## **RECENT ADVANCES IN THERAPEUTIC ORAL MEDICINE**

**Abstract**

Oral mucosal lesions which are treated in Oral Medicine department includes, Recurrent Aphthous Stomatitis, Allergic stomatitis, Lichen Planus, Pemphigus, Pemphigoid, OSMF, Leucoplakia, Erythema Multiforme, Herpes Simplex Viral Infections, Herpes Zoster viral infection. There are various treatment modalities available in this literature. This chapter aims to review only the recent advancement in therapeutic Oral Medicine in the management of oral mucosal lesions which are enlisted below.

* Crocin delivery system through Thiolated chitosan hydrogel-embedded niosomes
* Amlexanox-loaded nanoliposomes in oral mucosal lesions.
* Mmanagement of oral mucosal lesions with montelukast
* Electrospun patch delivery of anti-TNFα F(ab) for the treatment of inflammatory oral mucosal disease
* Topical calcineurin inhibitors (TCI)
* Kinase inhibitors
* Topical 5-fluorouracil be used as a viable treatment option for oral premalignant lesions and tumors.
* Anti-filarial drug diethylcarbamazine in treatment of oral submucous fibrosis
* Molecular targeted therapies
* ICI-based therapies
* Immunotherapy for keratinocyte cancers. Part II: Identification and management of cutaneous side effects of immunotherapy treatments
* Botulinum toxin in the management of head and neck disorders
* [Trends in orally viral vector gene delivery and therapy](https://www.sciencedirect.com/science/article/pii/B9780323477208000067)
* A novel approach to the oral delivery of bionanostructures for systemic disease
* Oral delivery of therapeutic proteins bioencapsulated in plant cells

# Thiolated chitosan hydrogel-embedded niosomes: crocin delivery system toward the management of aphthous stomatitis

# Introduction

[***Crocin***](https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/crocin)

[Crocin](https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/crocin) is a drug with anti-inflammatory properties. It is a natural [carotenoid](https://www.sciencedirect.com/topics/chemistry/carotenoid). The mucoadhesive hydrogels used for crocin drug delivery recently used are Thiolated chitosan (TCS)-based hydrogels containing [niosomes](https://www.sciencedirect.com/topics/chemistry/niosome" \o "Learn more about niosomes from ScienceDirect's AI-generated Topic Pages). These serve as a mucoadhesive crocin delivery system for aphthous stomatitis. Niosomes can carry both lipophilic and hydrophilic active as they are non-ionic surfactant-based vesicular carriers that form a closed bilayer structure in aqueous media. There are numerous advantages of using niosomes such as low toxicity, chemical stability, biocompatibility, biodegradability, and less expensive have made them preferable over other bilayer carriers. Niosomes also offer the ability to act as a local depot, protect drugs from the biological environment, release them in a controlled manner, and improve their skin penetration. The optimum niosomal formulation was loaded into the hydrogel and the hybrid system was characterized regarding the morphology, mucoadhesive properties, viscosity, chemical structure, in vitro drug release, and in vivo efficacy. The optimized niosome formulation showed 77% crocin entrapment, a particle diameter of 59 nm, and a [zeta potential](https://www.sciencedirect.com/topics/chemistry/zeta-potential) of −18 mV. The niosome-containing hydrogel exhibited pseudoplastic rheological behavior, mucoadhesive properties, suitable swelling, and [sustained release](https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/sustained-drug-release) of crocin. In vivo study revealed that the niosome-containing hydrogel improved ulcer healing and decreased the expression of tumor necrosis factor-alpha (TNF-α) and p53 while increasing the expression of vascular endothelial growth factor (VEGF) and alpha-smooth muscle actin (α-SMA). Collectively, TCS hydrogel-embedded crocin-loaded niosomes is a promising therapeutic option for aphthous stomatitis.

***Therapeutic effects of crocin***

Crocin is a carotenoid found in the stigmas of saffron flowers (Crocus sativus) has manifested diverse therapeutic effects such as anti-nociceptive, anti-inflammatory, and anti-oxidant activities. Crocin displays its great anti-oxidant and anti-inflammatory properties by reducing the production of reactive oxygen species and pro-inflammatory cytokines.

***Therapeutic effects of crocin in the management of aphthous ulcer***

Crocin has healing effects in aphthous ulcers. However, the low physicochemical stability, short retention time, and poor bioavailability of crocin can pose drawbacks to its effective topical delivery. Developing a drug delivery system may be beneficial to overcome the obstacles facing the application of crocin and also control the release of this agent. Vesicular systems have attracted significant attention in the field of topical drug delivery.

***Niosomes***

Niosomes are non-ionic surfactant-based vesicular carriers that form a closed bilayer structure in aqueous media and can carry both lipophilic and hydrophilic active.

*Advantages of niosomes*

* The numerous advantages of niosomes are biocompatibility, biodegradability, low toxicity, chemical stability, and being inexpensive have made them preferable over other bilayer carriers.
* Niosomes also offer the ability to act as a local depot, protect drugs from the biological environment, release them in a controlled manner, and improve their skin penetration.

