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Microneedles as an effective and minimally invasive delivery strategy for oral cancer treatment

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Oral cancer ranks among the top sixteen most prevalent cancers worldwide, with its onset strongly associated with risk factors such as viral infections, tobacco use, alcohol consumption, and prolonged exposure to physical and chemical stimuli. Conventional therapeutic modalities, like surgery, chemotherapy, and radiotherapy, often cause severe side effects and systemic toxicity, significantly compromising patients' quality of life. Microneedle technology has recently emerged as a promising minimally invasive platform for transdermal and transmucosal drug delivery. Microneedles facilitate the localized and controlled administration of therapeutic agents by creating microscopic pores that enhance mucosal drug permeation and retention. The versatility of microneedle systems *via* customizable design, material selection, and drug-release kinetics enables their adaptation for personalized and multimodal oral cancer management. This review discusses the emerging applications of microneedle-based platforms in oral cancer therapy and diagnosis, highlighting current progress, challenges, and future perspectives toward clinical translation.

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1. Introduction

Lip and oral cavity carcinoma is ranked as the 16th most common cancer worldwide. According to the World Health Organization GLOBOCAN 2022 data, more than 389 846 new cases of oral cancer were detected globally, and 188 438 people

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lost their lives from oral cancer in 2022.[1] Countries such as India, China, the United States, Bangladesh and other Southeast Asian countries have the highest incidences in the world.[2]

The risk factors for oral cancer can be categorized into epigenetic factors, genetic predisposition, immunosuppression from underlying conditions, and various environmental factors.[3] Epigenetic factors, such as smoking, alcoholism, and diet, are responsible for the lack of maintenance of the oral microbiome. Approximately 45% of case reports cite factors like smoking, alcoholism, and poor oral hygiene as the primary cause of oral cancer.[4] Several cases of viral infections (Human Papillomavirus-16 and Epstein–Barr virus),[5] along with lifestyle factors, such as the change in diet and everyday routines, may also contribute to its incidence. Moreover, emerging evidence suggests that the human oral cavity hosts a complex microbiome comprising over 500–700 bacterial species.[6] This heterogeneous microbe population engages in dynamic interactions with host tissues, impacting immunological response, inflammation, and cellular signaling pathways that may facilitate the development of cancer. Therefore, oral cancer significantly affects essential physiological functions such as speech, swallowing, and chewing, and induces pain due to the development of tumor lesions.

The probability of developing oral malignancies and the aggressiveness of oral squamous cell carcinoma (OSCC) is highly variable and incalculable, thus making early detection challenging.[7] Due to the complex nature of the disease and its multifactorial etiology, developing effective treatment strategies remains a major clinical concern. Conventional treatment methods for oral cancer include chemotherapeutic and immunotherapeutic agents like cisplatin, cetuximab, nivolumab, camrelizumab. The global impact of chemotherapeutic agents, used in combination with radiotherapy, photodynamic therapy (PDT),[8] surgery, and antibodies for oral and related cancers have gained a greater share of the market, although the efficacy of these methods varies on a case-by-case basis. Delivery of drugs through oral administration faced challenges like first-pass metabolism and low bioavailability; moreover, injections significantly increased costs and reduced patient compliance. Surgeries for oral cancers, such as partial glossectomy, *i.e.*, a surgical procedure to remove a tumor from the tongue, significantly impact the quality of life for tongue cancer patients.[9] It was reported in 2019 that only 19% of oral cancer patients survive a total glossectomy, and about 30.5% of the survivors were cancer-specific.[10] Other therapies, such as radiation therapy and combination therapy, have been shown to cause major complications, salivary gland dysfunction, toxicity, and drug resistance.[11,12]

Furthermore, non-systemic administration such as topical drug delivery for oral cancer faces significant challenges, including enzymatic degradation, rapid salivary washout, and short drug residence time, which lead to low bioavailability and ineffective dosing. These challenges limit the effectiveness of conventional gels, sprays, and rinses, which provide only transient relief. These limitations highlight the urgent need for more effective, patient-friendly, and targeted drug delivery strategies. In this context, alternative localized approaches are being increasingly explored. A buccal transmucosal delivery approach is therefore ideal for achieving a more localized and sustained therapeutic action.[13]

Microneedles for drug delivery is a novel system where therapeutic agent is administered through the oral mucosa to the target site.[14] More specifically, microneedles, which are micrometer-sized needles used for delivering drugs to the submucosa by puncturing microscopic pores in the buccal cavity, and can be used for oral cancer therapy. They are easy to use, effective, reduce drug first pass metabolism, can be prepared as biodegradable, and affordable. They have also been proven

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to be effective on different cancers such as skin cancer, head and neck cancer, breast cancer, and osteosarcoma.[15] They are superior to other transmucosal applications due to improved penetration, higher drug loading, and better retention in the oral mucosa.[16]

This review explores the pathophysiology of oral cancer and evaluates how microneedle technology can be strategically utilized for its treatment. It associates current microneedle types, their limitations, and existing applications in oral cancer therapy, supported by relevant case studies. By mapping the present landscape of microneedle research, this review highlights critical gaps and discusses strategic directions for future advancement.

2. Pathophysiology of oral cancer

The oral cavity, lined in most parts by non-keratinized stratified squamous epithelium, consists of the gingiva, buccal mucosa, soft palate, hard palate, retromolar trigone, tongue, tonsils, walls of the throat, the floor of the mouth, and lips. White, flat or wart-like (verrucous) lesions, called leukoplakia, on the oral epithelium can lead to cancer, depending on numerous factors such as age, anatomic location, underlying cause, *etc*.[17] Erythroplakia, a red patch/bruise with extensive vascularisation,[18] along with swollen lymph nodes, severe pain, and frequently bleeding sores, are some of the symptoms of oral cancer.[19]

Multiple factors facilitate oral cancer carcinogenesis, ranging from genetic predisposition to environmental exposure and others. Risk factors include various forms of tobacco, such as cigarettes, snuff, e-cigarettes, and vapes[20] along with alcohol, betel quid, areca nut, viruses like Human Papillomavirus-16 and Epstein–Barr virus, diet, ultraviolet rays, and candida infections (*Candida albicans*).[21] Tobacco products contain tobacco-specific nitrosamines and polycyclic aromatic hydrocarbons, which facilitate DNA mutation by causing damage and mispairing during replication and repair. Along with tobacco, alcohol is also a risk factor, helping the absorption of these carcinogens, and may also act as a carcinogen by itself, as there is abundant data correlating heavy drinking to oral cancer.[22,23]

