



Nanoemulsion and nanoemulgel-based carriers as advanced delivery tools for the treatment of oral diseases

Deepali Kumari¹ · Varnita Karmakar¹ · Sreenivas Patro Sisinthy² · Manisha Pandey³ · Neha Jain⁴ · Bapi Gorain¹ 

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Abstract

Oral diseases rank among the most widespread ailments worldwide posing significant global health and economic challenges affecting around 3.5 billion people, impacting the quality of life for affected individuals. Dental caries, periodontal disease, bacterial and fungal infections, tooth loss and oral malignancies are among the most prevalent global clinical disorders contributing to oral health burden. Traditional treatments for oral diseases often face challenges such as poor drug bioavailability, breakdown of medication in saliva, inconsistent antibiotic levels at the site of periodontal infection as well as higher side effects. However, the emergence of nanoemulgel (NEG) as an innovative drug delivery system offers promising solutions where NEG combines the advantages of both nanoemulsions (NEs) and hydrogels providing improved drug solubility, stability, and targeted delivery. Due to their minuscule size and ability to control drug release, NEGs hold promise for improving treatment of oral diseases, where versatility of these delivery systems makes them suitable for various applications, including topical delivery in dentistry. This review concisely outlines the anatomy of the oral environment and investigates the therapeutic potential of NE-based gels in oral disorder treatment. It thoroughly examines the challenges of drug delivery in the oral cavity and proposes strategies to improve therapeutic efficacy, drawing attention to previous research reports for comparison. Through comprehensive analysis, the review highlights the promising role of NEGs as a novel therapeutic approach for oral health management via research advancements and their clinical translation. Additionally, it provides valuable insights into future research directions and development opportunities in this area.

Keywords Nanoemulsion · Nanoemulgel · Oral disease · Local application · Sustained release · Mucoadhesion

Introduction

Oral diseases are highly widespread worldwide, imposing significant health challenges while substantially diminishing the well-being of those impacted. They are chronic and progressive in nature. The soft and hard tissues of the mouth are affected by a wide range of illnesses and conditions, such as several craniofacial disorders, congenital malformations, wounds, and infections. However, dental caries, tooth decay, periodontal disease, and oral malignancies are the main clinical disorders that are regarded as global public health issues [1]. Dental caries is mainly caused due to enamel destruction by acidic production from sugar breakdown by bacteria [2]. The lower the pH (more acidic), the more damage is caused to the teeth [1]. Periodontal diseases, characterized by inflammation and deterioration of gum tissues, pose significant challenges to oral health. In the early stage, it is typically manifested as gingivitis, marked by reversible inflammation of the soft tissues surrounding

Deepali Kumari and Varnita Karmakar contributed equally to this work.

✉ Bapi Gorain
bapi.gn@gmail.com; bapi.gorain@bitmesra.ac.in

¹ Department of Pharmaceutical Sciences and Technology, Birla Institute of Technology, Mesra, Ranchi, Jharkhand 835215, India

² School of Pharmacy, University of Nottingham Malaysia, Selangor, Semenyih 43500, Malaysia

³ Department of Pharmacy, Central University of Haryana, Mahendargarh, Haryana, India

⁴ Department of Pharmaceutics, Amity Institute of Pharmacy, Amity University, Noida, India

the teeth, leading to bleeding and swelling of the gums but in the case of individuals with weakened immune systems, gingivitis may progress to periodontitis. The main reasons behind the progression of gingivitis to periodontitis include factors such as poor oral hygiene practices, accumulation of plaque and tartar, genetic predisposition, systemic diseases, hormonal changes, smoking, and certain medications. These factors can exacerbate inflammation and compromise the ability of body to fight off bacterial infections, leading to the advancement of periodontal disease [3]. Another category of oral diseases includes oral infections i.e., bacterial infections (such as periodontal disease and dental abscesses) [4], viral infections (like herpes simplex virus and human papillomavirus) [5], and fungal infections [6]. Furthermore, another major problem is oral cancer, a serious and potentially life-threatening condition that poses a significant concern among oral diseases. It ranks as the sixth most common cancer worldwide [7]. It manifests as abnormal cell growth in the mouth, including the lips, tongue, cheeks, and throat [8]. Thus, the urgent need for addressing oral diseases is evident, given their significant impact on overall health and quality of life.

According to the World Health Organization (WHO) Global Oral Health Status Report (2022) estimation, oral illnesses afflict around 3.5 billion people globally, with middle-income nations accounting for three out of every four cases and 2 billion individuals account for permanent tooth decay, while 514 million children suffer from primary tooth decay worldwide (<https://www.who.int/publications/i/item/9789240061484>). Periodontitis ranked as the sixth most widespread health issue, impacting 10.8% of the global population, which equals to around 743 million individuals [9] as well as 158 million individuals, constituting 2.3% of the world's population, entirely without natural teeth. In 2018, cancers of the lips and mouth cavities were among the top 15 most prevalent cancers worldwide, as per research by the International Agency for Research on Cancer [1]. Oral cancer incidence indicates, 11.5 adults per 100,000 will develop oral cancer [10]. The statistics highlight a pressing global oral health crisis, with billions affected by various oral diseases, including tooth decay, periodontitis, and oral cancer. Urgent action is imperative to address these widespread issues, emphasizing the crucial need for improved prevention strategies in the form of novel formulation development.

The existing conventional treatment results in poor bioavailability of the drug in the buccal cavity, causing degradation of the therapeutics in salivary fluid, erratic antibiotic concentration at the periodontal site, and higher side effects. These issues can be resolved by using advanced and targeted delivery devices using nano-therapeutic approaches [11–13]. NEs represent an innovative drug delivery system, offering

enhanced delivery of active pharmaceutical ingredients while addressing limitations associated with conventional drug delivery systems. With globule sizes typically ranging from 10 to 100 nm, it improves stability and reduces interfacial tension between oil and water molecules. Their small size facilitates high penetration and increased bioavailability, enhancing drug solubility and potentially reducing both dosage and side effects [14]. Additionally, it can be tailored to deliver drugs precisely to targeted areas, making them a promising avenue for pharmaceutical research and development [15]. NEG is the integration of two components, NE into a hydrogel system, where dual characteristics i.e., the presence of both a gel base and an emulsion at the nanoscale act as suitable candidates for drug delivery. Its NE component prevents certain reactions like hydrolysis and enzymatic degradation to protect the active moiety while the gel base gives the emulsion thermodynamic stability by reducing surface as well as interfacial tension and thus increasing both viscosity and spreadability. Because of their rheological properties, NEGs are particularly well-suited for topical application, however, they can also be used in dentistry to improve patient acceptance [16]. NEG provides enhanced stability and prolonged retention at the site of application due to its gel-like consistency, ensuring sustained release of therapeutic agents [17]. Additionally, its mucoadhesive properties enable better adherence to oral mucosa, facilitating improved drug absorption and efficacy. This innovative formulation also offers controlled drug release, reduced dosing frequency, and enhanced patient compliance, ultimately leading to better therapeutic outcomes in the management of oral diseases [18]. Thixotropic, greaseless, readily spreadable, non-staining, excipients compatibility and soluble in water or miscible are a few of the advantageous qualities of NEG and its development is incredibly easy and economical. NEG also can overcome the limitations by dissolving the lipophilic drug within the oil phase of NE which is then subsequently combined with hydrogel base leading to NEG formation which facilitates the integration of lipophilic drugs into hydrogels while enhancing the viscosity of the NE concurrently [19].