*Disadvantages of niosomes*

* Insufficient retention time associated with the low viscosity of niosomal dispersions can hinder their topical use Incorporating niosomes into other carriers such as films (Arafa et al., 2018), hydrogels (Sohrabi, Haeri, Mahboubi, Mortazavi, & Dadashzadeh, 2016), and emulgels (Elsewedy et al., 2021) is a plausible strategy to improve their topical applicability and combine the advantages associated with different delivery systems.

***Hydrogels***

Hydrogels are polymeric networks with a three-dimensional structure and distinctive features such as biocompatibility, viscoelastic properties, physical similarity to soft tissues, and ability to protect their content from the harsh environment. Hydrogels based on synthetic polymers and modified biopolymers occupy a paramount status in the biomedical field

***Chitosan (CS)***

Chitosan (CS) is a biopolymer that has displayed a wide range of biological activities such as anti-oxidant, anti-inflammatory, and anti-microbial properties. Having all these benefits, this polymer has recently attracted researchers' interest in designing drug delivery systems.

Inspired by the anti-inflammatory effects of crocin as well as the controlled release and mucoadhesive properties of niosome-loaded TCS hydrogels, it is hypothesized that TCS hydrogels containing crocin-loaded niosomes can serve as an efficient topical drug delivery system for aphthous stomatitis.1

# Amlexanox-loaded nanoliposomes showing enhanced anti-inflammatory activity in cultured macrophages: A potential formulation for treatment of oral aphthous stomatitis

Nanoliposomes were prepared using Soya [phosphatidylcholine](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/egg-lecithin) (SPC) and Cholesterol (Chol) mixtures at three different molar ratios to formulate vesicles using thin-film hydration, and were characterised for size, [zeta potential](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/zeta-potential) and entrapment efficiency. The optimal formulation was found to be SPC:Chol 3:1 with drug entrapment efficiency of 94%, post sonication. It is established that the potential of using AMX nanoliposomes as a promising advanced formulation for reviving AMX treatment for management of inflammatory conditions of oral mucosa.

[Amlexanox](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/amlexanox) (AMX) is a small molecule of molecular weight 298.29 g/mol, poorly water soluble (146 μg/mL) lipophilic drug which is a well-established anti-inflammatory [immunomodulator](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/immunomodulating-agent) used to treat RAS, asthma and [allergic rhinitis](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/allergic-rhinitis). Topical application of AMX has been clinically verified to shorten the time for minor ulcers to heal.

AMX is an immunomodulatory agent that works via different mechanisms of action.

* It inhibits arachidonate 5-lipoxygenase enzyme preventing histamine and leukotriene release.
* AMX inhibits the release of S100A13 protein by blocking the [heat shock protein Hsp90](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/heat-shock-protein-90). S100A13 is an [acidic fibroblast growth factor](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/fibroblast-growth-factor-1) 1 (FGF1) implicated in a broad range of vital biological processes such as angiogenesis, cell differentiation, neurogenesis, and tumour progress. In essence, FGF1 binds to cell surface [tyrosine kinase](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/protein-tyrosine-kinase) FGFRs receptors triggering cell signal transduction cascade.
* AMX also inhibits the FGF1 release stimulating actin cytoskeleton. Thus, AMX has the ability to antagonize the angiogenic and mutagenic activity of FGF1.
* The most recently reported AMX mode of action is manifested by the ability of blocking the non-canonical IKK-ε and Tank Binding Kinase (IKB & TBK1). This mechanism is thought to be implicated in reduction of inflammation, reversible weight loss and improvement in insulin sensitivity.
* The topical application of AMX is clinically very efficient in controlling RAS as it has been proven to reduce the number, size, erythema and pain associated with ulcers, as well as the significant reduction in ulceration recurrence frequency.

AMX was thus approved in 2004 by FDA as an anti-inflammatory treatment for oral aphthous stomatitis ulcers, in the form of a mucoadhesive paste under the name Aphthasol.  [Clinical trials](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/clinical-trial) revealed that patients topically treated with AMX 5% paste showed significant reduction in ulcer size, healing time and duration of pain compared to [placebo](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/placebo). When applied during the prodromal stage, AMX dramatically reduced the number of patients who progressed to full ulcers.

Adverse effects of amlenox:

Transient pain, stinging, and burning, contact [mucositis](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/mucosa-inflammation), nausea, and diarrhoea.

[**Liposomal drug delivery**](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/liposomal-drug-delivery)

[Liposomal drug delivery](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/liposomal-drug-delivery) has become an established strategy for the development of such advanced delivery systems with great potential for clinical translation.

The enhancement of drug cellular uptake is through different postulated mechanisms, such as adsorption and fusion with [phospholipid](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/phospholipid) cell membranes and endocytosis

**Advantages of liposomal drug delivery**

* Liposomes can protect entrapped drug molecules from [metabolic enzymes](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/digestant) and may function as a drug reservoir for controlled release and selective targeting capacity, [biocompatibility](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/biocompatibility) and biodegradability of these lipid-based [nanocarriers](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/nanocarrier).
* Moreover, liposomal carriers have also shown to exhibit site-specific drug localisation in ulcerated areas and instinctively target mononuclear phagocytic system, particularly macrophages, where they are naturally phagocytosed, thereby enhancing the therapeutic efficacy of anti-inflammatory drugs.

