for the challenges associated with targeted drug administration. [15] These formulations are initially in liquid form, allowing for easy injection into the periodontal pocket, where they undergo a phase transition into a gel-like structure through solvent exchange. This gel conforms to the shape of the target site, ensuring close contact with the affected area. Under non-physiological conditions, the formulation remains liquid, but once exposed to physiological conditions, it solidifies in response to specific stimuli such as pH, temperature, ion concentration, or changes in solvent composition within the oral cavity. [18] This localized, controlled drug release system enhances therapeutic effectiveness, reduces systemic side effects, and improves patient compliance. [19]

Microcapsules: Gingival crevicular fluid (GCF) acts as the medium through which drugs are released from microspheres placed within the periodontal pocket. As intra-pocket drug delivery systems, microparticles present a promising approach for maintaining therapeutic drug concentrations in the GCF over extended periods, thereby improving clinical outcomes. [10] An ideal microparticulate system for periodontal therapy should possess excellent biocompatibility, allow for controlled and sustained drug release, be easily administered—preferably via syringe—maintain the stability of the therapeutic agent, and ensure effective retention within the periodontal pocket.

Injectable: A gingival injection involves the direct administration of a local anesthetic or therapeutic medication into the gingival (gum) tissue to achieve localized anesthesia or deliver targeted treatment. This technique is commonly utilized in dental procedures,

including periodontal treatments, extractions, and minor oral surgeries. Gingival injectables are used to manage gum diseases such as gingivitis and periodontitis. These injectables typically contain therapeutic agents, including antibiotics, anti-inflammatory medications, or growth factors, which are delivered directly into the gingival tissue for localized treatment.[9]

Types of Gingival Injectables

 Antibiotic injectables: These contain antibiotics such as minocycline or doxycycline and are used to target bacterial infections that cause gum disease.

 Anti-inflammatory injectables: These include anti-inflammatory medications like corticosteroids or NSAIDs, which help reduce inflammation and alleviate associated symptoms.

 Growth factor injectables: These injectables, which contain growth factors like PDGF or FGF, promote tissue regeneration and support the healing process. [12]

POLYMERS USED IN GINGIVITIS FORMULATION

Gingivitis gel formulations require biocompatible, mucoadhesive, and biodegradable polymers to ensure effective drug delivery and prolonged retention in the gingival tissues. [21]

1. Natural Polymers

1.1 Chitosan

- A biocompatible, biodegradable, and mucoadhesive polysaccharide derived from chitin.
- Provides antimicrobial and anti-inflammatory properties beneficial in gingivitis treatment.
- Forms cross-linked hydrogel structures that allow controlled drug release.
- Enhances tissue regeneration and wound healing.
- Improves penetration of active ingredients into inflamed tissues. [20]

1.2 Sodium Alginate

- A natural anionic polysaccharide derived from brown seaweed.
- Forms ionically cross-linked gels in the presence of divalent cations like Ca^{2+}.
- Provides a smooth and biocompatible matrix for prolonged drug release.
- Used in thermoresponsive and pH-sensitive gel systems. [22]

1.3 Pectin

- A naturally occurring polysaccharide with excellent mucoadhesive properties.
- Forms gel networks in acidic environments, making it ideal for gingival applications.

- Enhances the bioavailability of active ingredients. [25]

1.4 Gellan Gum

- A biocompatible, biodegradable gelling agent derived from microbial fermentation.
- Forms stable thermosensitive gels in the presence of monovalent and divalent cations.
- Commonly combined with chitosan or sodium alginate to improve mechanical strength.[22]

2. Synthetic and Semi-Synthetic Polymers

2.1 Carbopol (Polyacrylic Acid, PAA)

- A widely used synthetic polymer for mucoadhesive gel formulations.
- Exhibits excellent swelling properties, enhancing drug residence time.
- Forms viscous gels at low concentrations, improving drug retention on gingival tissues.[24]

2.2 Hydroxypropyl Methylcellulose (HPMC)

- A semi-synthetic, biocompatible cellulose derivative used in pharmaceutical gels.
- Exhibits thermal gelation, ensuring sustained drug release.
- Improves the viscosity and stability of gingivitis gels.[23]