This review provides a concise overview of the anatomy of the oral mucosa and explores the potential of NE-based gels in the treatment of oral disorders. Furthermore, it explores the challenges of drug delivery within the oral cavity and proposes strategies to improve efficacy, drawing upon insights from previous research findings. Through comprehensive analysis, this review sheds light on the promising role of NE-based gels as a novel therapeutic approach for oral health management via research advancements and their clinical translation, while offering insights into avenues for further research and development in this field.

Methodology

The information search in the literature was conducted through online databases like Google Scholar, PubMed, and ScienceDirect. The different keywords utilized for searching were “Nanoemulsions”, “Nanoemulgels”, “Oral diseases”, “Oral thrush”, and “Periodontitis”, “Oral cancer”, “Oral mucositis”, “Gingivitis”, “Challenges”, “Drug delivery”. The search was carried out for articles published since year 1999 up to May 2024. The inclusion criteria for the literature search of the manuscript involved the English language, keywords described above, NE in the treatment of oral disorders, NEGs in the treatment of oral diseases, and challenges associated with NEG delivery to the oral mucosa. Studies that were excluded include those not focused on oral diseases, publications with ambiguous or insufficient information, ongoing research with unavailable results, retracted, and non-English articles. According to the suitability of the review manuscript, articles were found in different electronic databases using the keywords in the abstract or title section.

Anatomy of oral mucosa: Hindrance in drug permeation

The oral cavity is a sophisticated environment designed for taste perception, speaking, mastication and ingestion of food, and extrinsic antigen surveillance. The oral mucosa, acting as a physical barrier in combination with saliva and healthy oral flora protects the mouth from infection by pathogenic bacteria [20], and shields the submucosal structures from the mechanical, thermal, and chemical stresses of food ingestion as it is a crucial sensory organ that also senses temperature, proprioception, touch, pain, and taste.

Additionally, it serves as a crucial entry point for antigen sampling, preparing the immune system for a prompt and effective response [21].

The oral mucosa has a total surface area of approximately 200 cm² and it comprises two functional layers: the vascular mesodermal layer (known as the chorion or lamina propria) and a thick, stratified squamous epithelium lacking blood vessels, serving as a protective barrier against various external threats [20]. The primary cells of epithelial tissues are keratinocytes, comprising 90% of the total, while the remaining 10% includes permanent cells like melanocytes, Langerhans cells, and Merkel cells, along with transient cells like granulocytes, lymphocytes, and monocytes. The thickness of the epithelium varies depending on location, ranging from 40 to 50 cell layers [22]. The basement membrane consists of a basal lamina and reticular lamina and acts as a barrier to negative charges and guides cell migration during the healing of a wound. The connective tissue is dense or semi-dense in nature as per its location in the oral cavity and it mainly plays an important role in providing nutritional support to epithelium. The cell population in this tissue consists mainly of fibroblasts, macrophages, lymphocytes, mast cells, and plasma cells [21].

Within the oral cavity, three distinct types of oral mucosa exist. Masticatory mucosa (includes the hard palate and gingivae) plays a significant function in providing support during masticatory movements by withstanding considerable friction and pressure [23] (Fig. 1). Specialized mucosa (includes the dorsum of the tongue) has defensive as well as taste detection functions, and lining mucosa (includes the floor of the mouth and buccal mucosa), is involved in safeguarding the interior of the oral cavity by serving as a barrier against microorganisms and various substances [21]. Additionally, the presence of abundant elastic fibres enables

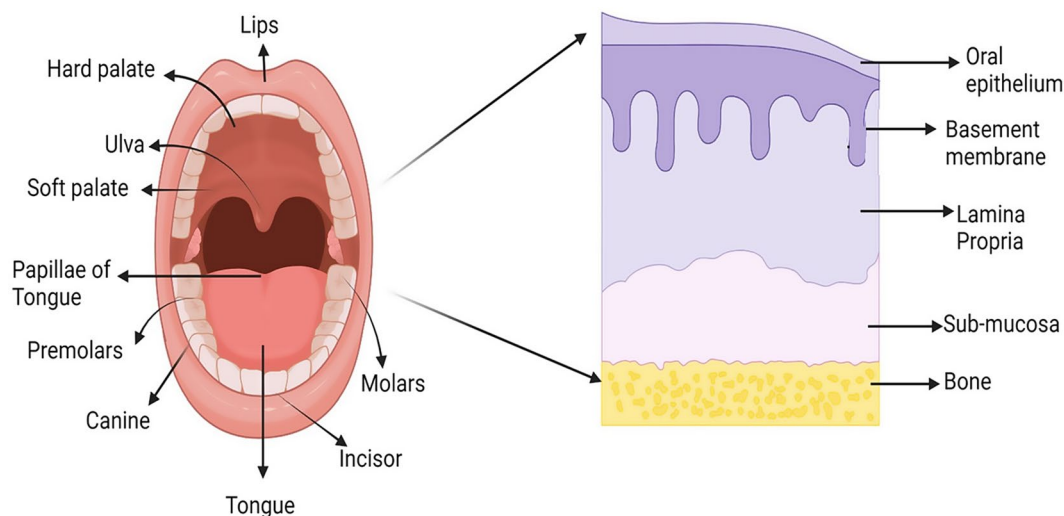


Fig. 1 Anatomy of oral mucosa suitable for application of in situ NEG for the treatment of oral diseases

the tissue to stretch and relax. These three forms make up 25%, 15%, and 60% of the oral mucosa, respectively [24].

The complex anatomy of oral mucosa, including layers of squamous epithelium, basement membrane, and connective tissue, presents a significant barrier to drug diffusion. While the outermost layer acts as a primary barrier, underlying layers are more permeable. Membrane-coating granules rich in keratohyalin further influence permeability, with nonkeratinized epithelium being more permeable than keratinized epithelium [22]. This complexity drives the development of tailored drug delivery systems, such as nanocarrier systems like nanoparticles and liposomes [25]. Specific regions like the sublingual and buccal routes offer higher permeability, enabling systemic drug delivery. However, challenges such as salivary flow necessitate the design of mucoadhesive delivery systems for optimal drug absorption [26]. Standardized oral mucosal models are lacking, highlighting the ongoing need for research to develop reliable methods to assess drug permeability and efficacy through this route.

Challenges in delivering therapeutics via oral mucosa

Oral mucosal delivery targets a variety of conditions, each requiring specific drug penetration and retention for optimal treatment and minimal side effects. Superficial infections like candidiasis necessitate delivery to the surface layers, while diseases like oral dysplasia demand deep epithelial penetration and retention. The drugs that target intracellular pathogens should readily enter host cells, whereas those targeting cell surface receptors benefit from extracellular penetration routes [27]. Oral mucosal drug delivery faces several challenges, including variable mucosal permeability, enzymatic degradation, limited drug retention, and patient compliance issues [20, 28]. These challenges are highlighted in Table 1. Mucosal permeability can vary greatly across different regions of the oral cavity, affecting drug absorption and bioavailability. Moreover, factors like storage conditions, pH stability, and interactions with gelling agents influence the stability and efficacy of the formulation. NEG's benefit from the inclusion of stabilizing agents, which protect the emulsion droplets from coalescence and phase separation. This stability ensures that the drug remains homogeneously distributed throughout the formulation, offering predictable and reliable drug release profiles [29]. Also, enzymes present in saliva and the mucosa can degrade drugs, reducing their effectiveness. Additionally, the dynamic environment of the oral cavity, including saliva flow and movement of the mucosa, can lead to poor drug retention and inconsistent dosing [30, 31]. To further enhance shelf life, packaging materials such as air-tight containers or specialized blister

packs can prevent moisture and light exposure, contributing to the long-term preservation of NEG-based formulations [32]. Studies have demonstrated that NEG formulations stored under appropriate conditions can maintain their physicochemical properties, such as droplet size and viscosity, for extended periods without compromising therapeutic effectiveness [33]. This long-term stability is critical for ensuring patient compliance and minimizing drug wastage due to expired or degraded products.