AMX into liposomes formulated using naturally occurring cell membrane components (phospholipids and cholesterol), could serve as a local delivery system enhancing the selective cellular uptake at the ulcerated areas of oral mucosa, augment AMX anti-inflammatory activity and minimise its adverse effects. For these reason **Abouzids A et al,**2 developed AMX-loaded liposomal formulations using various soya [phosphatidylcholine](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/egg-lecithin) (SPC) to cholesterol (Chol) molar ratios, which were characterised for particle size and distribution, [zeta potential](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/zeta-potential) and AMX entrapment efficiency. The anti-inflammatory effects were examined in pro-inflammatory macrophages M1 phenotype, which was developed by differentiation of Human [leukaemia Monocytic](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/monocytic-leukemia) cell line THP-1 into resting state macrophage M0, which was then polarised by [interferon gamma](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/gamma-interferon) (IFNγ) and [lipopolysaccharide](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/lipopolysaccharide) (LPS) into the M1 phenotype. Expression levels of the pro-inflammatory cytokine TNF-α in M1 phenotype treated with AMX, unloaded liposomes and AMX-loaded liposomes were evaluated in comparison to [aspirin](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/acetylsalicylic-acid) positive control.

In this study, done by **Abouzids A et al,**2 demonstrated the potential of using AMX-loaded nanoliposomes for the efficient targeting of macrophages and modulating their inflammatory responses. Macrophages showed dose-responsive reduction in TNFα expression with increasing AMX-liposome concentration. The combination of AMX and SPC:Chol nanoliposomes (D-L1 formulation) exhibited significantly stronger anti-inflammatory effect than that of either AMX alone or empty liposomes (E-Lipo), suggesting that the used lipids augment the anti-inflammatory activity of AMX. This was confirmed by the remarkable reduction in TNFα expression in cells treated with E-Lipo. Based on previously reported studies, it can be anticipated that the SPC component of liposomal formulations has suppressed the LPS-induced NF-κB activation leading to observed significant downregulation of TNFɑ, thus augmenting the AMX mediated TNFɑ inhibition [[42](https://www.sciencedirect.com/science/article/pii/S1773224722009637#bib42),[43](https://www.sciencedirect.com/science/article/pii/S1773224722009637#bib43),[45](https://www.sciencedirect.com/science/article/pii/S1773224722009637#bib45)]. In addition, considerable cellular uptake of FITC-loaded nanoliposomes was achieved within 2 h of treatment, implying possibility of further enhancement of AMX anti-inflammatory activity through better drug localisation in target cells. Further mechanistic studies on the interaction of E-Lipo and AMX-loaded nanoliposomes with LPS-induced macrophages and the consequent intracellular signalling cascade are required to gain a deeper insight of the anti-inflammatory activity of this system. In addition, developing AMX-loaded nanoliposome formulation in mucoadhesive vehicles will be considered in future for the localised administration in buccal cavity, though in vivo validation studies using an appropriate animal model.2

# Treatment of aphthous ulcers with montelukast

Aphthous ulcers are the most prevalent oral mucosal lesions, yet treatment is challenging. There is evidence that oral montelukast is efficacious in treating aphthous ulcers. A randomized placebo-controlled trial comparing montelukast against prednisone for recurrent aphthous stomatitis demonstrated montelukast has superior efficacy compared with placebo, decreased efficacy compared with prednisone, but decreased adverse effects compared to prednisone

Dosage of montelukast was 9 mg daily, with a range of 4-10 mg. 4-5 mg was prescribed to pediatric patients;10 mg for all others aged 15 and older. While 10% of patients in the aforementioned RCT reported side effect of diarrhoea from montelukast. In the study conducted by **Aquminoa TM et al3,** further strengthens support for montelukast as a safe and effective treatment option for recalcitrant aphthous ulcers with reduction in both number and frequency of ulcers. Montelukast has minimal adverse effects, even with long treatment duration, compared with other systemic medications used for management. Further studies to determine the recurrence rate after cessation of montelukast are warranted.3

# Electrospun patch delivery of anti-TNFα F(ab) for the treatment of inflammatory oral mucosal disease

# Electrospinning involves applying a high voltage electric field to anextruded polymer solution, resulting in the production of a micron-scale,non-woven mesh of polymeric fibres (PDF) Electrospun patch delivery of anti-TNFα F(ab) for the treatment of inflammatory oral mucosal disease.

