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Review Article

Newer Drug Delivery Systems in Treating Oral Submucous Fibrosis: A Narrative Review

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Abstract

Oral Submucous Fibrosis (OSMF) is a potentially malignant disorder affecting the oral cavity, oropharynx, nasopharynx and esophagus. It is a chronic, progressive, scarring disease highly prevalent among the people of South-East Asian origin which is characterized by juxta-epithelial inflammatory reaction in the oral mucosa, followed by fibro-elastic transformation of the lamina propria. This results in mucosal atrophy, burning sensation, rigidity, impaired oral function and trismus. Conventional drug delivery for treating Oral Submucous Fibrosis range from Corticosteroids, Hyaluronidase, minerals, micronutrients and antioxidants to surgical and laser therapies in severe conditions. While traditional drug delivery systems work, they are limited by factors like drug bioavailability, non-compliance of the patient and adverse effects caused due to continuous injections and steroid therapy. However other recent modalities like Nanotechnology based approach using micro RNAs, Immuno-modulatory strategies like Macrophage polarization and Cytokine modulation and Mucoadhesive drug delivery systems comprising Oral patches, Hydrogels and Microneedles are in pipeline. The present narrative review summarizes various treatment modalities in the management of OSMF emphasizing the newer drug delivery systems.

Keywords: Hyaluronidase; Hydrogels; Macrophage Polarization; Microneedles; Oral Submucous Fibrosis

Introduction

Oral Submucous Fibrosis (OSF) is a chronic, progressive, and potentially malignant disorder predominantly affecting South and Southeast Asian populations. It is characterized by juxta-epithelial inflammation, epithelial atrophy, and extensive subepithelial fibro-elastic alterations [1].

The primary etiological factor is habitual areca nut chewing (gutka, pan masala etc.), wherein arecoline induced microtrauma generates oxidative stress, upregulates transforming growth factor-beta (TGF-β) and connective tissue growth factor (CTGF), and drives myofibroblast differentiation to accelerate type I and III collagen deposition. Concurrently, elevated lysyl oxidase (LOX) facilitates collagen cross linking while tissue inhibitors of metalloproteinases (TIMPs) supress matrix metalloproteinases (MMPs), abolishing extracellular matrix degradation.

OSF presents clinically with mucosal blanching, loss of elasticity, stomatopyrosis (burning sensation), ulcerations, and severe trismus that impairs speech, mastication, and deglutition. Classified

as an Oral Potentially Malignant Disorder (OPMD), it carries a 1.9% to 13% malignant transformation rate into Oral Squamous Cell Carcinoma [1].

Conventional treatments like intralesional corticosteroid injections, hyaluronidase, and oral antioxidants can offer temporary symptomatic relief [1,3]. Furthermore, their utility may be limited by rapid salivary wash-out, low mucosal permeability, procedural injection pain, and steroid-related adverse effects [1,3]. Consequently, there is an urgent demand for advanced drug delivery systems such as mucoadhesive patches, silk fibroin microneedles, bioactive injectable hydrogels, nanocarriers, and stem cell derived exosomes to achieve targeted, sustained, and minimally invasive disease-modifying therapy [1].

Clinical features and staging of OSMF

The clinical features of Oral Submucous Fibrosis include [2].

Early symptoms and mucosal alterations:

- **Stomatopyrosis and Pain:** Persistent burning sensation in the mouth, provoked particularly when consuming spicy foods or hot beverages, and occurring even when the stimulus is removed in moderate to severe stages.
- **Vesicle and Ulcer formation:** Initial stomatitis marked by erythematous mucosa, superficial vesicles, recurrent ulcerations and mucosal petechiae.
- **Blanching and loss of texture:** Mucosal blanching progressing to a dense, pale, marble-like, mottled or leathery mucosal texture with loss of normal elasticity.
- **Sensory Disturbances:** Altered taste perception, dryness of the mouth or hyposalivation.