Furthermore, patients might find using gels or patches inconvenient or uncomfortable, impacting compliance. Overcoming these obstacles requires innovative formulation techniques, including mucoadhesive preparations, nanoparticle-based drug carriers, and controlled-release systems, to enhance drug stability, permeability, and retention, ultimately improving therapeutic outcomes. NEG's, through their small droplet size and mucoadhesive polymers, enhance penetration and prolonged drug release [34]. Moreover, patient-related factors like taste, comfort, and mouthfeel are crucial for compliance, and the incorporation of bioadhesive and taste-masking technologies, along with size-optimized formulations, shows promise in improving drug efficacy while maintaining therapeutic integrity [35].

Relative toxicity of nanoemulgels

The relative toxicity of NEG's in the treatment of oral mucosal disorders is primarily influenced by their composition, including the type of surfactants, co-surfactants, and polymers used in the formulation [36]. NEG's, due to their nanoscale size, enhance drug penetration and bioavailability, potentially increasing the therapeutic efficacy but also raising concerns about localized toxicity, particularly in sensitive oral tissues [37]. Surfactants, though essential for stabilizing the emulsion by forming a barrier between the two immiscible liquids, can irritate the mucosa if present in high concentrations. Smith and colleagues examined the penetration and skin disturbance properties of two surface active agents, sodium dodecyl sulphate and dodecyl trimethyl ammonium bromide. They concluded that higher concentrations of micelle agglomerate and monomers are what mostly induce disturbance in the skin layer [38]. Ionic surfactants are generally avoided due to their higher toxicity and lack of biocompatibility. In contrast, non-ionic surfactants are preferred for their safety, biocompatibility, and stability, as they are unaffected by changes in pH or ionic strength. In this context, it is pertinent to mention that surfactants derived from natural sources, such as bacteria, fungi, or animals, are emerging as promising alternatives due to their biodegradability, safety, and biocompatibility. These bio-surfactants function similar to synthetic surfactants by reducing surface tension through their amphiphilic

Table 1 Challenges in the delivery of drugs via oral mucosa

Major Problem	Type	Description	NEGs as a possible solution	Source
Complex physiology of the oral mucosa	Structural Complexity	• Distinct stratifications and differentiation patterns, result in functionally heterogeneous regions. • Keratinized tissues (e.g., gingiva, hard palate) have robust mechanical resilience and superior barrier properties due to pronounced keratinocyte differentiation and lipid accumulation. • Non-keratinized areas (buccal, sublingual) have higher permeability but lack the mechanical resilience of keratinized tissues, requiring tailored drug formulations for effective absorption.	• Nano-sized droplets in NEG formulations can efficiently penetrate both keratinized and non-keratinized mucosa, improving drug absorption. • NEGs adhere to mucosal surfaces, prolonging drug contact time, and ensuring localized delivery even in regions with diverse structural barriers.	[46, 47]
	Mucosal lubrication dynamics	• The interplay between mucins (large glycoproteins) and saliva orchestrates mucosal lubrication dynamics. • Also, the interaction makes it difficult for conventional drug formulations to adhere to oral mucosa. • Variations in saliva flow rates and composition can wash away drug formulations, reducing contact time and limiting drug absorption.	• NEGs interact effectively with mucins, adhering firmly to mucosal surfaces despite lubrication dynamics, ensuring prolonged drug retention. • NEGs also enhance mucoadhesion and prolong drug release. • Improved stability of mucoadhesive formulations maintains sustained drug delivery.	[36, 48–50]
	Regional Variability	• The permeability barrier of mucosal layers, primarily composed of lipids in the upper epithelial layers, slows the passage of hydrophilic substances. • The heterogeneity in mucosal permeability across distinct oral regions affects drug absorption. • The palatal mucosa presents formidable barriers due to lipid-rich keratinocytes and reduced vascularization.	• Understanding the permeability dynamics of different oral mucosal regions helps efficient delivery of NEGs. • NEGs also ensure prolonged contact and enhance drug retention and permeation.	[51–54]
Formulation-related challenges in oral cavity	Rapid Elimination	The effective local delivery of drugs via the oral mucosa is challenged by rapid elimination kinetics due to saliva flow dynamics and food ingestion, necessitating frequent dosing to maintain therapeutic concentrations.	• The development of mucoadhesive formulations increases the resident time of retention in the oral mucosal regions. • Advanced drug delivery systems such as NEGs improve the bioavailability profile.	[34, 55, 56]
	Diffusion-related issues	The drug's lipophilicity, molecular weight, and partition coefficient hinder its ability to effectively permeate the oral mucosa, limiting absorption and bioavailability in mucosal disorders.	• The use of NEGs enhances passive diffusion and carrier-mediated transport. • Research on NEG showed efficient drug diffusion regardless of molecular weight or lipophilicity.	[17, 56]
	Non-uniform distribution	The heterogeneous distribution of drugs within the saliva matrix after release from formulations leads to spatiotemporal variability in drug dispersion across oral mucosal regions, compromising consistent pharmacological effects.	• Techniques such as NEs or mucoadhesive formulations can facilitate extended contact, thereby improving drug retention and distribution. • Controlled-release systems and micro/nanoencapsulation offer potential solutions to overcome non-uniform distribution barriers.	[35, 57, 58]
Challenges related to permeation barriers	Permeability barrier	The intrinsic impermeability of large hydrophilic biopharmaceuticals poses challenge in delivery.	• NEGs utilize nano-sized droplets to enhance drug solubility and penetration through tight mucosal junctions in the oral cavity.	[53]
	Physico-chemical modulators	Lipophilic drugs prefer transcellular routes, facilitated by cell membrane partitioning, while hydrophilic compounds use paracellular routes via intercellular spaces. Lipophilic drugs struggle with poor solubility in hydrophilic environments, while hydrophilic drugs face difficulty penetrating the lipid-rich transcellular route.	• NEGs enhance partitioning of lipophilic drugs into cell membranes for transcellular permeation. • Hydrogel matrix in NEGs facilitates diffusion of hydrophilic compounds through paracellular routes. • Research indicates NEGs can optimize drug permeation for a broad spectrum of medications.	[59]
Patient-related barriers	Patient in compliance	Taste, irritancy, and overall mouth feel, unpleasant taste or discomfort	• NEGs mask unpleasant tastes and reduce irritancy by incorporating the drug within a smooth, gel-like matrix, offering a more comfortable and palatable mouthfeel, thus improving patient compliance.	[60]

nature, with non-polar short-chain fatty acids as the tail and polar groups at the head. Due to their enhanced biocompatibility and safety profile, bio-surfactants are considered a safer alternative to synthetic surfactants [17].

Furthermore, the polymers used to convert the NE to NEG play an important role in the safety of the product. Here, biocompatibility refers to non-toxic nature of the polymers to the body system while applied. Additionally, there will be no production of toxic degradation products over time, which could harm the quality of the product as well as produce toxic manifestations [39, 40]. Therefore, it is important to understand and control the interactions between biological elements (such as cells, cellular proteins, ions, water, fungi, bacteria, etc.) and the polymeric components in NEGs, which will allow successful conversion of the laboratory research to biomedical application to human patients [41].