# *Electrospinning system and fabrication of mucoadhesive dual-layer patches*

# Electrospun membranes as described by Edmans J et al, were fabricated using a system comprising a PHD2000 syringe pump and an Alpha IV Brandenburg power source Electro-spinning is performed at room temperature with a potential difference of 19 kV, a flow rate of 2 mL/h, and a flight path of 14 cm. Mucoadhesive protein-containing membranes were electrospun from solutions containing PVP (10% w/w) and EudragitRS100 (12.5% w/w) in 97% v/v ethanol. The required amounts of PVP and RS100 added to ethanol and mixed at room temperature using a magnetic stirrer until dissolved. F(ab) solutions added, contributing to 3% v/v to the final so ated (NM) patches were prepared by substituting the F(ab) solution with 3% v/v PBS. Electrospinning was started within 1 minute of addition. Polycaprolactone (PCL; 10% w/v) was added to a blend of DCM and DMF (90:10 v/v) and stirred at room temperature until d

# issolved. Hydrophobic backing layers were introduced by subsequent electrospinning of PCL solutions on top of themucoadhesive layer. The resulting materials were placed in a dry oven at70 ◦C for 15 minute to melt the PCL layer into a continuous film. Experimental samples were taken from the central region of the dual-layer patches and the thickness measured 6 times at 1 cm intervals using a digital micrometer

# Chronic ulcerative oral mucosal [inflammatory diseases](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/inflammatory-disease), including [oral lichen planus](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/lichen-planus) and [recurrent aphthous stomatitis](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/aphthous-stomatitis), are painful and highly prevalent, yet lack effective clinical management. In recent years, systemic biologic therapies, including [monoclonal antibodies](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/monoclonal-antibody) that block the activity of cytokines, have been increasingly used to treat a range of immune-mediated inflammatory conditions such as [rheumatoid arthritis](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/rheumatoid-arthritis) and [psoriasis](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/psoriasis). The ability to deliver similar therapeutic agents locally to the oral epithelium could radically alter treatment options for oral mucosal inflammatory diseases, where pro-inflammatory cytokines, in particular tumour-necrosis factor-α (TNFα), are major drivers of pathogenesis.

To address this, an electrospun dual-layer mucoadhesive patch comprising medical-grade polymers was investigated for the delivery of F(ab) biologics to the oral mucosa. A fluorescent-labelled F(ab) was incorporated into mucoadhesive membranes using electrospinning with 97% v/v ethanol as a solvent.

The F(ab) was detected within the fibres in aggregates when visualised by [confocal microscopy](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/confocal-microscopy). Biotinylated F(ab) was rapidly eluted from the patch (97 ± 5% released within 3 h) without loss of antigen-binding activity. Patches applied to oral epithelium models successfully delivered the F(ab), with fluorescent F(ab) observed within the tissue and 5.1 ± 1.5% cumulative transepithelial permeation reached after 9 h. Neutralising anti-TNFα F(ab) fragments were generated from whole IgG by [papain](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/papain) cleavage, as confirmed by SDS-PAGE, then incorporated into patches. F(ab)-containing patches had TNFα neutralising activity, as shown by the suppression of TNFα-mediated CXCL8 release from oral keratinocytes cultured as monolayers. Patches were applied to lipopolysaccharide-stimulated immune-competent oral mucosal ulcer equivalents that contained primary macrophages. Anti-TNFα patch treatment led to reduced levels of active TNFα along with a reduction in the levels of disease-implicated T-cell chemokines (CCL3, CCL5, and CXCL10) to baseline concentrations. This is the first report of an effective device for the delivery of antibody-based biologics to the oral mucosa, enabling the future development of new therapeutic strategies to treat painful conditions.4

# Advancement in therapeutic strategies for immune-mediated oral diseases

## **Topical calcineurin inhibitors (TCI)**

Calcineurin Inhibitors such as cyclosporine and tacrolimus are used to suppress the immune system in various conditions, including post-organ transplantation. Calcineurin inhibitors inhibit calcineurin, suppressing the synthesis of pro-inflammatory cytokines and inhibiting the formation of activated T cells. Systemic use of these drugs is indicated for severe conditions including Crohn's disease, refractory psoriasis, severe atopic dermatitis, Steven-Johnson syndrome, and refractory

## **Kinase inhibitors**

Protein kinases, also known as phosphotransferases, catalyzes phosphorylation reactions. In the immune system, phosphorylation is one of the first steps where tyrosine kinase enables phosphorylation of immune recognition receptors such as TCR, BCR, Fc receptors. While several kinase inhibitors are currently employed in cancer therapy, their use in anti-inflammatory and immune-mediated diseases are quite new. Janus kinase (JAK) belongs to the family of non-receptor tyrosine kinases and

## **Conclusion**

Immune-mediated diseases including lichen planus, pemphigus, and pemphigoid affect a significant percentage of the global population and are associated with significant patient morbidity. Conventional treatment strategies with corticosteroids and cytotoxic agents such as cyclosporine, azathioprine, and thalidomide carry significant side effects with chronic use. This makes the development of alternative strategies crucial.5

Recent advances in management of premalignant lesions

# Topical 5-fluorouracil be used as a viable treatment option for oral premalignant lesions and tumors?

5-Fluorouracil (5-FU), is a drug used in the treatment of cancers. It is results in cytotoxic effects. It acts by inhibiting [thymidine](https://www.sciencedirect.com/topics/medicine-and-dentistry/thymidine) synthase, causing depletion of nucleotides which are necessary for [DNA synthesis](https://www.sciencedirect.com/topics/medicine-and-dentistry/dna-synthesis) and repair. The enzyme which is contributing in the pathway is [dihydropyrimidine dehydrogenase](https://www.sciencedirect.com/topics/medicine-and-dentistry/dihydropyrimidine-dehydrogenase" \o "Learn more about dihydropyrimidine dehydrogenase from ScienceDirect's AI-generated Topic Pages) (DPD).