Fibrosis and Structural changes

- **Palpable Fibrous bands:** Vertical and circular fibrous bands detectable on palpation across the buccal mucosa (especially the premolar region), labial mucosa, faucial pillars, and soft palate.
- **Soft palate and Uvula alterations:** Stiff, rubbery soft palate with diminished mobility; shortened, thickened, and firm faucial pillars; and a shrunken, small, "bud-like" uvula.
- **Tongue involvement:** Stiff, small or fixed tongue with restricted mobility, limited protrusion, and diffuse papillary atrophy.

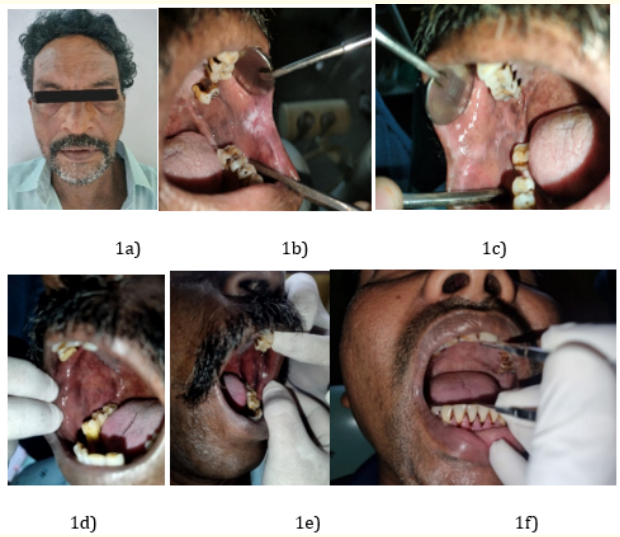

Figure 1: Images of patients with Oral Submucous Fibrosis, 1a) extraoral image of a patient, 1b) left buccal mucosa showing blanching and marble-like texture and 1c) right buccal mucosa showing marble-like texture, 1d) right buccal mucosa showing erythema and petechiae, 1e) left buccal mucosa showing erythema, 1f) showing restricted mouth opening.

- **Gingival and facial changes:** Pale, fibrotic, and depigmented gingiva; atrophy of the vermilion border of the lips; and sunken cheeks not matching the patient's nutritional age.

Functional deficits and advanced complications

- **Trismus:** Progressive decline in interincisal distance leading to impaired mastication and swallowing difficulty.
- **Diminished oral flexibility:** Demonstrable loss of cheek flexibility (inability to blow out cheeks fully or whistle) and restricted tongue protrusion.
- **Secondary deficits:** Speech impairments and hearing deficits resulting from tongue restrictions and eustachian tube involvement.
- **Lymphadenopathy and systemic manifestations:** Unilateral or bilateral cervical lymphadenopathy, anemia, and poor nutritional status/malnourishment.
- **Malignant transformation:** Co-occurrence of oral potentially malignant disorders (such as leukoplakia and erythroplakia) or progression to Oral Squamous Cell Carcinoma (OSCC).

Accurate clinical and functional staging of Oral Submucous Fibrosis is essential for evaluating disease severity, monitoring malignant risk, and selecting targeted therapeutic interventions [2].

Some of the most widely recognized and clinically practical staging systems include [2].

Khanna and Andrade (1995) – Functional and Clinical staging [2]

- **Group 1 (very early):** Interincisal opening , burning sensation, acute ulcerations, and recurrent stomatitis.
- **Group 2 (early):** Interincisal opening 26-35mm, mottled, marble like buccal mucosa, dense pale fibrous areas alternating with normal tissue, occasional erythroplakia.
- **Group 3 (moderately advanced):** Interincisal opening 15-25mm, pale buccal mucosa firmly bound to underlying structures, vertical fibrous bands in the premolar region, inability to whistle or blow cheeks.
- **Group 4 (advanced):** Interincisal opening , shrunken bud uvula, shortened faucial pillars, circular band around lips, severe tongue restriction, with or without malignant transformation.