Concurrently, mucoadhesive properties of the polymers incorporated in the NEGs should allow retention of the polymers at the mucosal site when applied for a desired period of time. Such conditions will allow prolonged release of the incorporated components [39]. Moreover, the interaction between the mucoadhesive polymers and mucosal layer should not be too firm to cause damage to the cells. Thus, biocompatible and mucoadhesive agents in the NEG formulations generally demonstrate minimal irritation and low systemic toxicity due to localized drug release [42]. Moreover, studies have shown that well-optimized NEGs offer superior tolerability compared to conventional topical treatments, with limited adverse effects on the oral mucosa, making them a promising alternative for localized therapy of oral mucosal disorders [43]. The methylcellulose-based NEG developed with *Nigella sativa* oil for oral health management showed non-toxic, safe delivery as assessed through in vivo evaluation in rabbits [44]. Also, the toxicity profile of the ebselen NEG indicates that the blank NE (without the active drug) demonstrated minimal toxicity toward fungal cells, with a MIC value greater than 100 μ M. This suggests that the excipients used in the formulation are safe and do not contribute significantly to antifungal activity, highlighting the formulation's biocompatibility [45]. Thus, the safety profile of well-optimized NEGs indicates minimal toxicity and high biocompatibility, making them a safe option for localized therapy in oral and topical treatments.

Technologies for improved delivery of therapeutics at the oral mucosa

NEs with particle sizes ranging from 10 to 100 nm present numerous benefits over traditional drug delivery systems. These advantages include enhanced stability owing

to their small size, reduced interfacial tension between oil and water, minimal agglomeration, higher permeation due to their small globule size, increased drug bioavailability, improved drug solubility, lowered dosage requirements and reduced side effects. They allow precise administration to specific regions and can form NEGs when thickening or gelling agents are incorporated. NEGs improve drug retention in the oral cavity, facilitate sustained drug release, and offer advantages over lipid nanoparticles, microemulsions, or liposomes in terms of higher drug loading capacity, enhanced diffusibility, permeability, and diminished skin irritation for transdermal or dental distribution [61]. Figure 2 highlights the mechanism of NEG absorption and penetration via oral mucosal route.

Size optimization

Smaller droplet sizes in NEs offer a larger surface area-to-volume ratio, which enhances their interaction with the oral mucosa. This means that a greater proportion of the drug-loaded nanoparticles come into contact with the mucosal membrane, facilitating efficient drug absorption and penetration into the bloodstream or local tissues [29]. In another study, a NEG formulation was developed for oral curcumin delivery to improve therapeutic efficacy in oral lichen planus (OLP). Through optimization of droplet size to less than 100 nm, the NEG exhibited enhanced oral mucosal penetration and sustained drug release. In vitro studies demonstrated prolonged curcumin release and ex vivo permeation studies on porcine mucosa (buccal) revealed enhanced tissue penetration compared to conventional gels. These findings suggest that size-optimized NEG formulations hold promise for improving oral mucosal drug delivery and may offer enhanced therapeutic benefits in managing oral inflammatory disorders like OLP [62]. Mohammed Alissa et al. revealed that NEs are sophisticated delivery systems made of oil droplets that are nanosized and stabilized by co- and surfactants. In the context of their study, the optimized cinnamon oil-loaded NEG1 with smaller droplet sizes likely exhibited superior oral mucosal delivery, resulting in enhanced antibacterial, antifungal, and analgesic actions in the treatment of oral disorders [63].

Polymer selection

The choice of polymers for the emulgel matrix leads to a deeper study of the release kinetics and stability of the formulation. For example, hydrophilic polymers like hydroxypropyl methylcellulose (HPMC) can extend the duration of medication release by enveloping the drug-loaded nanoparticles in a protective layer [64, 65]. Additionally, certain polymers may enhance mucoadhesion, extending the

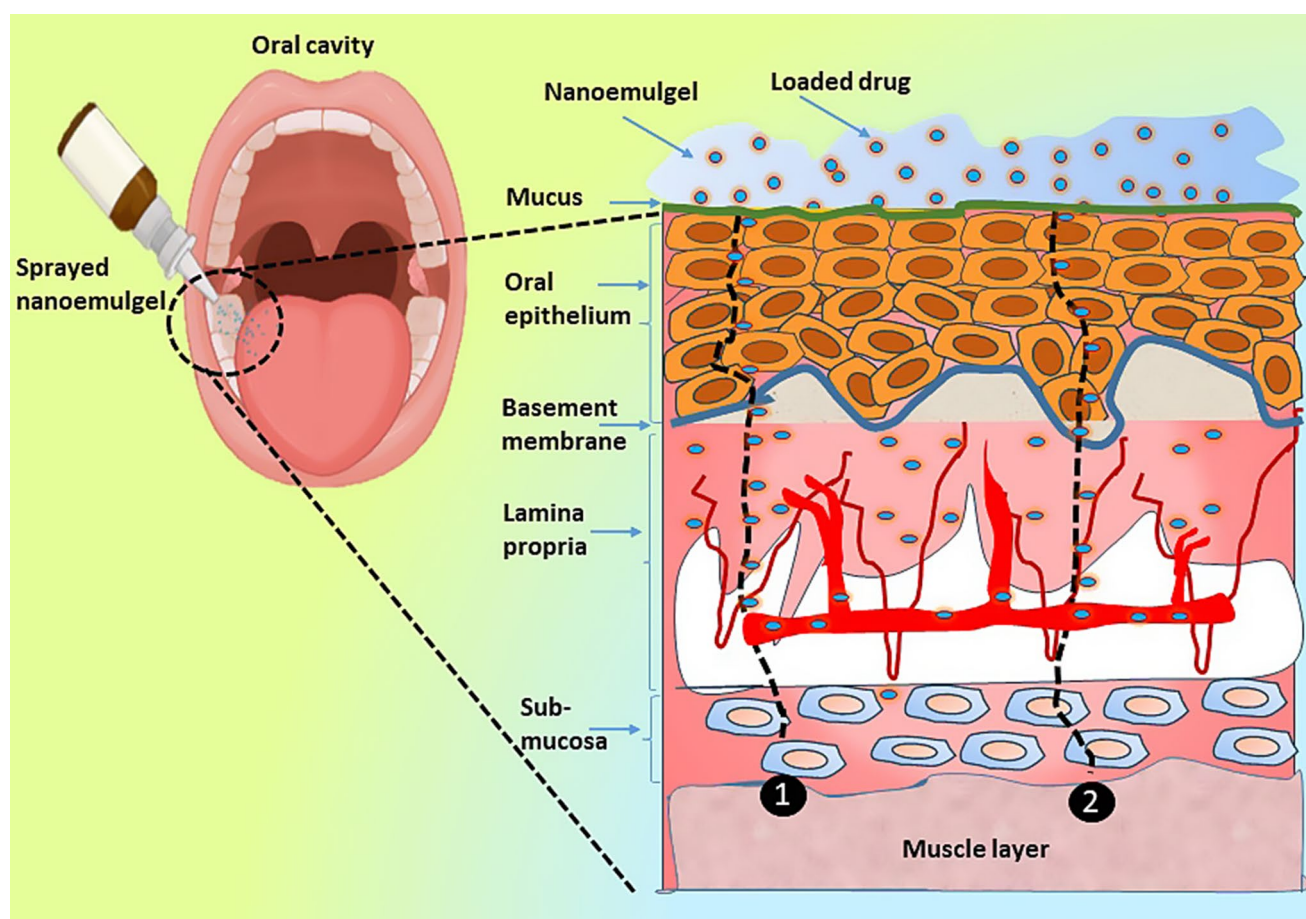


Fig. 2 Nanoemulgel administration and drug penetration through oral mucosal layer; (1) Paracellular drug transport; (2) Transcellular drug transport

duration of contact with the mucosal surface and improving drug absorption. Similarly, Carbopols, known for their non-irritant and non-toxic properties, have been widely employed as gelling agents due to their ability to maintain consistent consistency in NEG formulations [66]. To support this fact, a study carried out by Ullah et al., created a mucoadhesive NEG to treat bacterial infections in the mouth, utilizing Carbopol 940 as the gelling agent. The formulation's consistency, spreadability, and mucoadhesive strength were optimized, demonstrating its suitability for topical application. Additionally, the NEG exhibited a significant release of clove and cinnamon oils, with a permeation profile revealing effective delivery through buccal mucosa [67]. Furthermore, the choice of stimuli-responsive polymers to enhance the applicability of the formulation is a recent trend, where the storage condition of the formulation facilitates ease of application and the conversion into a gel by the stimuli at the application site allows longer retention at the application site [68–70]. However, such technologies have not yet much explored in the conversion of NE to NEG.