***Adverse effects***

Adverse effects are, [stomatitis](https://www.sciencedirect.com/topics/medicine-and-dentistry/stomatitis), diarrhoea palmar-plantar erythema, [bone marrow suppression](https://www.sciencedirect.com/topics/medicine-and-dentistry/bone-marrow-suppression), [hyperpigmentation](https://www.sciencedirect.com/topics/medicine-and-dentistry/hyperpigmentation), nausea. In topical consideration, [photosensitivity](https://www.sciencedirect.com/topics/medicine-and-dentistry/photosensitivity), erythema, [ulceration](https://www.sciencedirect.com/topics/medicine-and-dentistry/venous-ulcer), and rarely hyperpigmentation are the common side effects. Disadvantages like severe side effects due to topical use of 5-FU have been reported too. Still in high-grade vaginal [dysplasia](https://www.sciencedirect.com/topics/medicine-and-dentistry/dysplasia), use of 5-fluorouracil (FU) has been proved to reduce the recurrence rate, whereas topical 5-FU is universally accepted for the treatment of [dermatological conditions](https://www.sciencedirect.com/topics/medicine-and-dentistry/dermatological-disease) like [actinic keratosis](https://www.sciencedirect.com/topics/medicine-and-dentistry/actinic-keratosis), [melanoma](https://www.sciencedirect.com/topics/medicine-and-dentistry/nodular-melanoma), squamous cell carcinoma, and basal cell carcinoma. Weinstock et al, recently concluded in their trial that fluorouracil cream does reduce surgery chances for squamous cell carcinoma for 1 year. Even for [keratoacanthomas](https://www.sciencedirect.com/topics/medicine-and-dentistry/keratoacanthoma), short-contact topical 5% 5-FU has provided excellent cosmetic results and well-tolerated by the [patients](https://www.sciencedirect.com/topics/medicine-and-dentistry/patient).

It’s a recognized information that 5-FU has 90% success rate in treating potentially malignant lesions of skin. In context to [oral lesions](https://www.sciencedirect.com/topics/medicine-and-dentistry/mouth-lesion), literature search revealed a report as late in 1989, suggested the use of topical 5-FU and [carbon dioxide laser](https://www.sciencedirect.com/topics/medicine-and-dentistry/carbon-dioxide-laser) for management of [oral squamous cell carcinoma](https://www.sciencedirect.com/topics/medicine-and-dentistry/mouth-squamous-cell-carcinoma) in situ revealing good result. Later in 2014, 5-FU in [orabase](https://www.sciencedirect.com/topics/medicine-and-dentistry/orabase" \o "Learn more about orabase from ScienceDirect's AI-generated Topic Pages) form too presented as a resource in treating potentially malignant oral lesions.

In context to oral tumors, Ledderhof et al, stated that “keratocystic odontogenic tumor” (KCOT) treated with [enucleation](https://www.sciencedirect.com/topics/medicine-and-dentistry/enucleation), peripheral [ostectomy](https://www.sciencedirect.com/topics/medicine-and-dentistry/ostectomy) and 5-FU presented with lower recurrence rates and less morbidity compared to Carnoy’s solution. Though KCOT’s were earlier categorised as odontogenic keratocyst (OKC), in 2017 it was again reverted to the WHO classification of odontogenic developmental cysts, reconstituting with the original terminology “OKC”. Singh et al., in 2016 too had concluded that aggressive [treatment](https://www.sciencedirect.com/topics/medicine-and-dentistry/therapeutic-procedure) should be reserved for selective cases, in contrary to other authors, who

] believe that all OKCs behave as a tumor and should be treated aggressively making the recent reclassification a requisite. Pinheiro et al., treated a case of OKC with [marsupialization](https://www.sciencedirect.com/topics/medicine-and-dentistry/marsupialization) and 5-FU intralesional and observed exuberant bone neoformation, mainly in the basilar region of the [mandible](https://www.sciencedirect.com/topics/medicine-and-dentistry/lower-jaw).

On searching various databases for research details ministering the use of 5-FU in preventing transformation in premalignant lesion, we came crossways with just two reports in the journal OOOO, in almost three decades. Among the challenges to overcome the [malignant transformation](https://www.sciencedirect.com/topics/medicine-and-dentistry/malignant-transformation) blockades of premalignant lesions and the possibility of chemopreventive approaches for the treatment of premalignant lesions so as to prevent secondary pre-malignant lesions and their progression to cancer is to be considered on priority basis. Therefore, we the authors sturdily voice for more studies and research to be taken up for understanding the role of 5-FU in oral premalignancy and tumors to lower the rate of malignant transformation and recurrence.