HPV, or Human Papillomavirus, is a major causative agent for oral cancer. Most oral cancer cases induced by HPV are HPV-16 specific, which is speculated due to the unique environment of the oral cavity. The action in oral cancer carcinogenesis is focused on specific molecular pathways revolving around the E6 and E7 oncoproteins.[24,25] They are focused on disrupting normal cell proliferation signaling by dysregulating the cell cycle and facilitating malignancy by inhibiting tumor suppressor proteins (p53 and pRb, *i.e.*, retinoblastoma protein) and related targets. E7 also initiates DNA damage response pathways, which help viral DNA replication. E6 oncoprotein is focused on the degradation of the p53 tumor suppressor gene by polyubiquitination and proteasomal degradation, thus causing uncontrolled proliferation and tumorigenesis.[26,27] The least studied E5 protein of HPV-16 is also currently being investigated for being involved in growth factor signaling, which may synergistically increase the carcinogenesis caused by E6 and E7 viral oncoproteins[28]

Arecoline alkaloid and other derivatives found in Areca nut have been reported to cause DNA damage and impair DNA repair and p53 expression by generating reactive oxygen species (ROS).[29,30] It is extensively consumed by the Asian population and is classified as a group 1 carcinogen by the International Agency for Research on Cancer (IARC).[31] The ROS generated can enhance the expression and downstream signaling of fibrogenic cytokines-mainly TGF-β (tumor growth factor-β),[32] activating NF-kappa B (Nuclear Factor), Sma and Mad related protein (SMADs), p38 and c-Jun N-terminal kinase (JNK) pathway, and subsequently synthesizing connective tissue growth factor (CTGF).[33,34] Upon alteration of intrinsic pathways or genetic mutations, a cascade of reactions occurs, leading to metabolic alterations that may develop into cancer. Such alterations include inhibition of p53 (a tumor suppressor gene) and hypoxia, which can trigger uncontrolled cell growth.[35,36] TGF-β promotes OSCC metastasis by inducing epithelial–mesenchymal transition (EMT) (due to loss of Epithelial-cadherin protein),[37] aids tumor cells in escaping immune surveillance (by controlling the expansion and effector functions of Treg, antigen-presenting cells (APC), natural killer cells, and neutrophils),[38,39] and influences lineage plasticity in the tumor microenvironment.[36,40] Tabor and team.[41] have discussed the plausible malignancy and recurrence of head and neck squamous cell carcinoma due to loss of chromosome loci, microsatellite alleles, or a single nucleotide polymorphism.[42] According to a report by the American Association for Cancer Research,[43] microsatellite alterations like D2S206, D21S236, among others, can be detected by using a more sensitive and specific technique like microsatellite analysis in comparison with microscopic cytological analysis.

The PI3K/AKT/mTOR pathway, involved in cell proliferation, growth, survival, and metabolism, also has a significant role in oral cancer carcinogenesis.[44] The Cancer Genome Atlas (TCGA) study found that PIK3CA is overexpressed or mutated in 37% of HNSCC cases, specifically 34% of HPV− and 56% of HPV+ patients. Head and neck squamous cell carcinoma has been known to exhibit aberrant activation of the PI3K–AKT–mTOR signalling pathway, which is typically caused by changes in upstream regulators and activation of the PI3K–AKT–mTOR cascade.[45]

It is dysregulated by either overexpression of epidermal growth factor receptor (EGFR), mutation in PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha), or suppression of PTEN (phosphatase and tensin homolog) function, which is a tumor suppressor.[46] The pathway reduces apoptosis by phosphorylating pro-apoptotic factors and proteins, while increasing glucose metabolism *via* the mTORC1 pathway, thereby increasing cell proliferation and the cell cycle.[47,48] Further, the recent evidence has expanded the regulatory landscape of the PI3K/AKT/mTOR pathway in

OSCC through non-coding RNA-mediated mechanisms. A novel circEPSTI1/miR-942-5p/TPBP2 axis has been identified as a critical modulator of PI3K/AKT/mTOR pathway activation in OSCC. The circEPSTI1/miR-942-5p/LTBP2 axis accelerates OSCC progression and metastasis by activating the PI3K/Akt/mTOR pathway through phosphorylation. Especially, this axis increases the phosphorylation of PI3K, Akt, and mTOR (p-PI3K, p-Akt, p-mTOR) components. This mechanism further contributes to epithelial–mesenchymal transition (EMT) and increased cell proliferation, often in the context of oral submucous fibrosis (OSF).[49,50]

The WNT/β-catenin is another signaling pathway that can dysregulate and cause malignant transformations in the oral mucosa, promoting cellular replication and tumorigenesis in cells undergoing EMT. Triggered usually by mutations in specific components like E-cadherin (epithelial cadherin), vimentin, adenomatous polyposis coli (APC), and others.[51,52] More common pathways, like RAS/RAF/MEK/ERK (RAS/RAF/MPK), have been observed to be active in about 50% of oral cancer patients. It further activates proteins such as MEK/ERK kinase (Mitogen-Activated Protein Kinase and Extracellular Signal-Regulated) by phosphorylation, focused on cell survival, migration, and proliferation.[53,54] The interaction of this pathway with WNT/β-catenin and PI3K/AKT/mTOR pathways makes it an ideal target for oral cancer therapeutics.

Similarly, the JAK–STAT (Janus kinase–signal transducer and activator of transcription) and cancer stemness pathways help tumor cells evade immune cell detection and prevent an anti-tumor response.[54–56] Similarly, the JAK–STAT and cancer stemness pathways are associated with tumor immune evasion and impaired anti-tumor responses. The signal transducer and activator of transcription (STAT) pathway is abnormally activated in both HPV-positive and HPV-negative HNSCC. Upregulated STAT3 is associated with HNSCC malignancy, including OSCC, and resistance to chemotherapy, radiotherapy, and EGFR-targeted therapy. By increasing secretion of TGF-β1, VEGF, IL-6, and IL-10, STAT3 activation is linked to immune suppression in OSCC, limiting cytotoxic T-cell recognition and killing of tumour cells. Moreover, pro-survival genes like cyclin D1 and Bcl-xL are induced when STAT3 is activated by IL-6R, EGFR, VEGFR, JAKs, and Src kinases. Furthermore, the JAK/STAT pathway involves several factors, including the long non-coding RNA (lncRNA) P4713 and miR-548d-3p. In OSCC, miR-548d-3p functions as an oncogene by specifically binding to the 3′UTRs of SOCS5 and SOCS6, thereby suppressing their expression and regulating the JAK/STAT pathway. The JAK/STAT pathway is activated by 120 lncRNA P4713, which promotes OSCC cell metastasis and proliferation.[45]

Genetic alterations may also lead to an increase in the expression of EGFR, failure in the activation of tumor suppressors such as p53, and mutation in genes like CDKN2A (cyclin-dependent kinase inhibitor 2A) and HRAS (Harvey rat sarcoma viral oncogene homolog) can further facilitate these pathways.[57–59]

Even though the PI3K/AKT/mTOR, MAPK, JAK–STAT, and NF-κB pathways are often described separately, there is increasing evidence that OSCC involves substantial crosstalk among these signaling axes. The growing evidence suggests that the MAPK pathway interacts extensively with PI3K/Akt and other carcinogenic signalling pathways in OSCC, rather than operating independently. Ras mutations can promote parallel proliferation and survival signals by simultaneously activating the PI3K/Akt and MAPK pathways. Importantly, Akt inhibits Raf activity, highlighting the relationship between the two pathways.[60,61]

Additionally, PI3K/Akt activation enhances STAT3- and NF-κB-driven signalling, promoting tumour survival. Furthermore, NF-κb promotes the secretion of immunogenic cytokines such as IL-6 and VEGF, which activate the JAK–STAT pathway and support tumour survival. Moreover, the activation of NF-κB signalling due to EGF can promote the invasion and migration of OSCC cells.[62–65] These pathways affect important cellular functions, such as proliferation, survival, inflammation, EMT, and treatment resistance, through this integrated signalling network in oral carcinoma. Fig. 1 is a schematic representation of the pathophysiology of oral cancer progression.