Haider., et al. (2000) – Two-tier (Anatomical and Functional) staging [2].

Clinical staging: (Band distribution)

- Stage 1: Faucial bands only
- Stage 2: Faucial and buccal bands
- Stage 3: Faucial and labial bands

Functional staging: (Mouth opening)

- Stage A: Mouth opening 13-20 mm
- Stage B: Mouth opening 10-12 mm
- Stage C: Mouth opening

More., *et al*. (2012) – Modern Integrated Clinical and Functional staging [2].

Clinical classification (S):

- Stage 1 (S1): Stomatitis and/or mucosal blanching.
- Stage 2 (S2): Palpable fibrous bands in buccal mucosa and/or oropharynx, with or without stomatitis.
- Stage 3 (S3): Palpable fibrous bands involving the buccal mucosa/oropharynx and other parts of the oral cavity (e.g., palate, lips)
- Stage 4 (S4):
- S4a: Any stage associated with an oral potentially malignant disorder (e.g., leukoplakia, erythroplakia)
- S4b: Any stage associated with oral carcinoma.

Functional classification (M):

- M1: Interincisal mouth opening
- M2: Interincisal opening 25-35mm
- M3: Interincisal opening 15-25mm
- M4: Interincisal opening

Patients are scored combining both components, e.g., S_2M_3 or S_4aM_2

Pathophysiology

Oral submucous fibrosis is fundamentally an aberrant, non-resolving wound healing response resulting from repetitive chemical and mechanical microtrauma. Unravelling its intricate molecular networks is crucial for identifying targetable pathways for advanced drug delivery systems [1].

Transforming growth factor-beta (TGF-) and SMAD signaling

TGF- acts as the master upstream regulator of the fibrotic response in OSF. Chewing areca nut constituents promotes persistent TGF- activation, which binds to serine/threonine kinase receptors and induces the phosphorylation of receptor-regulated SMADs (SMAD2 and SMAD3). Phosphorylated SMAD2/3 forms a heterotrimeric complex with SMAD4, which translocates into the nucleus to drive the transcription of pro-fibrotic target genes, including *COL1A1*, *COL3A1*, connective tissue growth factor (*CTGF*), and smooth muscle alpha-actin (-*SMA*). Non-canonical pathways, such as JNK and p38 MAPK, further amplify this pro-fibrotic cascade [1].

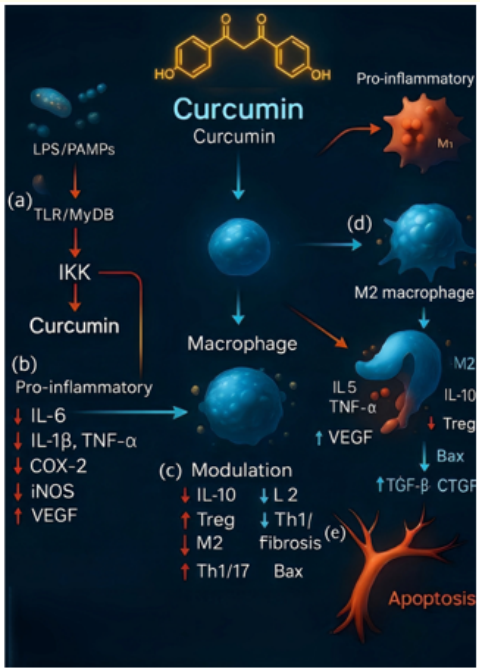

Figure 2: Schematic overview of the immunomodulatory and anti-inflammatory mechanisms of curcumin, illustrating IKK/NF-κB pathway inhibition, phenotypic modulation of M1/M2 macrophages, and downregulation of the pro-fibrotic TGF-β/CTGF signalling cascade (Adapted from Hu., et al. Frontiers in Pharmacology, 2026 under the CC by license) [4].