Bioadhesive formulations employ polymers including poloxamer 407, sodium carboxymethylcellulose, hyaluronic acid, carbopol, and xanthan gum to enhance retention and sustain drug release by undergoing a phase change [71]. Hydrogels, derived from hydrated polymers, demonstrate potential for buccal drug delivery, ensuring prolonged retention, effective penetration, and high therapeutic efficacy. These bioadhesive gels are particularly beneficial in periodontitis treatment, where mucoadhesive polymers help retain drugs within periodontal pockets, improving therapeutic outcomes.

Drug loading and encapsulation

Optimization of drug loading and encapsulation is crucial for NEGs for improved oral mucosal delivery of drugs. High loading efficiency ensures maximum drug delivery per dose, enhancing therapeutic efficacy. Techniques like solvent evaporation, nanoprecipitation, or supercritical fluid technology can efficiently encapsulate drugs within nanoparticles, optimizing their bioavailability [72]. Controlled release formulations within NEGs enable sustained

or triggered drug release, safeguarding a consistent beneficial outcome over time while diminishing fluctuations in drug concentration, thus improving patient compliance and treatment outcomes.

Khaled M. Hosny et al., have reported that cinnamon oil-loaded NE was optimized using a specific experimental design, resulting in a formulation with small droplet size (92 ± 3 nm), high stability ($95\% \pm 2\%$), and significant antibacterial activity (zone of inhibition: 23 ± 1.5 mm). The optimized formulation was transformed into NEG using hydroxypropyl cellulose that enhances its solubility and effectiveness against oral microbiota, while also providing analgesic benefits. Rheological testing indicated that NEG formulation exhibited pseudoplastic behavior. In vitro release studies demonstrated enhanced release and ex vivo permeation, indicating increased mucosal permeation of drugs using NEG when compared to cinnamon oil-loaded NE and pure cinnamon oil. Overall, the use of NEG formulations to improve oral health, relieve pain, and enhance antibacterial actions against oral microbiota shows potential [73, 74].

Enhanced penetration and targeting

Penetration enhancers can facilitate drug permeation across the mucosal barrier by disrupting tight junctions or increasing membrane fluidity. Common enhancers include surfactants like Tween 80 or bile salts like sodium deoxycholate [31]. Targeted delivery systems, on the other hand, enable precise delivery of drugs to specific cells or tissues by conjugating nanoparticles with ligands or antibodies that recognize surface receptors or antigens [75]. When formulated into oral gels, strategic delivery of essential oils to the oral cavity enhances drug efficiency. By incorporating a thickening or gelling agent, these formulations can be converted into NEGs, which prolong their residence in the oral cavity, promote sustained drug release, and enhance drug solubility, permeability, and efficacy [76].

To enhance oral mucosal drug delivery, penetration enhancers have garnered significant attention, particularly for poorly soluble drugs and large hydrophilic molecules. These enhancers are sought after for their safe, effective, and reversible properties, often resembling surfactants and exhibiting higher activity above critical micelle concentrations [74]. Mechanistically, they augment cell membrane fluidity, extract lipids, disrupt lipid structures, alter cellular proteins, enhance drug thermodynamic activity, overcome enzymatic barriers, and modify surface mucin rheology. Encouragingly, some enhancers have demonstrated a notable increase in the penetration of large molecules, with in vitro studies showing up to 10% absorption [72]. Various types of penetration enhancers include bile salts, fatty

acids and their derivatives, azones, surfactants, complexing agents, co-solvents, and miscellaneous compounds, all holding promise for improving oral mucosal drug delivery.

Targeted potential therapy

Sindi et al. developed NEs based on turmeric and curry leaf oil to improve the solubility and distribution of lipid-based drugs for oral health improvement, particularly targeting gingivitis. Utilizing a response surface Box-Behnken design, they formulated Curry leaf oil-Turmeric SNEDDS with varying concentrations of ingredients. The developed formulation exhibited potent antibacterial activity, with a marked (20 mm) bacterial zone of inhibition and demonstrated excellent drug-loading efficiency and enhanced transbuccal permeability when combined with hyaluronic acid gel. In animal testing, the formulation loaded into an emulgel showed reduced levels of IL-6 in serum compared to other formulations, suggesting its potential as a useful method for gingivitis treatment and oral health improvement [77].

Srivastava et al., have reported in situ gelling syringeable NEGs containing ketoprofen for periodontal drug distribution. A 3-factor 3-level experimental design was used to optimize the NE formulation, mainly focusing on oil concentration, Smix composition, and water content. The characteristics of the resulting NEGs were evaluated, including drug content, pH, mucoadhesion, syringeability, and sol-gel transition temperature. The in vitro drug release profiles were analyzed using various models indicating one of the optimized formulations exhibited optimal drug release. The Herschel-Bulkley model best described the flow behaviour of the optimized formulation. The formulation showed low toxicity according to in vitro HET-CAM assessment, indicating its aptness for intra-pocket drug delivery in periodontal treatment [15].

Overcoming bioavailability challenges and shelf-life consideration

Overcoming bioavailability challenges ensures effective drug absorption, maximizing therapeutic efficacy in oral mucosal drug delivery. Addressing shelf-life considerations maintains drug stability, ensuring product integrity and patient safety over time [32]. NE-based gels enhance drug solubility and stability, leading to improved bioavailability and prolonged drug release, thus addressing bioavailability challenges and ensuring shelf-life considerations in oral mucosal drug delivery [29]. Nano-emulsions also face challenges in spreadability due to their low viscosity, which limits their retention on the skin [78]. To overcome these challenges, researchers have developed NEGs by combining

NEs with gelling agents [33]. This innovative approach enhances the stability of the formulation and allows the controlled release of drugs over time, particularly benefiting those with short half-lives. NEGs offer several advantages over conventional emulgels, including improved skin permeation, higher drug loading, reduced irritation, and better spreadability leading to patient compliance [42]. Additionally, NEGs exhibit enhanced bioavailability and reduced side effects compared to other nanocarriers and their stability is further improved by minimizing issues like Oswald ripening and formulation destabilization. Therefore, NEGs address various limitations encountered with conventional dosage forms, making them a promising option for topical drug delivery [17].

Nanoemulsion and nanoemulsion-based gel in topical oral delivery for the treatment of oral diseases

NEs, a type of stable lipid-based drug delivery system consisting of tiny droplets of oil dispersed in water with the aid of surfactants, offer considerable potential in treating oral diseases [79, 80]. NEG formulations offer a promising avenue for the treatment of oral diseases due to their unique properties. Their stability and small size make them superior to traditional formulations like gels and emulsions, particularly in improving drug delivery through the skin. Studies have shown that NE gels, for instance, those containing caprylic acid, can enhance the penetration of drugs like meloxicam through the skin, offering a promising avenue for oral disease treatment [78, 81].