Microneedles have been extensively explored to deliver drugs targeting these specific cancer pathways to treat various ailments. Drugs such as EW-7197 (TGF- β inhibitor),[66] delivery of various siRNA and mRNA (which are used inhibiting and regulating PI3K–AKT, JAK and ERK pathways) have been observed to be delivered through microneedles improving targeted delivery, bioavailability by skipping first pass metabolism, reducing systemic toxicity and side effects.[67,68]

3. Overview of microneedle types, therapeutic applications, and limitations

Microneedle patches were initially fabricated and tested to deliver drugs through skin, but researchers later developed it into a comprehensive system, allowing detailed analysis of various engineering aspects like development process of this system which established fundamental principles, where researchers used to build three core elements that control insertion mechanics and structural strength and controlled release operations.[69,70] Microneedle technology allows researchers to create new systems, which expand beyond traditional applications that treat skin conditions. The microneedles facilitate the creation of transient micropores and perforations, thereby increasing the permeability of the drug into the target site through the stratum corneum.[71] Microneedles also help in the delivery of amphiphilic vaccines and other therapeutics into lymph vessels and nodes.[72] When compared to intradermal injections, microneedles deliver therapeutics to not only the dermis but also the epidermis, increasing the uptake of drugs by Langerhans cells and dendritic cells. This, in turn, offers a stronger immune response, making microneedles ideal for use in vaccines.[73]

In buccal applications, where blood vessels are approximately 600 μm below the mucosa, microneedles are about

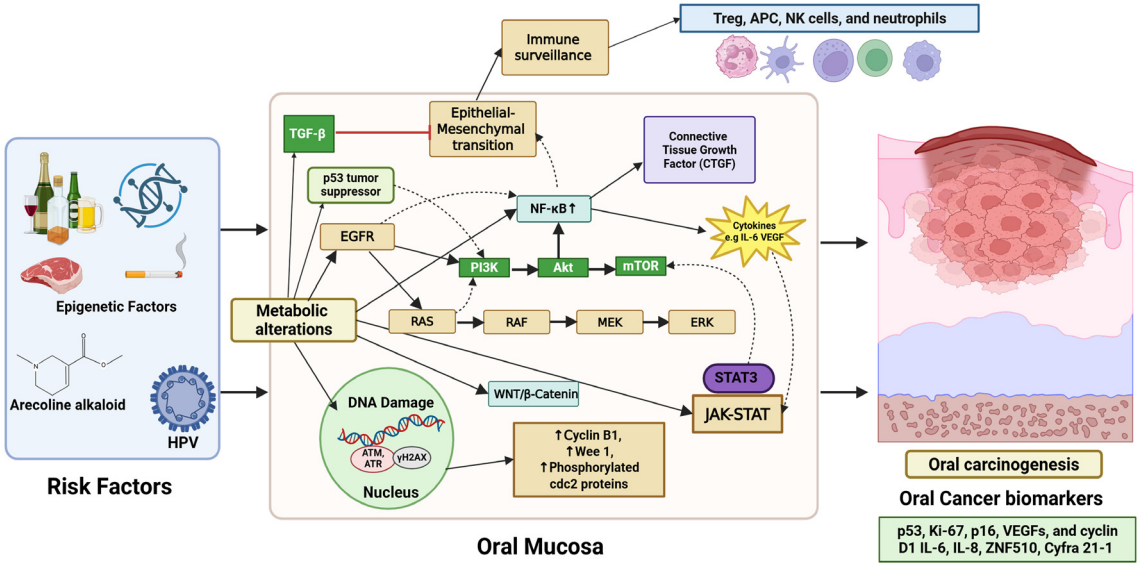

Fig. 1 Schematic representation of the pathophysiology of oral cancer progression. Created with Biorender.com. APC: antigen-presenting cells; ERK: extracellular signal-regulated kinases; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; PI3K/AKT: phosphatidylinositol 3-kinase-Ak strain transforming/protein kinase B; ATM: ataxia telangiectasia mutated; γH2AX: phosphorylated H2A histone family member X; TGF-β: tumor growth factor-β; NK cells: natural killer cells; RAS/RAF/MEK/ERK (MAPK pathway): RAS/RAF/mitogen-activated protein kinase kinase/extracellular signal-regulated kinase (mitogen-activated protein kinase); JAK–STAT: janus kinase-signal transducer and activator of transcription; mTOR: mammalian target of rapamycin; EGFR: epidermal growth factor receptor; CDC2: cyclin-dependent kinase 1.

200–500 μm in length to ensure adequate penetration of the therapeutic agents and to prevent discomfort.[74]

Contrasting with submucosal injections, microneedles ease delivery of drugs directly to the hard and soft palate, gingiva, oropharynx, epithelium and oral mucosa. Transdermal delivery involves traversing the stratum corneum for delivery of poorly permeable lipophilic drugs with low molecular weight, whereas buccal transmucosal mode escapes this mechanical tissue barrier but encounters hindrance from enzymes, localized fluids and immune cells.[75] Various other factors such as the mucus layer and non-keratinized epithelium along with wet (saliva), variable pH, constant saliva flow causes microneedles fabrication more specific for application in the buccal cavity. Microneedles based on function are fabricated in different shapes in the longitudinal axis as well as the base. A study by Martino and team explored the effects of various microneedle shapes on skin penetration and drug administration. It concluded that star-like microneedles had the highest skin penetration, demonstrating that a greater number of vertices in the shape is directly linked to faster release kinetics, while cone-like designs exhibit higher mechanical strength.[76] The reduced pain response arises from the microneedle's limited penetration depth, which avoids the dermal nociceptors, while still reaching capillary networks and immune cell-rich regions, enabling pharmacological efficacy without stimulating sensory neurons.