# Anti-filarial drug diethylcarbamazine in treatment of oral submucous fibrosis

## **Abstract**

[Oral submucous fibrosis](https://www.sciencedirect.com/topics/medicine-and-dentistry/oral-submucous-fibrosis) (OSMF) has impacted over 5 million people worldwide and has had a significant role in mortality and morbidity due to its high [malignant transformation](https://www.sciencedirect.com/topics/medicine-and-dentistry/malignant-transformation) rate. Because of the high prevalence of OSMF, there has been a rush to repurpose current medications. In the present paper, we discussed the use of [diethylcarbamazine](https://www.sciencedirect.com/topics/medicine-and-dentistry/diethylcarbamazine) (DEC), an anti-filarial medication with anti-inflammatory and immunomodulatory properties, in the [treatment](https://www.sciencedirect.com/topics/medicine-and-dentistry/therapeutic-procedure) of OSMF. DEC's anti-fibrotic properties make it a viable [treatment](https://www.sciencedirect.com/topics/medicine-and-dentistry/therapeutic-procedure) option for OSMF which not only reduces [fibrosis](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/fibrosis) but also decreases the malignant potential. The potential mechanism of action is discussed in detail.6

Molecular targeted therapies

Transforming growth factor β (TGFβ) is upregulated in OSMF and plays an explicit role in OSMF pathogenesis by modulating the production and degradation of products of extracellular matrix (ECM).

Imatinib

Imatinib has anti-fibrotic action by interfering with TGFβ signalling pathways. It has obtained successful results as an antifibrotic drug in preclinical models for treatment of scleroderma. Therefore, it can play an efficacious role in OSMF treatment.

# ICI-based therapies: A new strategy for oral potentially malignant disorders

Oral potentially malignant disorders (OPMDs) are linked with an escalated risk of developing cancers, particularly oral squamous cell carcinoma (OSCC). Since prevailing therapies cannot effectively forestall the exacerbation and recurrence of OPMDs, halting their malignant progression is paramount. The immune checkpoint serves as a cardinal regulator of the immune response and the primary cause of adaptive immunological resistance. Although the exact mechanism remains elusive, elevated expression of multiple immune checkpoints in OPMDs and [OSCC](https://www.sciencedirect.com/topics/medicine-and-dentistry/mouth-squamous-cell-carcinoma) relative to healthy oral mucosa has been ascertained. This review delves into the [immunosuppressive](https://www.sciencedirect.com/topics/medicine-and-dentistry/immunosuppressive-drug) microenvironment of OPMDs, the expression of diverse immune checkpoints such as programmed death receptor-1 (PD-1) and programmed death receptor-1 ligand (PD-L1) in OPMDs, and the potential application of corresponding inhibitors. In addition, synergistic strategies incorporating combined immune checkpoint inhibitors, such as cGAS-STING, costimulatory molecules, cancer vaccines, and hydrogels, are discussed to gain a more comprehensive understanding of the role and application of immune checkpoint inhibitors (ICIs) in oral carcinogenesis.7

<https://www.sciencedirect.com/science/article/abs/pii/S1368837523000830>

# Fabrication of astaxanthin-loaded electrospun nanofiber-based mucoadhesive patches with water‐insoluble backing for the treatment of oral premalignant lesions

Oral premalignant lesions (OPL) are one of the most common oral diseases, affecting the quality of life and even leading to oral cancer. Current treatments commonly use steroids/retinoids in mouthwashes, films, or ointments. However, conventional drugs/formulations have significant side effects/limitations. Herein, astaxanthin-loaded polycaprolactone (PCL)/gelatin (GT) nanofiber-based mucoadhesive patches (PGA) with the water‐insoluble PCL nanofiber backing (PCL/PGA) are developed via electrospinning for the management of OPL. The saliva-insoluble PCL backing could greatly prevent drug loss after application in the oral cavity. The prepared PCL/PGA patches exhibit a suitable astaxanthin release rate for achieving high local drug concentration, which permeated into buccal mucosa. In addition, the developed thin patches display excellent wet tissue adhesion and great air permeability due to their high porosity. Notably, the in vivo experiment shows that the bioactive mucoadhesive patches significantly promote the recovery of OPL by suppressing the expression of Ki67 and cyclooxygenase-2 (COX-2), comparable to clinical tretinoin cream formulation. Also, the patches did not induce any side effects (i.e., hair loss and oral ulcers) compared to clinical tretinoin cream formulation. The results demonstrate that this novel electrospun mucoadhesive bilayer patch holds great potential for the treatment of OPL.8

**Immunotherapy for keratinocyte cancers. Part II: Identification and management of cutaneous side effects of immunotherapy treatments**