This suggests the potential for the NEG as an alternative therapy for topical fungal infections. These NEs have advantages such as increased drug solubility, better permeation through oral tissues, and reduced side effects. Additionally, they exhibit broad-spectrum antimicrobial properties, making them effective against various bacteria commonly associated with oral diseases [32, 36]. To ensure optimal clinical outcomes, it is crucial to fine-tune the mechanical and drug-release properties of nano-formulations for controlled and sustained drug delivery. Furthermore, mucoadhesive drug delivery systems offer advantages such as targeted drug release and prolonged retention at specific sites, while also bypassing first-pass metabolism [18]. Hence, to showcase a vivid in-depth demonstration of NE-based gels in the treatment of various oral diseases, a detailed overview has been described hereafter.

Topical application of nanoemulgel in the treatment of periodontitis

Periodontitis is a widespread inflammatory oral condition globally recognized as a leading cause of tooth loss. It progresses slowly, affecting the tissues surrounding the teeth due to bacterial plaque and calculus buildup. *Porphyromonas gingivalis* is a key pathogen implicated in periodontitis, triggering inflammatory responses that damage the periodontal ligament and bone [82]. Inflammatory mediators like IL-1 β , IL-6, TNF- α , and RANKL play significant roles in its onset and progression. *P. gingivalis* infection induces bone loss and activates osteoclasts, while TNF- α stimulates bone resorption [83]. IL-10, an anti-inflammatory cytokine, helps regulate periodontitis progression by suppressing inflammation and osteoclastogenesis. Understanding these mechanisms is crucial for developing effective treatments for periodontitis [84].

The mechanical properties of the formulation and the drug's release pattern both play a major role in the effectiveness of treatment [85]. Therefore, an optimal formulation for treatment should be effortlessly inserted into the periodontal pocket, ensure controlled drug release into the crevicular fluid, retained within the pocket for the required duration (without relying on mechanical bonding to tooth surfaces), and possess characteristics of biodegradability, non-toxicity, and non-irritation [86]. NEG emerges as an efficient delivery platform for oral healthcare, as demonstrated by Sultan et al.. Their study aimed to develop a dental NEG using *Nigella sativa* oil (NSO) for periodontal disease treatment. NSO was characterized via GC-MS, and an NE was formulated into a methylcellulose gel base, optimized using a Box-Behnken design. The optimized formulation exhibited pH 7.37, viscosity 2343 cp., droplet size 342 ± 36.6 nm, with sustained drug release over 8 h, and enhanced antimicrobial activity compared to plain NSO [87]. Another study formulated, in situ NEG of azithromycin with eugenol for targeted intra-pocket drug delivery in periodontitis treatment, demonstrating sustained release and non-irritating properties, thus highlighting its potential for therapeutic use. Thus, NEG formation system holds significant promise for periodontitis treatment, enabling precise control over drug release timing tailored to specific treatment sites.

Management of oral thrush using nanoemulsion and NEG platforms

Oral thrush, a fungal infection primarily caused by *Candida albicans*, manifests due to dysregulation in host-microbe interactions within the oral cavity [88]. Adhesion of *Candida* to oral epithelial cells is facilitated by specific adhesion

molecules, enabling colonization and subsequent invasion *Candida albicans*, typically a commensal organism, undergoes pathogenic transformation under conditions favouring its overgrowth, such as immunosuppression, antibiotic use, or alterations in oral microbiota [89]. Molecular mechanisms underlying *Candida* pathogenesis involve morphological changes from yeast to hyphal forms, regulated by environmental cues, promoting tissue invasion and virulence contributing to tissue damage and immune evasion.

NEG formulations offer a promising avenue for treating oral thrush by delivering antifungal agents directly to the affected tissues, targeting *Candida albicans* at a molecular level within the oral cavity. These formulations provide a controlled release of therapeutic agents, potentially disrupting *Candida* pathogenesis by inhibiting adhesion, reducing hyphal formation, and neutralizing virulence factors, thus addressing both the molecular mechanisms and clinical manifestations of oral thrush. A study performed by Sindi et al., showed the development of itraconazole and thyme oil-based self-nanoemulsifying drug delivery systems (ItZ-ThO-SNEDDS) as a potential defense against oral microbial infections. The optimized formulation, incorporated into a honey-based gel, showed enhanced drug release and transbuccal permeation, along with reduced ulcer index in rat models, demonstrating its efficacy in protecting oral health [90]. Another study, aimed to develop fluconazole-loaded mucoadhesive nanogels to address fluconazole's hydrophobicity. The nanogels, formulated with Carbopol 940 and gelatin, showed promising results with enhanced mucoadhesion, improved drug content, and significantly enhanced permeation, suggesting their potential as an effective therapy for candidiasis [91]. In another study, a topical NEG of ebselen to overcome the limitations of conventional formulations for treating superficial mycoses. The NEG, utilizing ebselen-loaded self-nanoemulsifying preconcentrate, demonstrated enhanced solubility and permeability, offering a promising alternative therapy for candidiasis with marked anti-fungal activity against *Candida albicans* and *Candida tropicalis* [45].

Treatment of oral cancer using nanoemulsion and nanoemulgel

Oral cancer pathology involves the abnormal growth of cells in the mouth, potentially leading to malignant tumor [92]. These tumorous conditions typically originate from abnormal cell growth and mutation, often linked to risk factors such as tobacco use, alcohol consumption, and human papillomavirus infection. As the cancer progresses, it can invade surrounding tissues and spread to other parts of the body, leading to severe complications and reduced survival rates if not diagnosed and treated promptly [93]. Conventional

treatments for oral cancer, such as surgery, radiation therapy, and chemotherapy, often carry significant side effects [94]. Surgery can result in functional impairments, such as difficulty in chewing, swallowing, and speaking, while radiation therapy and chemotherapy can cause oral mucositis, xerostomia (dry mouth), nausea, vomiting, and fatigue, significantly impacting individuals.

NEG, a novel drug delivery system, holds promise in mitigating the side effects of conventional oral cancer treatments [17]. By encapsulating therapeutic agents in nanoscale emulsion droplets dispersed in a gel matrix, NEG facilitates targeted delivery of drugs to the tumor site, minimizing systemic exposure and reducing off-target effects [95]. Moreover, the gel-based formulation provides sustained release kinetics, ensuring prolonged drug retention at the tumor site for enhanced efficacy while minimizing adverse reactions in healthy tissues [96]. Thus, NEG offers a more precise and tolerable approach to oral cancer treatment, improving patient outcomes and quality of life.