Epithelial-to-mesenchymal transition (EMT) and basal stem cell alterations

Chronic exposure to arecoline damages the stratified squamous epithelium, arresting the keratinocyte cell cycle and triggering EMT. During EMT, epithelial cells lose intercellular adhesion complexes and E-cadherin expression while acquiring a mobile, mesenchymal phenotype characterized by elevated vimentin, Snail, Twist, and -SMA. These transformed cells migrate into the underlying subepithelial stroma, augmenting the collagen-producing pool. Concurrently, tissue hypoxia stabilizes hypoxia-inducible factor 1-alpha (HIF-1α), aggravating oxidative stress and promoting the acquisition of stemness traits that facilitate malignant transformation into oral squamous cell carcinoma [1].

Extracellular matrix (ECM) Remodelling and the LOX/TIMP/MMP imbalance

The hallmark of OSF is the dense accumulation of mature, cross-linked extracellular matrix within the lamina propria. Areca nut alkaloids stimulate fibroblasts to overexpress lysyl oxidase (LOX), a copper-dependent enzyme that cross-links collagen fibrils into insoluble, degradation-resistant bundles. Simultaneously, chronic mucosal inflammation upregulates tissue inhibitors of metalloproteinases (TIMP-1 and TIMP-2) and plasminogen activator inhibitor (PAI-1) while downregulating matrix metalloproteinases (MMP-1, MMP-2, MMP-3). This blocks collagenase activation and suppresses normal fibroblastic collagen phagocytosis, culminating in progressive tissue sclerosis [1].

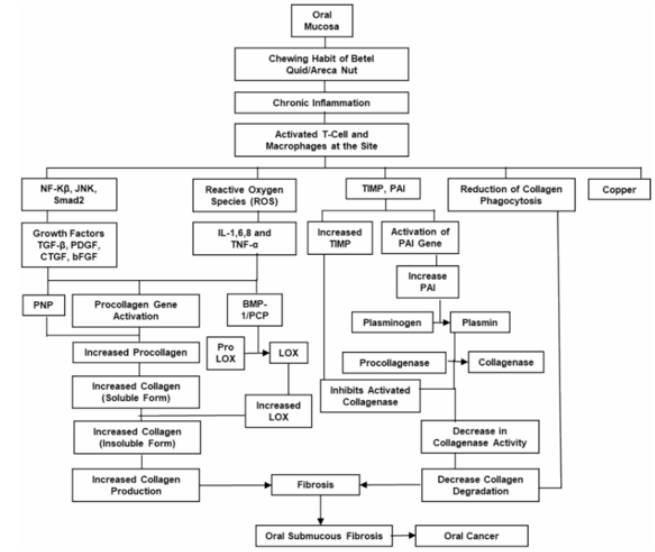

Figure 3: Molecular pathogenesis and signalling pathways driving extracellular matrix accumulation and fibrosis progression in Oral Submucous Fibrosis (Adapted from Kotian., *et al*. 2026) [1].

Vascular impairment, endothelial dysfunction, and hypoxia

Early-stage OSF exhibits transient microvascular proliferation; however, advanced stages are marked by endothelial apoptosis, cell cycle arrest, and Endothelial-to-Mesenchymal Transition (EndMT) mediated via PERK and YAP/TAZ signaling pathways. Microvascular obliteration and luminal narrowing compromise local perfusion, creating a chronic ischemic and hypoxic microenvironment. This

sustained hypoxia triggers further release of vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and pro-inflammatory cytokines, maintaining the self-perpetuating fibrotic cycle [1].

Conventional therapy and their limitations

Conventional pharmacological management of OSF has historically relied on empirical regimens aimed at reducing local inflammation, degrading extracellular ground substance, and improving peripheral perfusion. Despite widespread use in clinical practice, evidence-based evaluations reveal significant shortcomings in efficacy, safety, and patient compliance [1,3].