Oral mucosal tissues exhibit different structural characteristics compared to skin tissues because their hydration levels remain high and they experience continuous saliva flow and enzymatic activity and mucus turnover and the mechanical stresses which occur during mastication and speech.[77] The different body systems and structural elements of the body affect how deep medical instruments can penetrate and how long devices can remain in place and how stable formulations remain and how medications are released from the products. The design of transdermal microneedle systems serves as a basic reference point; however, the delivery of drugs through mucosal membranes needs special design changes to create effective and safe methods for treating oral cancer.[78]

Microneedle design for oral cancer therapy must be applicable to the anatomical complexity of the oral cavity, as every site presents different structural and functional characteristics. Non-keratinized tissues such as the buccal mucosa and soft palate exhibit epithelial thicknesses of approximately 500–800 μm and high vascular density this leads to facilitating both local and systemic drug absorption. For these sites, microneedle lengths of 200–500 μm are generally appropriate to obtained desired penetration into the lamina propria while avoiding stimulation of deeper nociceptive pathways, thereby enhancing safety and patient comfort.[77] However, the continuous saliva flow (0.3–2 mL min^{-1}) and the tongue creates movement, so the patch needs flexible backing layers and mucoadhesive polymers to stay attached while exposing the tumor site. The gingiva and hard palate show higher mechanical stiffness but lower permeability when compared to keratinized areas which need tip geometries modifications. The properties of the material show their most important application when scientists need to study OSCC lesions that exhibit both changes in epithelial structure and vascular permeability and localized tissue inflammation, which will affect the movement

and storage of medications. Dissolution kinetics must also be adapted to therapeutic objectives. Rapidly dissolving microneedles may be advantageous for localized cytotoxic delivery, whereas controlled or sustained-release systems may improve intratumoral retention and therapeutic exposure. Dose loading is inherently limited by the confined application surface area of the oral cavity (typically 1–3 cm^2), restricting total drug payload and favoring highly potent chemotherapeutic, immunotherapeutic, or gene-based agents. Collectively, these site-specific anatomical and pathological factors directly inform microneedle geometry, length, backing layer composition, mucoadhesion strategy, release profile, dose capacity, and safety considerations in oral cancer management.[77]

Microneedles are further classified into 4 different types such as solid, coated, hollow, and dissolving microneedles, as shown in Fig. 2. Each of the types has specific advantages and disadvantages in drug delivery. Solid microneedles are used to form small perforations on the epidermis to improve the absorption of topical dosage forms applied on the skin after puncturing the skin. They usually have very high mechanical strength and are easy to manufacture but have less compliance due to the two-step method of application.[79]

Coated microneedles are used popularly in vaccines where the antigen is coated on the surface of the microneedles, which provides a superior immune response than that of intramuscular vaccines.[80] Coated microneedles can also be used to deliver macromolecules[81] insulin[82] and various hormones as well.[83] One of the major limitations coated microneedles face is the limited drug loading capacity due to their small surface area.[84] Surface coating efficiency is influenced by parameters such as polymer viscosity, surface energy, and coating thickness uniformity. Optimizing these factors through techniques like electrostatic deposition or dip-coating with surfactant modifiers can significantly improve stability and loading density on the microneedle surface.

Hollow microneedles have been popularly used for drug and vaccine delivery. It has regained popularity in the monitoring and detection of diseases.[85] They have a higher drug loading due to reservoirs and can carry the highest dosage of drug among microneedles. The biggest advantage of hollow microneedles is the development of flexible dosing systems, which are integrated with electrical components (microelectromechanical systems or MEMS) for accurate dosing in a timely manner.[86] Incorporation of microfluidic flow regulators within hollow microneedles allows control over hydrostatic and capillary-driven drug transport. This enables pulsatile or continuous dosing, essential for drugs with narrow therapeutic windows, while reducing risks of backflow and tissue leakage. Although there are various advantages of using hollow microneedles, they lack in mechanical strength due to a hollow lumen and have a higher tip diameter, causing a decrease in penetration. The hollow channels may clog or block, preventing drug release.[85]

Hydrogel-forming microneedle patches formed from crosslinking hydrophobic polymers, which swell on insertion into the epidermis by absorbing tissue fluid and release the drug through pores formed during the swelling. The formed hydrogel network facilitates faster release and much higher loading.[87] They also allow molecules up to 500 kDa due to swelling ratios of up to 3800%.[88]

Due to such characteristics, hydrogel microneedles have also been used to deliver proteins and macromolecules[89] along with drugs and hormones like insulin.[90] The swelling rate and mechanical integrity of hydrogel microneedles depend on polymer crosslink density, chain hydrophilicity, and network elasticity. Fine-tuning these parameters enables control over

Types of Microneedles for Oral Mucosal Delivery

Features	Solid Microneedles	Coated Microneedles	Hollow Microneedles	Dissolving Microneedles	Hydrogel Microneedles
Payload Suitability	NA	Low–moderate doses of potent APIs	Large volumes, viscous biologics, and APIs	Systemic proteins (insulin, hGH), macromolecules, and drugs	Sustained-release biologics and hydrophilic macromolecules
Drug loading capacity	NA	Generally < 1 mg per array	Very High (Limited only by external reservoir)	Moderate to High (1-2 mg)	High (Slow release from an adherent drug reservoir)
Penetration depth in oral mucosa	Unexplored	50–150 micrometers into mucosal layers	500–800 micrometers	500–800 micrometers	500–800 micrometers
Dissolution / swelling rate	Undissolved	Very Rapid	N/A (Pressure-driven infusion)	Rapid (50% height loss in 5–30 seconds in saliva)	Slow (Tips swell but do not dissolve/disintegrate)

Fig. 2 Schematic representation of various types of microneedles explored for oral cancer: solid microneedle, coated microneedle, hollow microneedle, dissolving microneedle, and hydrogel microneedle. Created with Biorender.com.

diffusion kinetics and responsiveness to physiological stimuli such as pH or glucose concentration, making them ideal for smart, feedback-driven drug delivery systems. In contrast to this, hydrogel microneedles face storage and manufacturing difficulties due to their complex preparation procedure and integrity issues in hot and moist conditions.[84]

Dissolving microneedles are formulated using biocompatible polymers, which dissolve on transdermal application and release the encapsulated active ingredient. They are preferred over other types of microneedles because they dissolve quickly and do not cause irritation or break, which can leave fragments and lead to infections. They are commonly used for skin cancer, psoriasis, atopic dermatitis, and acne, and have also been widely researched for oral cancer applications.[91] They have also been utilized to deliver vaccines for diseases like hepatitis B,[92] HIV (human immunodeficiency virus),[93] and HPV, which can contribute to the pathogenesis of oral cancer.[94,95] The dissolution rate and release kinetics are influenced by polymer molecular weight, hydrophilic-hydrophobic balance, and glass transition temperature. Tailoring these physicochemical properties allows for controlled release profiles ranging from rapid burst to sustained delivery, ideal for localized chemotherapeutic or immunomodulatory drug administration. Although dissolving microneedles have certain limitations, such as poor drug loading capacity and low mechanical strength, dissolving microneedles have been extensively used in oral cancer due to their sustained and controlled release, along with their versatility and simple manufacturing process.[96] Unlike most transdermal therapies, microneedles help penetrate through the epithelial layer and improve drug penetration while being painless, and by having a superior penetration along with potential for combination therapy, further discussed in the review below.