To enhance treatment outcomes, researchers are exploring novel therapeutic combinations and more effective drug delivery systems. Smart hydrogel-based drug delivery devices can be tailored to treat oral cancers by varying stimulation parameters [97]. Similarly, NEGs have shown promise in delivering berberine (BER), a phytochemical, in combination with 5-fluorouracil (5FU) formulated and delivered to evaluate their synergistic effects for oral cancer therapy using a targeted drug delivery approach. A dual drug-loaded NE was developed and incorporated into a mucoadhesive buccal gel. The formulation's rheological properties, mucoadhesion, drug content, permeability, biocompatibility, and apoptotic activity were assessed. The gel contained 0.55% w/w of each drug, and permeability studies demonstrated retention of both drugs in porcine buccal mucosa for up to 6 h. In vitro studies revealed a significant increase in apoptotic activity of the dual drug-loaded gel compared to 5FU alone, particularly in oral cancer cell lines and CD44-positive stem cells. In vivo biocompatibility studies in rabbits showed no significant buccal irritation after 7 days of gel application. Overall, the combination of BER and 5FU exhibited synergy, and the nanoparticle-mediated buccal gel delivery system showed promise as a site-specific therapy for oral cancer [98]. Another study aimed to create an NEG combining lovastatin (LV) and eucalyptus oil (Eu oil) for potential tongue cancer treatment. Utilizing an optimal mixture design, NEs were optimized for droplet size and stability. The resulting LV-Eu-SNEDDS-loaded NEG exhibited pseudoplastic flow and thixotropic behaviour, with improved cytotoxicity against human chondrosarcoma-3 (HSC3) cells, suggesting its potential as a local therapy for tongue cancer [99]. The study demonstrated that CUR-loaded lipid NEs (CUR-NEs) exhibit significant

cytotoxic effects on oral squamous cell carcinoma (OSCC) HSC-3 cells in a dose-dependent manner. CUR-NEs reduced the percentage of cells in proliferative phases and downregulated PI3K/Akt/mTOR protein expression while upregulating miR-199a expression in OSCC cells. Furthermore, CUR-NEs effectively counteracted the effects of a miR-199a inhibitor on OSCC cell proliferation, suggesting

their potential as a therapeutic agent for oral squamous cell carcinoma [100].

Similarly, genistein NE was prepared and entrapped in a buccal tablet for sustained release to treat oral cancer. The chitosan-free (negatively charged) and chitosan-coated (positively charged) NE was rendered with the size of 110 nm (Fig. 3). The entrapped buccal tablet displayed

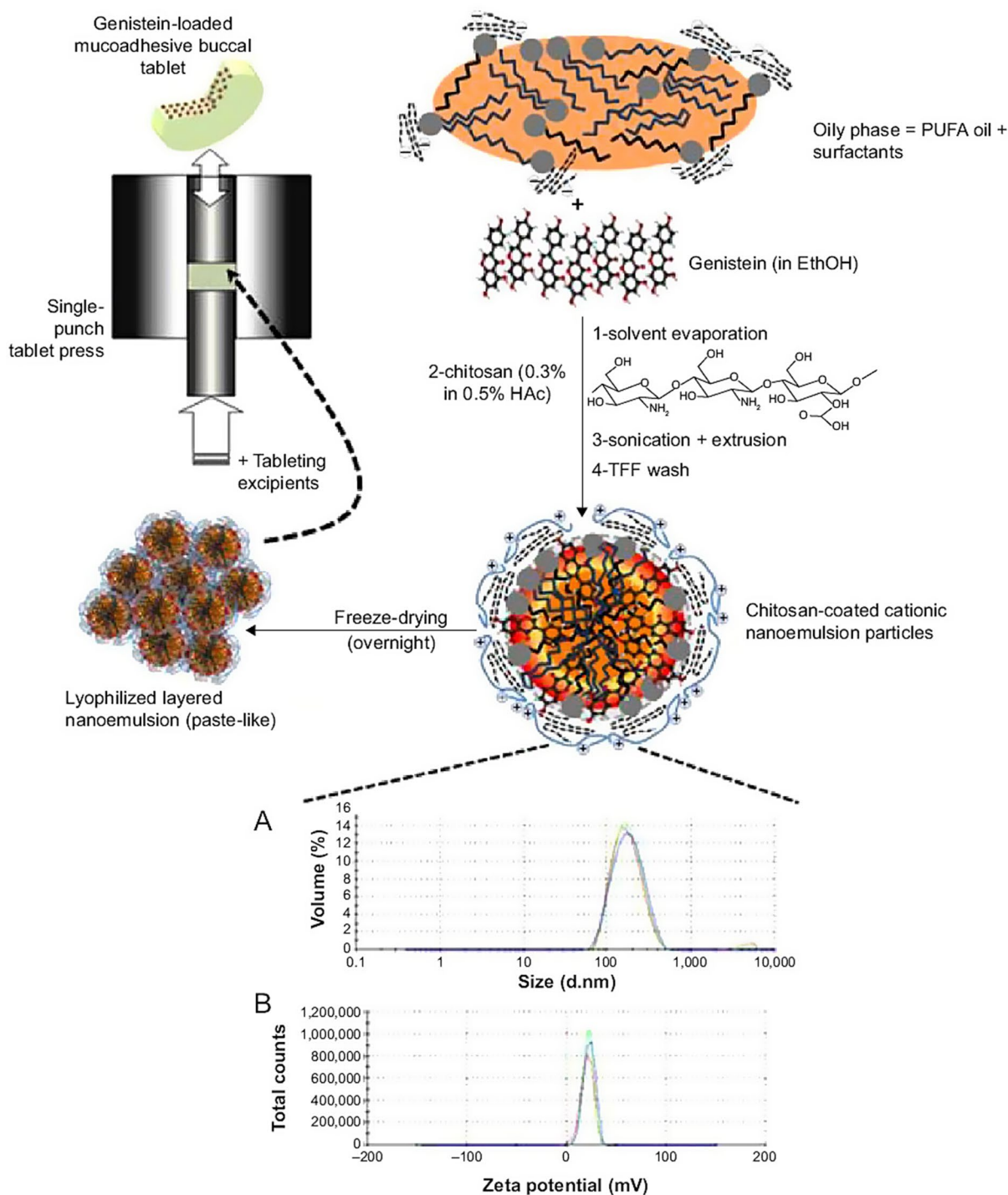


Fig. 3 Pictorial representation of layered nano-emulsion for oral cancer [101]

higher muco-adhesion and controlled release compared to primary NE. Both NE and buccal tablets showed significant action against cancer cell lines which concludes the futuristic potential of site-specific NE delivery for cancerous lesions [101].

Nanoemulsion and nanoemulgel in the treatment of oral mucositis

Oral mucositis is characterized by inflammatory processes triggered by chemotherapy or radiotherapy, leading to epithelial damage and ulceration. Molecular pathology involves the upregulation of pro-inflammatory cytokines, activation of transcription factors like NF- κ B, and increased production of reactive oxygen species, exacerbating tissue injury and impairing mucosal healing [102]. Additionally, disrupted signaling pathways, including those involving growth factors and cell cycle regulators, contribute to the pathogenesis of oral mucositis [103]. Drug delivery to oral mucositis poses challenges due to the dynamic and complex nature of the oral environment. Factors such as saliva flow, mastication, and speech movements can affect the retention and duration of drug contact with the mucosal surface [28]. These challenges can be overcome by NEG delivery, and to support this fact, some of the literature proofs are summarized in Table 1.

As reported in a study, the efficacy of quercetin (QRC) in treating oral mucositis induced by 5-FU in mice was evaluated. Mice receiving QRC posttreatment in the form of emulsion and NE alleviate oxidative damage caused by chemotherapeutic agents compared to the untreated group. Moreover, QRC administration, especially in nano-post-treatment form, significantly increased antioxidant enzyme activity, indicating its potential to ameliorate oxidative stress associated with oral mucositis induced by 5-FU. Additionally, QRC treatment showed trends towards decreased expression of inflammatory genes Hif-1 α and Nf κ B, suggesting its anti-inflammatory effects in this context [104]. Thus, NEG holds promise in oral mucositis treatment, offering targeted drug delivery, improved drug retention, and enhanced therapeutic efficacy for effective symptom relief and mucosal healing.