- **Intralesional Submucosal Injections:** The administration of intralesional corticosteroids (such as dexamethasone, triamcinolone acetonide, and betamethasone) alone or in combination with hyaluronidase remains a common therapeutic approach. While corticosteroids suppress pro-inflammatory signaling and hyaluronidase temporarily hydrolyzes hyaluronic acid to reduce intercellular matrix viscosity, their clinical benefit is often transient [1,2]. Repeated needle punctures into stiff, fibrotic buccal tissues cause severe procedural pain, high patient attrition, local hematoma, secondary ulceration, and paradoxical rebound fibrosis from repeated needle trauma. Furthermore, repeated local steroid exposure carries risks of mucosal atrophy, localized candida infection, and rare ocular complications such as central serous chorioretinopathy [1,3].
- **Topical Formulations and the Salivary Clearance Barrier:** Standard topical preparations—including conventional gels, ointments, and mouthwashes containing steroids, anesthetics, or plant extracts—fail to achieve therapeutic concentrations within deeper mucosal layers [1,3]. Continuous salivary flow, mechanical flushing during speech and mastication, and enzymatic activity rapidly dilute and clear active molecules from the mucosal surface [1,3]. Moreover, the hyperkeratinized, thickened epithelial barrier typical of OSF severely limits the passive permeation of hydrophilic or macromolecular therapeutics into the underlying diseased lamina propria [1,3].
- **Evidence Syntheses on Functional Outcomes:** High-level systematic reviews and network meta-analyses highlight a substantial gap between statistical improvements and true clinical recovery [5-7]. While systemic antioxidants and vasodilators demonstrate modest improvements in subjective symptoms like burning sensation, changes in maximal interincisal opening rarely exceed 2 to 4 mm in pooled analyses [5-7]. This falls well short of the 10 mm threshold recognized as the Minimal Clinically Important Difference (MCID) needed to restore normal chewing, speech, and oral health-related quality of life. Furthermore, conventional medical approaches do not actively dismantle mature, cross-linked collagen bundles or halt malignant transformation risks, underscoring the necessity for advanced, sustained, and targeted delivery systems [1,3].

Advanced drug delivery systems in OSMF management

To overcome the physiological challenges of the oral environment—including continuous salivary flow, mechanical friction from mastication, enzymatic degradation, and the dense, hypovascular fibrotic tissue barrier—advanced bioengineered drug delivery systems have been developed to provide sustained, targeted, and localized therapy [1].

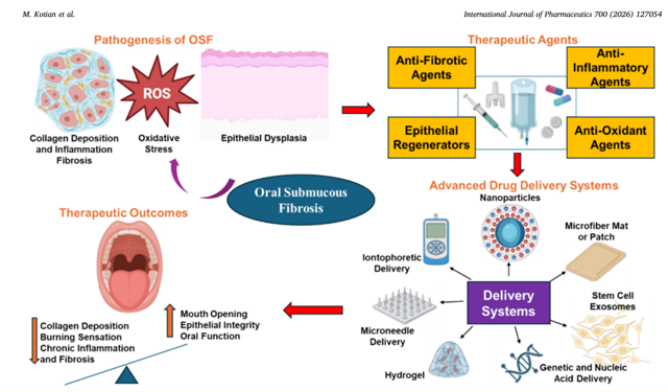

Figure 4: Overview of pathophysiological drivers, bioactive agents, and bioengineered drug delivery platforms (nanocarriers, microneedles, hydrogels, and exosomes) in Oral Submucous Fibrosis management (Adapted from Kotian., *et al*. 2026) [1].

Mucoadhesive buccal patches and polymeric films

Mucoadhesive patches utilize hydrophilic and bioadhesive polymers—such as chitosan, sodium alginate, hydroxypropyl methylcellulose (HPMC), and carbopol—to prolong residence time on the buccal mucosa [1,8].