4. Microneedle-based therapy for oral cancer treatment

Microneedles have been explored to delivery multiple anticancer drugs, photosensitizers, and immunotherapeutics for various types of cancers. They are preferred over other dosage forms due to its higher dermal penetration and potential for combination therapy. Drugs such as 5-fluorouracil,[97] doxorubicin,[98] paclitaxel[99] along with gene therapy can be delivered through microneedles revolutionizing cancer therapy.[100] Microneedles are already being employed in clinical trials for skin cancer such as NCT05377905 [101] and NCT04928222 [102] focused on using doxorubicin for cutaneous squamous and basal cell carcinoma.[70]

Microneedles can be utilized to treat oral cancer by penetrating the non-keratinized mucosa (sublingual or buccal) and administering the therapeutic ingredient directly to the site of action. They can be coupled with traditional therapy to overcome their limitations and improve bioavailability, as well as help them bypass first-pass metabolism and minimize side effects. Microneedles have already been explored for the treatment of oral leukoplakia, which is a precancerous lesion. Studies and various clinical trials have shown how PDT agents such as 5-aminolevulinic acid can be useful in managing oral leukoplakia when delivered through microneedles, providing non-invasive delivery to the target site.[103,104]

Head and neck cancer encompasses many different types of cancers, such as oropharyngeal cancer, laryngeal cancer, and other cancers in the oral cavity.[105] Microneedles have often been used in head and neck cancer cells. A study developed a dissolving microneedle system for delivering indocyanine green, a US FDA-approved photothermal and photodynamic drug, which improves cellular uptake as observed in *in vivo* NIR fluorescence. The microneedles were administered in athymic nude mice with FaDu xenograft tumors (hypopharyngeal squamous cell carcinoma) and irradiated by a near infrared (NIR) laser. The tumors showed regression by 97% in tumor volume, *i.e.*, from 600 mm^3 to 15 mm^3, after three dose applications and within 6 days, while intra-tumor injection demonstrated increased systemic toxicity.[106]

Microneedles are also popularly used with chemotherapeutic agents such as 5-fluorouracil (5-FU), used in gastric adenocarcinoma and oral cancer. Matta *et al.* developed dissolving microneedles for the delivery of 5-FU, where the microneedle system improved the *ex vivo* permeation as the cumulative amount of 5-FU in 48 h was found to be 135.7 ± 2.25 μg cm^{-2}, while 5-FU, when administered as a solution, only permeated 117.1 ± 11.39 μg cm^{-2}. It also significantly increased the flux values for 5-FU by 1.8 times compared to the solution through the excised porcine buccal mucosa. A preclinical study in a Wistar rat model revealed that, in *in vivo* conditions, about 82.7 ± 6.41% of 5-FU remained at the application site in the buccal mucosa of the Wistar rat, while intravenous administration resulted in a peak plasma concentration of 51.7 ± 16 ng ml^{-1} at 20 minutes after administration (Fig. 3). The study concluded that the microneedle system helped reduce systemic toxicity and side effects due to its localized retention and undetectable plasma concentration compared to an intravenous injection.[107]

Microneedles mediated chemodynamic therapy have been explored to produce reactive oxygen species in the cancer cell by chemical reactions, causing apoptosis. In a study, microneedle patch was designed to deliver Fe_3O_4 along with vitamin C. Fe_3O_4 helps produce free radicals by reacting with H_2O_2, while vitamin C is taken by cancer cells, where it converts into dehydroascorbic acid, which depletes intracellular glutathione, a known antioxidant, and helps produce more H_2O_2. The study showed that the Fe_3O_4 and vitamin C microneedles showed high anti-tumor efficacy and reduced tumor volume, cellular migration. The microneedles provide localized drug action with minimal systemic toxicity and biocompatibility, as confirmed by the stained organ images showing no damage (Fig. 4).[108]

Curcumin and its analogues have shown significant anticancer effects, including the inhibition of signal transduction and transcription factors that regulate tumor proliferation and migration with low systemic toxicity.[109] An analogue 4-arylcur-

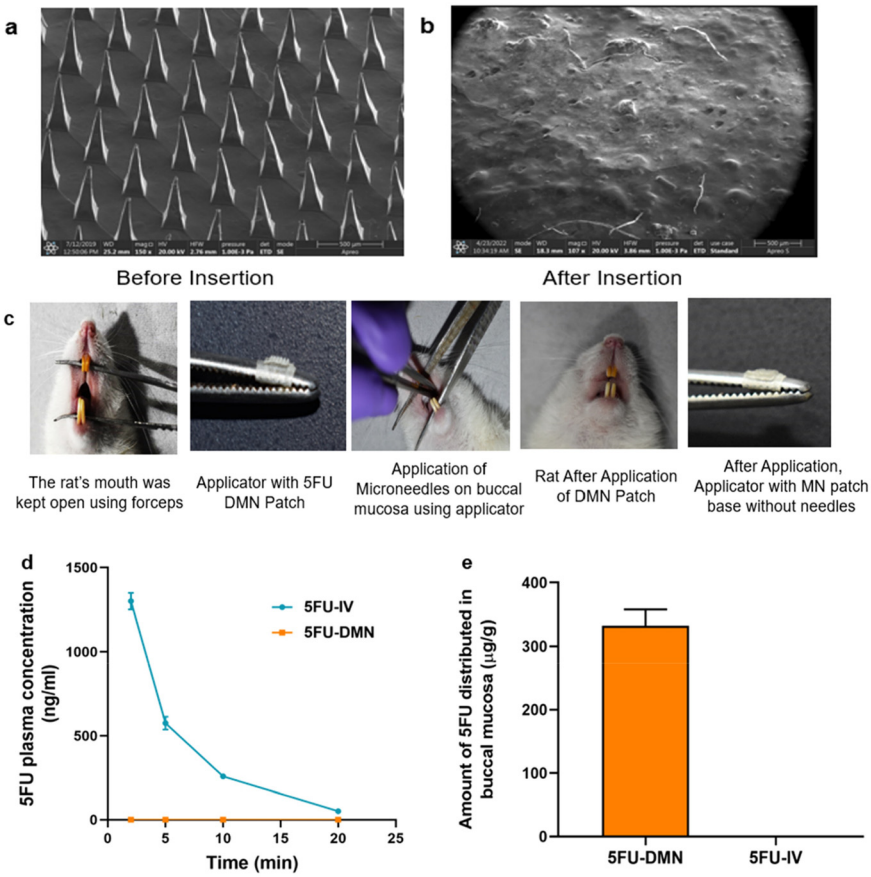

Fig. 3 Representative SEM images of DMN before (a) and after (b) insertion into the rat buccal mucosa. (c) Application of 5FU-DMN patch on buccal mucosa by using an applicator. (d) Plasma concentration–time profile of 5FU following IV administration and buccal application of DMN. (e) Disposition of 5FU in the buccal mucosa after DMN application and IV administration. Reproduced from ref. 107, copyright 2023 with permission from Springer Nature.