2.3 Poloxamers (Pluronic F127)

- A thermosensitive triblock copolymer that forms gels at body temperature.
- Ensures prolonged drug retention in the gingival pocket.
- Used in combination with chitosan, sodium alginate, or Carbopol to enhance mucoadhesion.[25]

3. Smart Polymers for Responsive Drug Delivery

3.1 Poly(N-isopropylacrylamide) (PNIPAAm)

- A temperature-sensitive polymer that undergoes sol-gel transition at body temperature.
- Ensures controlled drug release and longer retention in gingival tissues.[26]

3.2 Thiolated Chitosan (Thiomers)

- A mucoadhesive biopolymer with enhanced retention in the oral cavity.
- Forms disulfide bonds with mucins, improving adhesion and drug penetration. [27]

CLINICAL STUDIES FOR GINGIVITIS

Fibers

Tetracycline fiber is a local drug delivery system used as an adjunct to scaling and root planing (SRP) for the treatment of gingivitis and periodontitis. It provides a sustained release of tetracycline directly into periodontal pockets, enhancing antimicrobial efficacy and reducing inflammation.[7]

Mechanism of Action

- Tetracycline is a broad-spectrum antibiotic that inhibits bacterial protein synthesis, particularly effective against Actinobacillus actinomycetemcomitans and other periodontal pathogens.
- It possesses additional properties, such as collagenase inhibition, anti-inflammatory action, inhibition of bone resorption, and fibroblast attachment promotion, which contribute to periodontal tissue healing.[37]
- The fibers are typically collagen-based, resorbable, and impregnated with tetracycline, ensuring high local drug concentration in the sulcular fluid.[8]

Advantages of Tetracycline Fibers

- Targets subgingival bacterial biofilm, overcoming limitations of systemic antibiotics.
- Reduces risk of bacterial resistance compared to systemic antibiotic therapy.
- Offers sustained drug release, ensuring prolonged antimicrobial activity.
- Avoids systemic side effects of oral tetracycline therapy.[35]

  Tetracycline fiber is a promising non-surgical adjunct for gingivitis and periodontitis treatment, effectively reducing inflammation and probing depth. However, mechanical therapy (SRP) remains the cornerstone of periodontal management, with tetracycline fibers serving as a valuable complementary therapy.[28]

Films

Drug-Loaded Mucoadhesive Films for Periodontal Disease Treatment

Drug Components in the Films

The study formulated mucoadhesive polymeric thin films incorporating chlorhexidine (25 mg) as an antimicrobial agent, combined with one of the following drugs.

Diclofenac sodium (10 mg or 50 mg): Anti-inflammatory and analgesic

Lidocaine hydrochloride (10 mg): Local anesthetic

Betamethasone dipropionate (10 mg or 50 mg): Corticosteroid with strong anti-inflammatory effects.

The goal was to simultaneously combat bacterial biofilm (the primary cause of periodontitis) and reduce inflammation in periodontal tissues.[36]

Drug Release Profile

Chlorhexidine release was low (~10% of initial loading) from all films, ensuring prolonged antimicrobial action.

Diclofenac, lidocaine, and betamethasone exhibited rapid release, with more than 50% drug release within 30 minutes.

The 50 mg betamethasone film released 4 times more drug than the 10 mg version.[29]

In situ gel

In Situ Gel Formulations

In situ gel formulations are liquid dosage forms that transform into gels upon application to the body due to stimuli such as temperature, pH, or ions. These formulations offer sustained drug release and prolonged residence time at the site of administration.

Key Points

Polymers Used: Common polymers include Poloxamer 407, Poloxamer 188, Carbopol 934P, and Gellan gum.

Gelation Mechanism: Gelation occurs due to temperature-induced micellar aggregation (in the case of Poloxamers) or pH-sensitive gelling (as with Carbopol).

Evaluation Parameters: Formulations are assessed for clarity, pH, viscosity, drug content, gelation temperature, spreadability, and drug release profile**.**[19]

1. Clarity & pH

All formulations (except the first three) were clear.

The pH ranged from 6.72 to 7.10, ensuring compatibility with the oral environment**.**

2. Gelation Temperature

Increased Poloxamer 407 and Carbopol 934P concentration led to a decrease in gelation temperature.