- **Adhesion Mechanisms:** Polymer retention is driven by hydrogen bonding between polymeric functional groups and mucin glycoproteins, electrostatic attraction between cationic polymers (e.g., chitosan) and negatively charged sialic acid residues, and polymer chain interpenetration into the mucus network [1,8]. Controlled swelling enhances surface contact and polymer chain mobility without causing early matrix collapse [1,8].
- **Structural Engineering:** Advanced bilayered designs combine a mucoadhesive drug-loaded layer with a water-insoluble backing membrane (such as polycaprolactone or ethylcellulose). This architecture prevents drug loss into the oral cavity from salivary washing, promoting unidirectional diffusion toward the underlying lamina propria. These patches have successfully sustained the localized release of bioactive phytochemicals and antifibrotic agents, including bromelain, astaxanthin, and curcumin, providing continuous anti-inflammatory and matrix-regulating activity with reduced dosing frequency [9].

Microneedle-based transmucosal delivery systems

Microneedle (MN) arrays represent a minimally invasive modality designed to overcome the dense, hyperkeratinized epithelial diffusion barrier without causing pain.

- **Barrier Penetration Mechanism:** Featuring micron-scale projections (typically 200–1000 m in height), MNs pierce the epithelium to create transient, self-sealing aqueous microchannels. This bypasses the stratified squamous layer and delivers therapeutics directly into the subepithelial connective tissue and lamina propria, where active collagen deposition occurs [1].
- **Bilayered Wet-Adhesive Platforms:** To prevent displacement caused by oral fluids and jaw movements, double-layered patches have been engineered using a biomimetic silk fibroin/tannic acid (SF-TA) wet-adhesive backing layer. Non-covalent hydrogen bonding between phenolic hydroxyls of tannic acid and mucosal amino/sulfhydryl groups generates strong wet adhesion (41.28 kPa), significantly outperforming standard commercial oral patches (4.5 kPa).
- **Sustained Release via Pre-Assembled Nanospheres:** Standard dissolving microneedles often exhibit rapid drug clearance (releasing ~80% within 3 days). Cheng., *et al*. addressed this by incorporating pre-assembled silk fibroin nanospheres (SFN, ~46.25 nm) into the microneedle under-layer loaded with triamcinolone acetonide [9]. The 5% SFN composite maintained sufficient mechanical fracture strength (0.07 N/needle) to ensure reliable epithelial penetration while extending drug release from 4 days to 14 days, matching the standard clinical dosing interval for corticosteroid therapy [10].

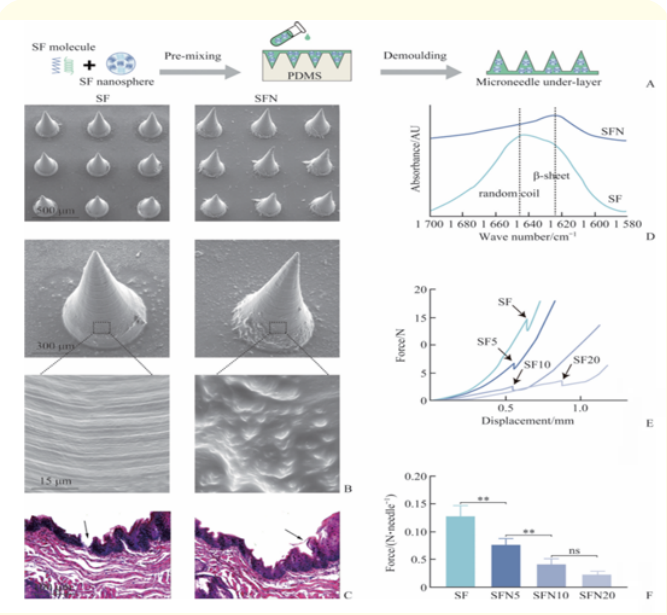

Figure 5: Fabrication, morphology, and mechanical characterization of Silk Fibroin (SF) microneedles: (A) Schmeatic illustration of microneedle under-layer fabrication via PDMS mold casting, (B) SEM micrographs showing cone-shaped arrays and nanosphere-textured surfaces, (C) Histological H&E cross-sections demonstrating microchannel penetration across mouse oral epithelium (arrows), (D) FTIR spectra of β-sheet conformation, and (E, F) Compression force [10].