cumin (AC-17) is approximately 1.8 times more effective and potent in inducing apoptosis in oral cancer cells while being biocompatible. AC-17 works by arresting cancer cell growth by blocking DNA synthesis and mitosis at the S and G2 phases of the cell cycle. It inhibits CDK1/CDK2, preventing cancer cell replication. Another study fabricated hyaluronic acid-based microneedle for delivering AC-17, enhancing its efficacy in both *in vitro* and *in vivo* studies. *In vivo* study with a rat model injected with CAL-27 cells (ectopic) demonstrated that the microneedles penetrate the tongue tissue and deliver over 90% of the drug within three minutes, demonstrating high local efficacy with low systemic toxicity.[110]

Immunotherapy is a type of cancer treatment where immune cells of the body are sensitized to kill cancer cells. In immunotherapy, the immune checkpoint inhibitors (ICI) are drugs that can be used to restore anticancer T cell immunity. Gilardi and colleagues developed a microneedle patch to deliver anti-cytotoxic T-lymphocyte antigen-4 (αCTLA-4) (popular ICI) directly to the tumor, which helps to reduce the risk of immune-related adverse effects (irAEs). αCTLA-4 activity depends on conventional dendritic cell type 1 (cDC1) for antigen presentation. These APC then utilize CD8+ T-cells or killer T cells to kill cancer cells. The αCTLA-4 was loaded into microneedle patches and the study compared the systemic as well as local administration of αCTLA-4 and found that in low immune tolerance threshold mice, systemic administration caused multiple irAEs such as splenomegaly and blepharitis, while the microneedle administration showed no such irAEs. They also reduced the tumor response in mouse xenograft model by more than 90%, thus proving to be effective in cancer immunotherapy and in reducing immune checkpoint inhibitor.[111]

Combination therapy has emerged as a groundbreaking method for treating various cancers. While developing new therapeutic molecules take time, combining two or more existing therapeutics has become more feasible strategy. This approach leverages synergistic effects to boost effectiveness, minimize toxicity and overcome drug resistance.[112] Dissolving microneedle showed hope for effective delivery of combination therapy. In a study, microneedles were utilized for administering both the p53 gene and a photothermal agent, IR820 (an indocyanine green derivative). The p53 gene is a well-known tumor suppressor gene used in gene therapy, targeting the root cause of the cancer. However, it displays low therapeutic

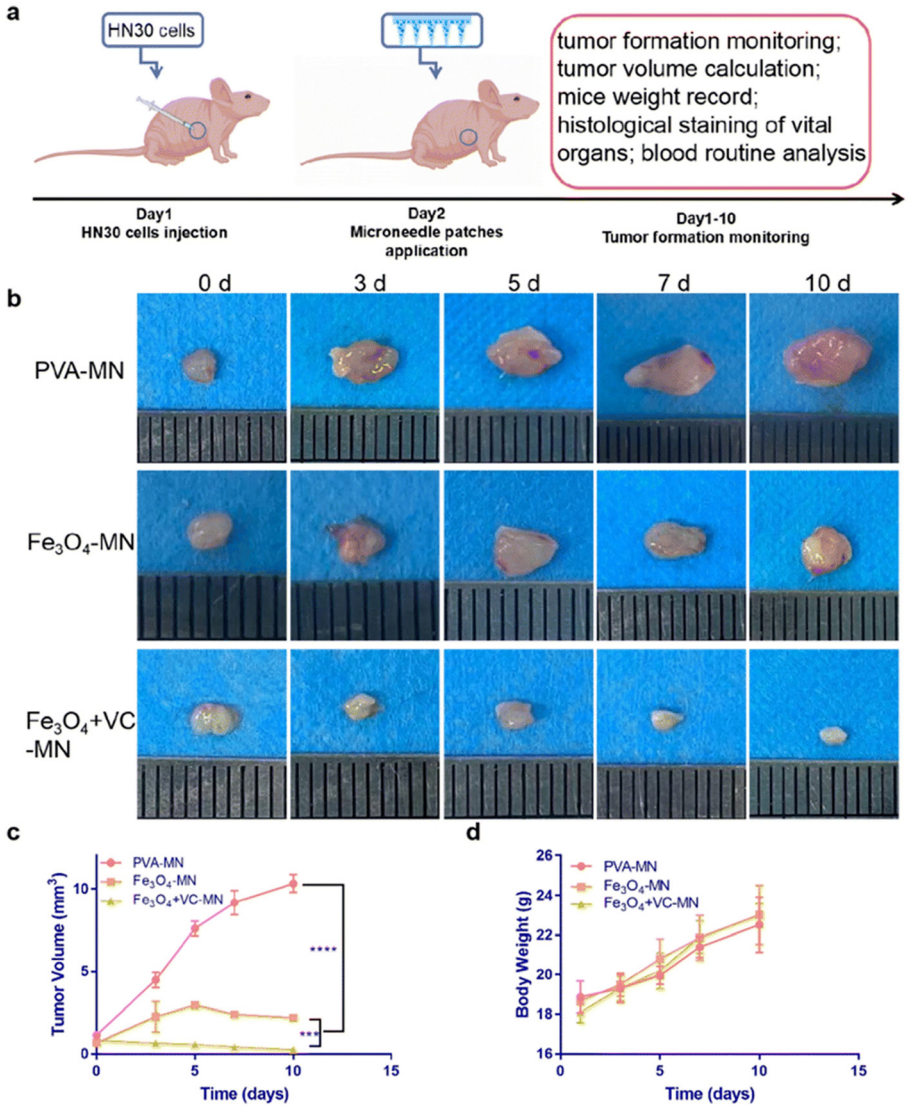

Fig. 4 (a) Schematic diagram of the *in vivo* experimental process. (b) Pictures of tumors from three groups at different time points. (c) Tumor volume changes. (d) Weight variation in the nude mice. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$. Reproduced from ref. 108, copyright 2023 with permission from Royal Society of Chemistry.

efficacy when administered alone and can be enhanced by combining it with IR820, a near-infrared (NIR) light-activated photothermal agent. The study used sodium hyaluronate in a 5 × 5 microneedle array for administration due to their ability to deliver hydrophilic and macromolecular drugs directly to the site of action. The *in vivo* study in nude mice injected with KB cells compared various treatment groups and their relative tumor volume where only the p53 DNA/IR820 microneedle patch irradiated with NIR displayed a 40% decrease in relative tumor volume (Fig. 5). The results indicated a significant synergistic effect of both the p53 gene and IR820.[113]

