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Review

Development and Evaluation of a Microemulsion-Based Gel System for Improved Delivery of Therapeutic Agents in the Management of Oral Submucous Fibrosis

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Abstract:

Background: Oral Submucous Fibrosis (OSMF) is a long-term, progressive condition affecting the oral mucosa, marked by fibrotic changes, restricted mouth opening (trismus), and a persistent burning sensation. Existing treatment options are often inadequate, mainly due to issues like poor drug solubility, instability, and low bioavailability. Lycopene and Coenzyme Q10 possess significant antioxidant and anti-fibrotic activities, making them promising therapeutic agents; however, their clinical effectiveness is limited by formulation-related challenges.

Aim: The objective of the study was to develope, optimize, and evaluate a microemulsion-based gel incorporating lycopene and coenzyme Q10. A systematic Quality by Design (QbD) framework, supported by a Design of Experiments (DoE) approach, was employed to ensure an efficient and targeted formulation for the management of Oral Submucous Fibrosis (OSMF).

Keywords: Oral submucous fibrosis (osmf); microemulsion gel; lycopene; coenzyme Q10; quality by design (qbd); box–behnken design; antioxidants; drug delivery; in vivo study; wistar rats.

Introduction: Oral Submucous Fibrosis (OSMF) is a long-standing, progressive disorder of the oral cavity that carries a high potential for malignant transformation. In its early stages, patients commonly experience blanching of the oral mucosa along with a burning sensation, particularly when consuming hot or spicy foods.**(Cai et al., 2026)** As the condition advances, fibrotic changes occur in the submucosal tissues, involving the oral cavity, pharynx, and upper portion of the esophagus, which can result in restricted mouth oispening (trismus) and difficulty in swallowing (dysphagia).**(Gupta et al., 2020)**

Arecoline is a naturally occurring alkaloid predominantly present in areca nuts. It has been shown to induce oral submucous fibrosis in experimental animal models. Studies indicate that the development of oral fibrosis is strongly linked to the habitual chewing of areca nut, which in turn elevates the risk of oral cancer. The alkaloid components of betel nut are known to promote the transformation of fibroblasts into myofibroblasts. In addition, findings suggest that fibroblasts acquire a fibrogenic behavior when they are co-cultured with oral keratinocytes exposed to arecoline.**(Shieh et al., 2025)**

A strong body of evidence supports the role of areca nut consumption as a primary etiological factor in OSMF. Certain constituents of areca nut, particularly alkaloids such as arecoline, are known to influence collagen metabolism. This leads to excessive collagen deposition and progressive fibrosis, with studies

suggesting a dose-dependent relationship between areca nut use and the development of the disease.**(Shesha Prasad & Pai, 2018)**

2. Materials and methods:

The materials used were IPM, polyoxyethylene 20 sorbitan mono-oleate (Tween 80), propylene glycol (PG; Merck-Schuchardt, Germany), SA (BP), and double distilled water.**(Badawi et al., 2009)**

The key materials used in this study included Lycopene and Coenzyme Q10 as the active pharmaceutical ingredients, Olive oil as the oil phase, Tween 80 as the surfactant, and Glycerol as the co-surfactant. Lycopene and Coenzyme Q10 were selected for their potent antioxidant properties relevant to the management of oral submucous fibrosis.**(Nilesh et al., 2021)** Olive oil was used to enhance the solubility and bioavailability of the lipophilic actives, while Tween 80 and Glycerol facilitated the formation and stabilization of the microemulsion system. All chemicals and reagents were of analytical grade and used without further purification.**(Yadav et al., 2023)**

2.1 Microemulsion:

A microemulsion is a clear, stable, and uniform system formed by mixing oil and water with the help of surfactants. It contains very small droplets (5–200 nm), which make it transparent.**(Fang et al., 2026)** These systems form easily, often without high energy input, due to low interfacial tension. A co-surfactant is sometimes added to improve stability. Microemulsions can exist as oil-in-water, water-in-oil, or bicontinuous structures depending on their composition.**(Mishra et al., 2014)**

Depending on their internal structure, microemulsions can be categorized into oil-in-water (O/W), water-in-oil (W/O), and bicontinuous systems, where both phases form interconnected networks. Their unique structure enhances drug solubilization and facilitates improved drug delivery performance.**(Umar et al., 2022)**

Depending on their composition and structure, microemulsions are generally classified into three main types:

- Oil-in-water (O/W) microemulsions, where oil droplets are dispersed within a continuous aqueous phase.
- Water-in-oil (W/O) microemulsions, where water droplets are dispersed in a continuous oil phase.
- Bicontinuous microemulsions, where both oil and water form interconnected, interpenetrating domains throughout the system.**(Mishra et al., 2014)**

Advantages of Microemulsions:

- They are thermodynamically stable systems, which contributes to an extended shelf life.
- Microemulsions enhance drug solubility and can act as excellent solubilizing media.
- They can serve as effective reservoirs for both lipophilic and hydrophilic drugs.
- Their very small droplet size provides a large surface area, promoting faster drug release and improved absorption.
- These systems are capable of incorporating both water-soluble and oil-soluble drugs.
- Preparation is simple and does not require high energy input. **(Kumar, n.d.et al., 2022)**

2.2 Microemulsion Gel Preparation Method: The formulation of a microemulsion gel is carried out in two key phases: first, the development of the microemulsion system, followed by its incorporation into a suitable gel matrix.**(Sabale & Vora, 2012)**

Step 1: Microemulsion Preparation:

Initially, the drug is dissolved in an appropriate oil phase such as olive oil. A surfactant (e.g., Tween 80) is then combined with a co-surfactant like glycerol or ethanol in a predetermined ratio. The oil phase is slowly introduced into this mixture under continuous stirring. **(Singh et al., 2014)** Subsequently, distilled water is added dropwise while maintaining constant agitation until a clear and thermodynamically stable microemulsion is obtained. The prepared system is left undisturbed for some time to achieve equilibrium and ensure stability.**(Mishra et al., 2014)**

Step 2: Gel Base Preparation:

A suitable gelling agent, such as Carbopol 934 or Carbopol 940, is dispersed in distilled water and allowed to hydrate fully. After complete swelling, the pH of the dispersion is adjusted, typically using triethanolamine, to convert it into a smooth and uniform gel base.**(Zheng et al., 2016)**

Step 3: Preparation of Microemulsion Gel:

The optimized Lycopene and CoQ10 microemulsion was incorporated into a gel using Carbopol 934 (100 mg) as the gelling agent. Carbopol was dispersed in 1

mL of distilled water using a mechanical stirrer (Remi, Mumbai, India) at 1200 rpm.**(Okur et al., 2020)**

The drug-loaded microemulsion (10 mL) was then added to the gel base and stirred for 15 minutes to ensure uniform mixing. Triethanolamine (50 µL) was added to neutralize the dispersion, and the gel was allowed to stand overnight for complete swelling, resulting in a homogenous microemulsion-loaded gel suitable for topical application.**(Pratap Singh Rajpoot H et al., 2025)**

2.2 Formulation Optimization Using DoE:

A three-factor, three-level Box–Behnken design (BBD) was utilized to investigate the effect of independent variables—olive oil (X_1), Tween 80 (X_2), and glycerol (X_3)—on the critical properties of the microemulsion. The evaluated responses included particle size, polydispersity index (PDI), zeta potential, and entrapment efficiency. **(Pratap Singh Rajpoot H et al., 2025).** A total of seventeen experimental trials were conducted as per the design matrix. Data analysis generated nineteen possible optimized formulations, out of which the formulation showing the most favorable characteristics was selected as the final optimized microemulsion.**(Knights & Millaku, 2023)**

3. In- Vivo Study:

Animal Model: Fibrosis was experimentally induced in animal models using bleomycin, a chemotherapeutic agent known to promote excessive collagen deposition and tissue stiffening. The drug was administered locally to mimic the pathological features of fibrotic conditions such as oral submucous fibrosis.**(Zhang et al., 2016)** Repeated exposure led to progressive epithelial atrophy, increased fibroblast activity, and reduced tissue elasticity. Following successful induction, treatment was initiated using a standard formulation of Kenacort ointment, which contains triamcinolone acetonide as an anti-inflammatory corticosteroid.**(Singh K. et al., 2020).** The ointment was applied topically to the affected area to reduce inflammation and limit further collagen accumulation. Therapeutic response was evaluated based on histological changes and improvement in tissue flexibility.**(Rai et al., 2020)**

Conclusion: Microemulsion-based gel formulations represent an effective strategy for the localized treatment of Oral Submucous Fibrosis. These systems enhance drug solubility, improve penetration through mucosal tissues, and provide prolonged retention at the site of action. Experimental findings, including in vivo studies, indicate improved therapeutic outcomes with reduced systemic exposure. With further clinical validation, such formulations hold significant potential for advancing OSMF treatment.

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