Injectable composite hydrogels and stimuli-responsive matrices

In situ-forming and shear-thinning injectable hydrogels provide localized depot delivery while minimizing tissue trauma [1].

- **Bioactive Inorganic Composites:** Formulations such as sodium hyaluronate combined with 45S5 bioglass (BG/HA) act as bioactive matrices that release physiologically active silicate ions. In animal models, these silicate ions stimulate angiogenesis and epithelial regeneration by upregulating CD31, while concurrently downregulating CD68 macrophage infiltration, -SMA, and pro-fibrotic mediators (TGF-, TNF-, and TIMP-1) [1].
- **Stimuli-Responsive Hydrogels:** "Smart" polymeric networks engineered to respond to microenvironmental triggers—such as acidic pH, elevated matrix metalloproteinase activity, or local reactive oxygen species (ROS)—undergo controlled matrix relaxation or degradation. This ensures site-specific drug release at active inflammatory and fibrotic foci while minimizing systemic exposure [1].

Nanoparticle-loaded colloidal systems and nanocubo gels

Colloidal nanocarriers enhance the solubility, chemical stability, and cellular uptake of hydrophobic antifibrotic compounds [1].

- **Nano-Lipidic Cubogels:** Nano-cubogels feature a three-dimensional bicontinuous lipid bilayer network forming water-filled nanochannels. Their structural stability enables them to withstand physiological shear stress from saliva flow and mastication, preventing the burst release of entrapped compounds such as epigallocatechin-3-gallate (EGCG) [11].
- **Surface Charge Optimization***:* Functionalizing the surface of lipidic nanoparticles with cationic agents (e.g., stearylamine) imparts a positive surface charge. This promotes electrostatic engagement with the negatively charged mucosal lining, facilitating deeper transcellular penetration into submucosal fibroblasts [1,8].

Iontophoresis-assisted drug delivery

Iontophoresis utilizes low-intensity electrical currents to drive ionic and polar therapeutic molecules across the mucosal epithelium via electromigration and electroosmosis [1].

- **Overcoming Diffusional Resistance:** When paired with non-ionic hydrogel matrices (such as 2% hydroxyethyl cellulose), iontophoresis reduces ionic competition and enhances drug transport across the epithelium.
- **Enhanced Bioavailability***:* Studies utilizing buflomedil hydrochloride demonstrated that iontophoretic delivery increases drug deposition within the lamina propria and submucosal layers by more than 50-fold compared to passive topical diffusion, providing an effective, non-invasive method to restore blood flow in ischemic fibrotic tissues [1].

Limitations and safety considerations of advanced drug delivery systems

While advanced drug delivery platforms demonstrate significant therapeutic potential in laboratory and preclinical models, several critical formulations, biological, and clinical hurdles must be overcome to translate them into routine clinical practice [1].

- **Long-Term Biocompatibility and Local Mucosal Toxicity:** The oral mucosa in OSF is chronically inflamed, atrophic, and hypovascular, making it highly sensitive to foreign materials and chemical additives. Synthetic polymers, cationic surfactants (e.g., stearylamine), and degradation byproducts may provoke localized tissue irritation, contact mucositis, or chronic inflammatory flare-ups with repeated exposure. Furthermore, nanoparticles with high surface reactivity can inadvertently generate intracellular reactive oxygen species (ROS) or induce cellular apoptosis in compromised tissue. Comprehensive in vivo biocompatibility profiling and extended histological safety assessments are essential before clinical adoption [1].
- **Manufacturing Scalability, Reproducibility, and GMP Standards:** Fabricating complex advanced delivery systems—such as micro-molded silk fibroin microneedles, electrospun nanofiber mats, and nanoscale cubogels—requires precision engineering and multi-step processing. Maintaining batch-to-batch uniformity in critical parameters like particle size, encapsulation efficiency, drug release kinetics, and mechanical fracture strength is difficult to scale up from bench to industrial scale. Ensuring sterility, physical stability, and reproducibility under strict Good Manufacturing Practice (GMP) guidelines represents a major challenge for mass production [1].