Nanoparticles have been approved to deliver anticancer medication such as Doxil®[114] and DaunoXome®.[115] Since then, various chemotherapeutics have been formulated into nanoparticles to ensure controlled and targeted drug delivery along with reduced systemic toxicity.[116] Cisplatin is a first-line chemotherapeutic drug used in the treatment of oral cancer. Although it has high efficacy, it is riddled with various side effects when administered in the systemic circulation. Nanocarriers such as solid lipid nanoparticles, nanostructured lipid carriers, and liposomes have been popularly used to administer cisplatin for oral cancer due to their controlled release, enhanced cellular uptake, biocompatibility, and improved drug retention characteristics.[117,118] Microneedles can be used to directly administer such nanoparticles of cisplatin to improve its bioavailability in tumors. Microneedle assisted administration of lipid-coated cisplatin nanoparticles showed a 60% increase in cancer cell apoptosis, while only 20% cells showed a chance of proliferation in tunnel assay. The platinum content in the systemic circulation in reference

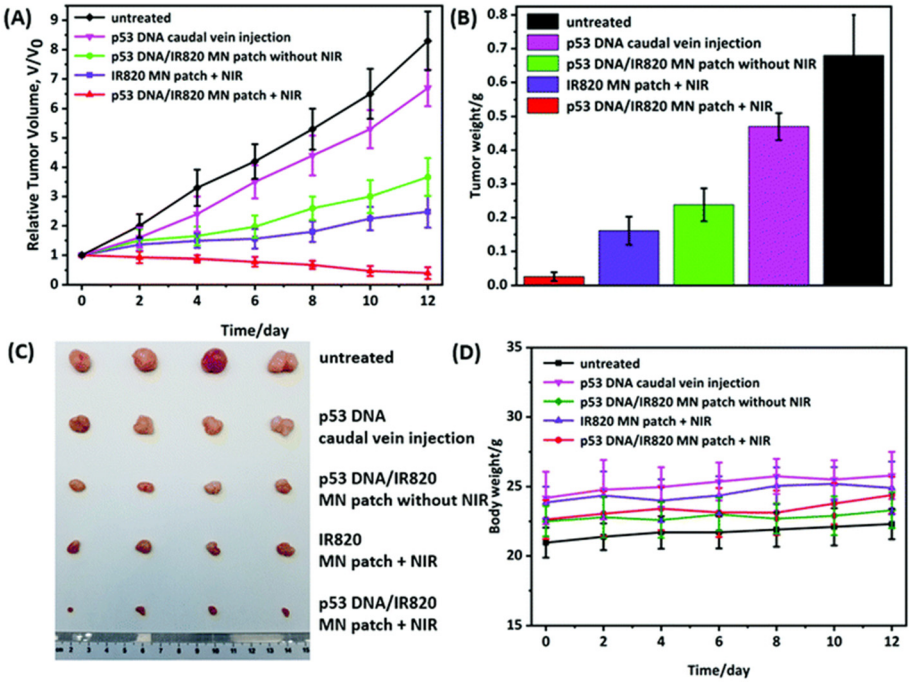

Fig. 5 *In vivo* antitumor efficacy: (A) relative tumor volume of each group for 12 days; (B) tumor weight of each group on day 12; (C) images of excised tumors of each group on day 12; (D) body weight of mice in each group. $p < 0.05$. Reproduced from ref. 113, copyright 2020 with permission from Royal Society of Chemistry.

to an I.V. injection of Cisplatin was measured and found to be negligible. Thus, the microneedle application of lipid coated nanoparticles improved antitumor efficacy and reduced systemic toxicity in comparison to I.V administered cisplatin.[119]

Intratumoral drug delivery approaches are a preferred option for recurring oral cancers as an aid to surgery as they offer localized and sustained delivery of anticancer drugs. The most used approach for intra tumoral delivery is hypodermic injections, however they have limitations such as painful application, irregular drug distribution, limited control over injection volume and pressure leading to drug leakage and systemic exposure. In such cases, microneedles offer a minimally invasive and safer alternative for effective transdermal administration. Yunzhe Ma and team developed a microneedle patch coated with PEGylated DOX nanoparticles. Their team investigated microneedles for uniform intratumor drug delivery and characterized *in vitro* using a 3D tissue phantom and porcine buccal tissue. The developed patch was observed to release 66% of DOX within 24 h, providing a controlled and sustained release over a period with an appropriate depth to penetrate porcine buccal tissue. Moreover, cytotoxicity studies further demonstrate that DOX can induce cell death in 3D tissue phantoms. Furthermore, leakage of fluid during tissue injection was quantified to check drug leakage issue, in which it was observed that the coated microneedles, unlike injections, do not require fluid injections and can deliver drugs to controlled and well-distributed regions in the tissue, resulting in higher overall performance than hypodermic needles.[120] A recent study loaded a synergistic combination of chemotherapy and photodynamic therapy into dual-length microneedles. Dasatinib was the chemotherapeutic agent of choice which acts as a tyrosine kinase inhibitor along with Aza-BODIPY (photosensitizer) which has already been explored to inhibit oral squamous cell carcinoma when delivered through microneedle.[121] A combination index < 0.6 was observed where the chemotherapeutic agent helps induce cell death in hypoxic cells. As the photosensitising light may not reach deep into the tumour, the microneedles were strategically layered in dual lengths using a micromolding technique, with shorter needles of 390 ± 10 μm loaded with the PDT agent and longer needles of 780 ± 30 μm loaded with the chemotherapeutic, ensuring better spatial distribution. The combination showed an 82 ± 3.2% reduction in MOC2 oral cancer cells. While *ex vivo* permeation studies showed a 3.9 and a 2.5-fold increase in flux of the chemotherapeutic and PDT agent, respectively. The microneedles ensured retention of 86% of Dasatinib in *ex vivo* porcine mucosa and approximately 1.8 times bioavailability compared to intravenous injection in *in vivo* mice along with a tumor regression of approximately 9.9 ± 3.5 mm^3 compared to the untreated control group which stayed at approximately 300 mm^3.[122] Microneedles have also been used to deliver vaccines for HPV, a causative agent of oral cancer. They offer a way to target immune cells, dermal APC, and Langerhans cells, thus eliciting a more robust response.[123] Similarly a study also explored the potential of photodynamic and chemodynamic therapy for oral cancer using manganese-doped carbon dots loaded in a hyaluronic acid-based microneedle. These manganese carbon dots (Mn-CDs) have proven to have a dual action in cancer cells, where they react with H_2O_2 in a Fenton-like reaction, only feasible in the

slightly acidic environment of tumours, causing the release of free radicals. Adding on to this effect, the nanodots can be laser irradiated at 635 nm wavelength, causing an acceleration in the production of the free radicals, improving the quantum yield of singlet oxygen species while depleting GSH, interrupting the redox balance, and causing apoptosis of 86.14% due to the rise of reactive oxygen species. The ectopic mouse model also displayed a 95.5% reduction rate in tumor growth inhibition.[124]

Microneedles have also been utilized for diagnosis of cancers. Oral cancer is detected using various tools, such as optical coherence tomography (OCT), which requires gold nanoparticles to increase the average optical scattering intensity in deep tissue. A study formulated PEGylated gold nanoparticles and delivered them through microneedles, improving delivery and increasing optical scattering. The microneedles help in delivering gold nanoparticles across the stratum corneum and improve the OCT signal by 33% in dysplastic tissue, and 20% in normal tissue. The method utilized 200 times less concentration of gold nanoparticles used for imaging in previous studies and thus provides a highly effective and safe method to enhance OCT imaging for early cancer detection.[125] The summary of some investigations have been compiled in Table 1.