Keratinocytic cancers (KCs), specifically cutaneous [squamous cell](https://www.sciencedirect.com/topics/medicine-and-dentistry/squamous-cell) and [basal cell carcinomas](https://www.sciencedirect.com/topics/medicine-and-dentistry/basal-cell-carcinoma), can respond to topical, intralesional, or systemic [immunotherapies](https://www.sciencedirect.com/topics/medicine-and-dentistry/immunotherapy), but cutaneous adverse events (CAEs) may occur. Understanding these risks, early recognition of these CAEs, and effective [treatment](https://www.sciencedirect.com/topics/medicine-and-dentistry/therapeutic-procedure) may enable [patients](https://www.sciencedirect.com/topics/medicine-and-dentistry/patient) to continue their anticancer [immunotherapies](https://www.sciencedirect.com/topics/medicine-and-dentistry/immunotherapy) without dose impact. Immune checkpoint inhibitor-related CAEs after KCs can have multiple clinical presentations, with specific observed types including [psoriasis](https://www.sciencedirect.com/topics/medicine-and-dentistry/psoriasis) and [bullous pemphigoid](https://www.sciencedirect.com/topics/medicine-and-dentistry/bullous-pemphigoid). [Cutaneous toxicities](https://www.sciencedirect.com/topics/medicine-and-dentistry/skin-toxicity) can require biopsies to confirm the diagnosis, especially [in patients](https://www.sciencedirect.com/topics/medicine-and-dentistry/inpatient) who are not responsive to topical or oral steroids, since the selection of biologic [drugs](https://www.sciencedirect.com/topics/medicine-and-dentistry/chemotherapeutic-agent) depends on accurate diagnosis. Different types of CAEs from immune checkpoint inhibitors have been associated with different oncologic outcomes in various primary [cancer types](https://www.sciencedirect.com/topics/medicine-and-dentistry/cancer-types), and this remains to be determined for KC [patients](https://www.sciencedirect.com/topics/medicine-and-dentistry/patient). CAE characterization and management after immune checkpoint inhibitors in KC patients is a rapidly growing field that needs specific and prospective studies.9

[**LOW-LEVEL LASER THERAPY FOR SEVERE ORAL PEMPHIGUS VULGARIS MANAGEMENT**](https://www.sciencedirect.com/science/article/pii/S2212440323003905)

LLLT has been introduced as a new treatment option for patients with PV lesions unresponsive to conventional therapy. It is also claimed that LLLT can lead to increased mitochondrial activity with a consequent increase in adenosine triphosphate (ATP), vasodilation, protein synthesis, decrease in prostaglandin levels, presence of cellular mitosis, migration and proliferation of keratinocytes and neoangiogenesis.[10](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5642165/#R10)-[13](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5642165/#R13) Biometrical and histological analyses indicated faster lesion contraction showing quicker reepithelization and reformed connective tissue with more organized collagen fibers in irradiated wounds.[14](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5642165/#R14) Laser therapy reduces inflammatory reaction and provokes a greater proliferation of myofibroblasts in experimental cutaneous wounds.[15](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5642165/#R15),[16](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5642165/#R16) LLLT is a nondestructive, non-thermal and painless procedure with no thermal damage effects. LLLT has biostimulatory effects on surrounding tissues and cells, and an increase in systemic microcirculation and tissue oxygenation, cell metabolism and tissue regeneration and potential tissue healing. 10

# Botulinum toxin in the management of head and neck disorders

[Botulinum toxin](https://www.sciencedirect.com/topics/medicine-and-dentistry/botulinum-toxin) is a [polypeptide](https://www.sciencedirect.com/topics/medicine-and-dentistry/polypeptide) [protoxin](https://www.sciencedirect.com/topics/medicine-and-dentistry/protoxin) synthesized by [Clostridium botulinum](https://www.sciencedirect.com/topics/medicine-and-dentistry/clostridium-botulinum) that results in localized reduction of muscle activity by inhibiting [acetylcholine release](https://www.sciencedirect.com/topics/medicine-and-dentistry/acetylcholine-release) at the [neuromuscular junction](https://www.sciencedirect.com/topics/medicine-and-dentistry/neuromuscular-junction). In 2004, the US Food and Drug Administration approved its application in the [treatment](https://www.sciencedirect.com/topics/medicine-and-dentistry/therapeutic-procedure) of various medical conditions, such as facial [wrinkles](https://www.sciencedirect.com/topics/medicine-and-dentistry/wrinkle), strabismus, [cervical dystonia](https://www.sciencedirect.com/topics/medicine-and-dentistry/spasmodic-torticollis), [blepharospasm](https://www.sciencedirect.com/topics/medicine-and-dentistry/blepharospasm), and [hyperhidrosis](https://www.sciencedirect.com/topics/medicine-and-dentistry/hyperhidrosis). Later, its application extended to improving [dental esthetics](https://www.sciencedirect.com/topics/medicine-and-dentistry/dental-procedure) and gummy smile. It was found to be a safe and effective alternative to medical therapy to treat various head and neck disorders that have a neurologic component. In this review, we will highlight the mechanism of action and therapeutic benefits of botulinum toxin in the management of head and neck disorders.

## **Biochemistry of BTX**

Botulinum toxin is isolated from an anaerobic spore-forming bacterium, Clostridium botulinum. Chemically, it is a 2-chain metalloprotease composed of heavy and light chains with 8 immunologically distinct serotypes (A, B, C1, C2, D, F, G). All but one (C2) are neurotoxins. Serotype A (BTX type A or onabotulinum toxin A, Botox [Allergan, Parsiippany, NJ]) has been the most widely used for a variety of movement and spasticity disorders as well as in cosmetic procedures.