- **Patient Variability and Dynamic Mucosal Heterogeneity:** The clinical presentation of OSF varies widely in terms of epithelial thickness, degree of hyperkeratinization, submucosal density, and salivary flow rates across different disease stages. This disease-stage heterogeneity directly affects the adhesive strength of mucoadhesive patches, the penetration depth of microneedles, and the diffusion rates of hydrogel formulations. Additionally, dynamic mechanical forces during mastication and speech can cause premature detachment or uneven drug release across patients [1].
- **Application Discomfort and Procedural Limitations:** Although microneedles avoid deeper pain receptors, repeated application on severely fibrotic and restricted oral mucosa may cause localized tenderness, minor bleeding, or superficial micro-ulcerations. In iontophoresis-assisted delivery, continuous exposure to electrical current can cause tingling, mild electrical burns, or epithelial barrier disruption, potentially reducing patient tolerance and long-term compliance [1].
- **Complex Regulatory Classification and Approval Pathways:** Advanced platforms that combine medical devices with active pharmaceutical agents or biologics (e.g., drug-loaded microneedle patches or miRNA-nanoparticle complexes) fall into ambiguous regulatory categories. Regulatory bodies such as the FDA and EMA require extensive preclinical toxicology, precise pharmacokinetic (PK) biodistribution data, and large-scale, double-blind randomized clinical trials demonstrating clear superiority over conventional therapy before granting market approval [1].

Future perspectives

- **Biomarker-Driven Personalized Therapy**: Future clinical paradigms should leverage patient-specific cytokine profiles (e.g., salivary TGF-, IL-6, IL-1β), microRNA signatures (miR-21, miR-29), and tissue stiffness measurements to tailor drug carrier selection and dosing to the patient's individual disease stage [1].
- **Integration of Artificial Intelligence (AI) and Digital Diagnostics**: Implementing deep Convolutional Neural Networks (CNNs) and standardizes histology databases such as the ORCHID repository, which demonstrates 97.5% to 98.5% diagnostic accuracy, enables automated morphometric analysis of epithelial atrophy and dysplastic transformation [12]. Furthermore, combining clinical intraoral photographic classification models (e.g., Roboflow ML algorithms achieving ~88.9% accuracy) with salivary metatranscriptomic profiling facilitates non-invasive, early detection and patient-tailored optimization of targeted drug delivery systems [12].
- **Stimuli-Responsive and Multi-Targeted Matrices**: Developing "smart" bioresponsive carriers capable of dynamically releasing antifibrotic or antioxidant molecules in response to disease-specific microenvironmental triggers (such as acidic pH, elevated MMPs, or reactive oxygen species) will maximize local precision while minimizing off-target exposure [1].
- **Regenerative Biotherapeutics**: Combining targeted drug delivery platforms with stem cell-derived secretomes, exosomes, and cellular therapies (such as dental pulp stem cells) offers a translational strategy to not only suppress chronic inflammation but actively restore normal mucosal elasticity and microvascular architecture [1,13].

Conclusion

Oral Submucous Fibrosis is a progressive, potentially malignant condition whose conventional treatments offer only temporary relief due to rapid salivary clearance, low tissue permeability, procedural discomfort and minimal functional improvement in the mouth opening. To address these limitations, advanced bioengineered platforms like mucoadhesive patches, silk fibroin microneedles, bioactive hydrogels and other newer drug delivery systems have emerged, which offer targeted, sustained, and minimally invasive delivery. Resolving hurdles like scalability, biocompatibility, and regulatory compliance through well-designed clinical trials will be essential to establish standardized therapies that prevent malignant transformation.

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