Gingivitis management using nanoemulsion and nanoemulgel tools

Gingivitis is primarily caused by the accumulation of dental plaque, a biofilm composed of bacteria, food debris, and saliva, along the gum line. When plaque is not adequately removed through regular oral hygiene practices such as brushing and flossing, bacteria in the plaque release toxins and other byproducts that trigger an inflammatory response

in the surrounding gum tissues [105]. This immune response leads to the characteristic signs of gingivitis, including redness, swelling, and bleeding of the gums. Gingivitis conventional treatments often cause irritation and discomfort due to their harsh chemicals [106]. NEG offers an effective solution with its targeted delivery and controlled release of active ingredients, minimizing side effects while promoting healing.

Similarly, a novel self-nanoemulsifying drug delivery system containing posaconazole, calendula oil, and chitosan for gingivitis treatment. Utilizing a response-surface Box–Behnken design, the optimized formulation exhibited a 22-mm bacterial growth suppression zone, 25-mm fungal growth inhibition zone, droplet sizes of 110 nm, and a viscosity of 750 centipoise. The formulation showed controlled drug release, larger inhibition zones against bacterial and fungal growth, and reduced ulcer index in rats, suggesting its efficacy against microbially induced gingivitis [63]. In another study, observations revealed that the application of ketoprofen NEG resulted in a notable decrease in gingival index, tooth mobility, and alveolar bone loss. The pharmacodynamic effects were indicated by cytokine levels approaching normalcy in the group treated with ketoprofen NEG. Moreover, histopathological analysis of the experimental molar teeth showed a significant decrease in inflammatory cell infiltration, alveolar bone resorption, and cementum compared to the group treated with ketoprofen NEG [79]. Thus, NEG emerges as novel drug delivery for oral disorders by encapsulating drugs in nanoscale emulsion droplets within a gel matrix, ensuring targeted delivery to oral tissues. Its sustained release kinetics optimize drug retention at the site, enhancing efficacy while minimizing systemic side effects. This evidence-backed approach represents a promising advancement in oral disorder treatment.

Clinical translation of nanoemulsion/nanoemulgel for oral diseases

NEGs are being explored in clinical settings for oral disorders, particularly for delivering poorly soluble drugs like anti-inflammatory agents and antimicrobials. While still in the early stages of clinical research, they show promise in improving drug retention, stability, and therapeutic outcomes in conditions like oral mucositis and periodontal disease [36]. A phase 3, randomized, parallel and interventional double-blind clinical trial was conducted to check the efficacy of 0.3% of NB-001 with placebo for the treatment of Recurrent Herpes Labialis. NanoBio corporation is the sponsor of the clinical trial. NB-001 is an oil-in-water emulsion comprised of cationic globs with a mean diameter of 180 nm. NB-001 is made up of two different surface-acting agents

i.e., cetylpyridinium chloride and polysorbate (Tween) 20, oily phase: highly refined soybean oil, and water phase as purified water, ethanol, and edetate disodium dihydrate. The inclusion criteria are both sexes with an age of more than 18 years having a history of 3 or more cold sore relapses on the lips or skin surrounding the lips in the previous year and being ready to give up using systemic corticosteroids or topical or systemic antiviral medications for four weeks. The primary and secondary outcome measures the time of healing for the primary lesion complex, expressed in days or fractions thereof and the percentage of patients whose primary lesion complex stays at the papule/edema stage or below respectively. Furthermore, the safety and tolerability of NB-001 were also assessed via the number and intensity of adverse events (NCT01695187).

A phase 1 randomized parallel open-label interventional clinical trial was conducted to evaluate the efficacy of QRC NEG as a supplemental topical delivery for treating periodontitis without surgery. The QRC NEG was developed to overcome the drawbacks associated with QRC i.e., low aqueous solubility and poor bioavailability. The intervention includes intra-pocket application of NEG after isolating teeth, and further full-mouth scaling and root planning were performed in 1–2 sessions within 2 weeks. The inclusion criteria are the patients with stage I and II periodontitis with ages of 18–65 years, either sex. The primary outcome measures interferon IFN- γ analysis, reactive oxygen species quantification, and probing depth. The secondary outcome measures plaque and gingival index (NCT05928546). Another clinical study evaluated the efficacy of a topical Omega-3 NEG in preventing radiation-induced oral mucositis in head and neck cancer patients undergoing radiotherapy. Oral mucositis, a common and painful side effect of radiotherapy, severely impacts patients' quality of life and nutritional intake. Omega-3 polyunsaturated fatty acids, known for their anti-inflammatory, antioxidant, and wound-healing properties, were used in the NEG to manage oral inflammation. Thirty-four head and neck cancer patients were divided into two groups: one receiving conventional preventive treatment and the other using the Omega-3 NEG. Results showed that patients treated with the NEG had significantly lower visual analogue scale pain scores and WHO mucositis grades after six weeks compared to the control group. Moreover, the MD-Anderson Symptom Inventory for head and neck cancer revealed a higher symptom burden in the control group at three and six weeks. Microbial analysis also demonstrated a reduction in the *firmicutes/bacteroidetes* ratio in the NEG group, indicating improved oral microbial balance and reduced dysbiosis [43].

While the findings suggest that NEG is effective in preventing and curing oral mucosal diseases, the clinical translation of NEG for oral diseases poses several challenges.

Key challenges include ensuring the stability of the NE system, achieving consistent drug release and penetration in the oral mucosa, and overcoming variability in patient responses. Additionally, the complexity of formulating NEs with biocompatible and safe components for long-term use in sensitive tissues like the oral cavity requires careful consideration. Finally, regulatory hurdles, cost-effectiveness, and large-scale manufacturing processes are important factors that need to be addressed before such NE-based treatments can be widely adopted in clinical practice [42, 63].

Conclusion and future trend

In conclusion, oral mucosal drug delivery presents targeted therapy across a spectrum of conditions, but it also possess numerous challenges. One major challenge of oral mucosal localized drug delivery is the heterogeneous permeability and structure of the oral mucosa, which can affect drug absorption and distribution, posing challenges to achieving consistent therapeutic outcomes. In addition, the mucosal adhesion and retention of the formulation is a factor that reduces drug absorption. The presence of enzymes in the oral cavity also interferes with drug absorption and metabolism. More specifically, the absorption and effectiveness of drugs can be impacted by food, drinks, or other medications in the mouth. To address these challenges, innovative technologies such as NEs and NEGs offer significant potential. By optimizing droplet size, selecting appropriate polymers, enhancing drug loading and encapsulation, utilizing penetration enhancers, and employing targeted delivery strategies, NEGs can overcome bioavailability hurdles, improve drug stability, enhance tissue penetration, and ensure sustained release. These advancements hold promise for revolutionizing oral mucosal drug delivery, offering more effective and patient-friendly treatment options. Looking ahead, oral mucosal drug delivery may continue to focus on refining NEG formulations, exploring novel penetration enhancers, and advancing targeted delivery systems. Additionally, personalized medicine approaches, incorporating patient-specific factors such as genetic profiles or oral microbiota composition, could further optimize treatment outcomes.

For the treatment of oral disorders, NEs and NEGs have demonstrated great potential as cutting-edge delivery methods. To reach their full potential, there are a few upcoming obstacles that must be overcome. The physical and chemical stability issues with NEs i.e., Ostwald ripening, and oxidation of drugs need to be carefully addressed during their formulation and storage. It's difficult to design production methods that are both scalable and economical. For both commercial and clinical uses, production homogeneity and consistency are essential. Furthermore, to comprehend any

possible effects on oral health, research on the interactions among the oral microbiota and NE and NEGs is essential. To address these hurdles, a healthy and sound collaboration between pharmaceutical scientists, clinicians, and biotechnologists will be essential in driving these advancements forward, ultimately translating into improved therapeutic efficacy and patient satisfaction in oral healthcare.

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