## **Neuromuscular blockade**

BTX has a neuromuscular blocking effect that results from inhibiting the exocytosis of acetylcholine from presynaptic nerve terminals.7 BTX is internalized into the cytosol from the neuromuscular junction by binding to different gangliosides, namely synaptic vesicle –2, synaptotagmin I, or synaptotagmin II. Heavy chains of BTX facilitate uptake of the whole molecule into the cytosol, where light chains cleave soluble N-ethylmaleimide–sensitive factor attachment protein receptor (SNARE)

## **Preparation**

Botulinum toxin is prepared by laboratory fermentation of C botulinum, which lyses and liberates the toxin into the culture. The toxin is then harvested, purified, crystallized with ammonium sulfate, diluted with human serum albumin, lyophilized, bottled in vials, and sealed. Each vial of BTX contains 100 U of C botulinum type A neurotoxin complex. It retains its potency for 9 months at room temperature (25° C) and for 3 years at refrigerated temperatures (2-8° C).11, 12

## **Therapeutic Uses in Head and Neck Disorders**

Botulinum neurotoxins have been used for years to treat a wide variety of medical and dental diseases. They were used initially in improvement of facial esthetics but have since gained popularity in pain management and treatment of disorders with accelerated muscle contraction. Table I summarizes the therapeutic uses of botulinum toxin.

## **Conclusion**

Various conservative therapies, medicines, and minor and major surgical procedures have been used in the past to treat facial pain, secretory disorders, and head and neck movement disorders. Few patients failed to respond to these treatment modalities, with variable responses. BTX has progressed from being used in cosmetic procedures only to a spectrum of clinical applications, as discussed above. It is a superior treatment option over pharmacotherapy or surgery for head and neck disorders.11

## [**Trends in orally viral vector gene delivery and therapy**](https://www.sciencedirect.com/science/article/pii/B9780323477208000067)

By the statistics, the account of oral medicine makes up about half of the total each year. Oral medicine is one of the main methods for disease prevention and treatment because of its noninvasive nature. It is popular in health care due to its convenience, efficiency, comfort, and safety. Viruses have evolved to efficiently express their genes in host cells, which makes them ideally suited as gene delivery vectors for gene and immunotherapies. Replication competent (RC) viral vectors encoding foreign or self-proteins induce strong T-cell responses that can be used for the development of effective cancer treatments. Replication-defective (RD) viral vectors encoding self-proteins are non-immunogenic when introduced in a host naïve for the cognate virus. RD viral vectors can be used to develop gene replacement therapies for genetic disorders and tolerization therapies for autoimmune diseases and allergies. Degenerative/inflammatory diseases are associated with chronic inflammation and immune responses that damage the tissues involved. These diseases therefore strongly resemble autoimmune diseases. This review deals with the use of RC and RD viral vectors for unraveling the pathogenesis of immune-related diseases and their application to the development of the next generation prophylactics and therapeutics for todays' major diseases.12

**A novel approach to the oral delivery of bionanostructures for systemic disease**

[Nanostructures](https://www.sciencedirect.com/topics/materials-science/nanocrystalline-material) for oral medicine can efficiently encapsulate drugs at high concentrations cross the [cell membrane](https://www.sciencedirect.com/topics/materials-science/cell-membrane) and release the drugs at the target site in a controlled manner for a prescribed period of time. Nanostructures are used as sustained delivery carriers in chronic therapies to reduce the frequency dose/dosing, minimizing side effects and increasing patient compliance. The focus of this chapter is to provide an overview of the role of nanostructures for oral medicine like synthesis, characterization, drug delivery mechanisms, and in vitro and in vivo techniques of the biodistribution and bioimaging of [nanoparticle](https://www.sciencedirect.com/topics/materials-science/nanoparticle). However, stability, bioavailability, and solubility in the gastrointestinal tract create a challenge in the preparation of these nanostructures. This chapter sheds light on oral delivery nanostructures researched in medicine, including synthesis techniques and materials that can be effectively used for controlled oral drug delivery applications used in diseases treatments.13

**Oral delivery of therapeutic proteins bioencapsulated in plant cells: Preclinical and clinical advances Im**

Abstract Oral delivery of protein drugs (PDs) made in plant cells could revolutionize current approaches to their production and delivery. Expression of PDs reduces their production cost by elimination of prohibitively expensive fermentation, purification, cold transportation/storage, and sterile injections and increases their shelf life for several years. The ability of plant cell wall to protect PDs from digestive acids/enzymes, commensal bacteria to release PDs in gut lumen after lysis of plant cell wall, and the role of gut-associated lymphoid tissue in inducing tolerance facilitate prevention or treatment of allergic, autoimmune diseases or antidrug antibody responses. The delivery of functional proteins facilitates treatment of inherited or metabolic disorders. Recent advances in making PDs free of antibiotic resistance genes in edible plant cells, long-term storage at ambient temperature maintaining their efficacy, production in Current Good Manufacturing Practice (cGMP) facilities, Investigational New Drug (IND)-enabling studies for clinical advancement, and Food and Drug Administration approval of orally delivered PDs augur well for advancing this novel drug delivery platform technology.14

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