Optimal gelation was achieved between 31–39°C, making it suitable for periodontal application**.**

3. Spreadability

Higher Poloxamer 407 improved spreadability, while Carbopol 934P reduced it.

Formulations showed good spreadability, ranging from 17.21 to 25.48 g·cm/sec.

4. Drug Content & Release Profile

Drug content was within 96.89–100.32%, indicating uniform drug distribution.

Sustained Chlorhexidine HCl release for up to 6 hours, with t_{50}% (time for 50% release) ranging from 153 to 258 minutes.

Higher polymer concentration delayed drug release due to increased gel strength and viscosity.[25]

MARKETED PRODUCTS

Table 1: Marketed products[46,47]

BRAND	MANUFACTURED BY COMPANIES	DRUG	DELIVERY	POLYMER MATRIX
Arestin	OraPharma, US	Minocycline Hydrochloride	Microspheres	Poly (glycolide-co-dl-lactide)
Actisite	Schiff and Company	Tetracycline Hydrochloride	Fiber	Ethylene vinyl acetate
Atridox	Atrix Laboratories	Doxycycline	Gel	Poly (dl-lactide) and N methyl pyridine
Periochip	Pterio Products Ltd., Israel	Chlorhexidine Gluconate	Chip	Gelatin crosslinked with glutaraldehyde
Dentomycin	Wyeth, United Kingdom	Minocycline Hydrochloride	Ointment	Hydroxyethyl-cellulose, aminoalkyl-methacrylate, triacetine and glycerine
Elyzol 25	Dumex-Alpharma	Metronidazole Benzoate	Gel	Glyceryl mono-oleate and sesame oil
Chlo-Site	Ghimas Company, Italy	Chlorhexidine	Gel	Xanthan gel

Table 2: Strips Available in market.

POLYMER MATRIX	DRUG INCORPORATED
Ethyl cellulose	Chlorhexidine[41,42]
Hydroxypropylcellulose +methacrylic acid	Ofloxacin[42]
Polyhydroxy-butyric acid	Tetracycline Hydrochloride[28,42]
Polylactide co glycolic acid	Tetracycline[30]
Hydroxypropyl cellulose	Tetracycline[31] Doxycycline[32]
Polymethacrylate	Tetracycline[33]

Table 3: Gels Available in market.

POLYMER MATRIX	DRUGS INCORPORATED

Poly (lactic-co-glycolic acid)	Tetracycline[30]
Chitosan	Metronidazole[34]
Glycerol monooleate +sesame oil	Metronidazole[38]
Hydroxyethylcellulose and Polyvinyl pyrollidone	Tetracycline[39]

Table 4: Films available in market.

MATRIX	DRUGS INCORPORATED
Polycaprolactone	Minocycline (43)
Ethyl cellulose	Metronidazole[40] Minocycline[40]
Eudragit L and S	Clindamycin[43]
Cross linked atelocollagen	Tetracycline[44]

Table 5: Nanoparticles available in market.

POLYMER MATRIX	DRUGS INCORPORATED
Poly (lactic-co-glycolic acid)	Triclosan[43]
Cellulose acetate phthalate	Triclosan[43]
Chitosan	Antisense oligonucleotide[44]

Table 6: Microparticles available in market.

POLYMER MATRIX	DRUGS INCORPORATED
Poly (lactic-co-glycolic acid) + Polycaprolactone	Doxycycline[45]
Pluronic f127	Tetracycline[42]

CONCLUSION

Gingivitis remains one of the most prevalent oral health issues, primarily driven by bacterial plaque accumulation and exacerbated by various systemic and local factors. Understanding its etiology is crucial in guiding effective therapeutic approaches. The integration of advanced drug delivery systems, particularly those incorporating polymers like chitosan, Carbopol and Poloxamers has significantly improved the efficacy and patient compliance in gingivitis management. These polymers not only enhance the muco-adhesiveness and retention time of formulations but also enable the development of site-specific, controlled release products. A wide array of marketed products-ranging from medicated gels to mouthwashes and periodontal inserts-have demonstrated clinical effectiveness, offering both prophylactic and therapeutic benefits. Continued research and innovation in formulation science, particularly through the application of nanotechnology and novel polymers, hold promise for more effective and targeted management strategies for gingivitis in the future.

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