6. Challenges and design considerations in microneedle therapy for oral cancer

Microneedles are an emerging drug delivery system but are still riddled with various limitations. The largest hurdle in microneedles in oral therapy is the action of saliva to wash out the drug from the buccal cavity. Saliva, while essential for hydrating the buccal mucosa and maintaining mucosal elasticity, also plays a dual role by enhancing drug solubilization yet accelerating its clearance from the mucosal surface. This presents a physicochemical paradox where higher mucosal hydration facilitates diffusion across epithelial layers, but excessive fluid turnover disrupts residence time and concentration gradients critical for absorption. Therefore, the design of microneedle systems for oral use must incorporate strategies that balance hydration and retention through mucoadhesive or barrier-forming components along with physiological conditions which may affect drug absorption and kinetics such as dry mouth (xerostomia) or salivary gland hypofunction.[126] A microneedle delivery system, while offering numerous transdermal advantages, often causes minor tissue injury during skin penetration when given alone. This cellular disruption leads to the release of extracellular adenosine triphosphate (ATP), which acts as a danger-associated molecular pattern (DAMP) signalling molecule. This extracellular ATP further binds to $P2Y_2$ receptor, a subtype of purinergic G protein-coupled receptor in neighbouring cells, initiating downstream signalling pathways. These further activate the Src, a member of the kinase family. The active Src kinase can transactivate the epidermal growth factor receptor and stimulate the PI3K–AKT pathway, both of which play vital roles in cell proliferation.[127,128]

Salivary washout, mucosal permeability, enzymatic degradation, and local irritation are just a few of the physiological and anatomical obstacles that traditional topical or trans buccal administration platforms frequently encounter. Addressing the issue of salivary washout, there is a need for more focus on the performance parameters that are reproducible, especially in terms of residence time and mechanical stability in the dynamic oral environment. One factor to consider is the relationship between the dissolution of the microneedle tip and the time course of mucoadhesion, where the backing layer should be stable for a duration sufficient for adequate mucosal penetration and drug deposition before the layer detaches.[129] The experimental assessment can include the use of modified flow-through systems, such as Franz diffusion cells or USP Apparatus 4, with simulated salivary fluid to determine the relative contributions of drug permeation, tissue retention, and washout loss.

In terms of design, the addition of a non-permeable backing layer made of hydrophobic polymers (such as ethylcellulose or polycaprolactone) can facilitate drug diffusion in the direction of the mucosa while preventing premature hydration from the external surface. In view of the mechanical forces induced by mastication and swallowing, the measurement of mucoadhesive properties by detachment force or tensile testing using texture analyzers offers a useful approach to the durability of mucoadhesion under shear forces. The use of strong mucoadhesive (such as carbomer or thiolated polymers) in combination with a mechanically stable backing layer can potentially improve the resistance to dynamic clearance in the oral environment. The inclusion of these fluidic and mechanical properties in addition to the permeation properties would make the oral microneedle platform more relevant to the treatment of localized cancer. These obstacles reduce the effectiveness of biomarker monitoring and drug retention. These considerations are highlighting the suitability of microneedle-based patches for localized delivery within the oral cavity and have gain a significant interest by smooth targeted intramucosal delivery while limiting off target effects. Microneedles, attached to the surface patch, are micro-sized hollow or solid, biodegradable needles that penetrate the dermis, thus offering direct drug release, reduced side effects, and frequency of administration.[130]

Studies have been conducted to optimize the *in vitro* model for microneedle-assisted drug delivery at the buccal cavity. Microneedles coated with sulforhodamine as a model fluorescent drug tested on porcine buccal mucosa, maintaining a dynamic flow rate of 100 μL h^{-1} or a static solution of phosphate buffer solution (PBS) in different concentrations (100, 200, and 300 μL) to emulate saliva. It was found that the 100 μL PBS setup showed 12% permeation, 75% retention, and 14% drug loss due to back diffusion or washout. This model provided balanced drug delivery with minimal washout. Dynamic models although are more realistic but convey the

Table 1 Summary of case studies for microneedle-assisted treatment strategy for oral cancer

Sr. No.	Type of therapy	Microneedle type	Dimensions	Material of microneedle construction	Active agent and payload	*In vitro* (cell line)/ *in vivo* (species)	Study outcome	Ref.
1	Diagnostic	Dissolvable	200 μm long and 87 μm wide at base, pyramidal geometry	Carboxymethylcellulose sodium salt + sucrose	Gold nanoparticles	*In vivo* orthotopic (hamster)	Improved gold nanoparticle delivery for optimal imaging using OCT and reduced the dose of gold nanoparticles	125
2	Monotherapy	Dissolvable	501 μm long and 291 μm wide at base, pyramidal geometry	Carboxymethylcellulose sodium salt, sodium alginate, polyethylene glycol 400	Indocyanine green	*In vivo* (ectopic FaDu xenograft)	Provided a localized action of photosensitizer and improved accumulation in tumor cells	106
4		Dissolvable	>1 mm long and ~500 μm diameter, conical geometry	Polyvinyl pyrrolidone	αCTLA-4 antibody – 100 μg in 10 × 10 mm array	*In vivo* orthotopic (mouse)	Reduced irAE in immunocompromised mice and proved to be a viable drug delivery route for other immunotherapy drugs	111
5		Dissolvable	300 μm side at the base, 20 μm side at the tip, and 600 μm length, pyramidal geometry	Sodium carboxymethyl cellulose, sodium alginate, and polyethylene glycol 40	5-Fluorouracil	*In vivo* orthotopic (mouse)	The formulated microneedle drastically improved the permeation and reduced systemic toxicity when compared to systemic injections	107
6		Dissolvable	900 μm needle length, pyramidal geometry	Polyvinyl alcohol (PVA)	Fe_3O_4 + VC	*In vivo* (mouse)/ectopic HN30 cells (OSCC) human oral epidermoid carcinoma (KB) cells injected in armpit of mouse	The developed microneedle patch system provided a tumor microenvironment-mediated action, improving the action and effectiveness of the chemodynamic therapy in ROS generation	108
7		Dissolvable	Height of 590.82 ± 7.54 μm and a base diameter of 270.09 ± 8.81 μm, conical geometry	Hyaluronic acid (HA)	Curcumin analogue, AC17 – 5 mg in 10 × 10 mm array	*In vivo* ectopic (mouse)	Developed a microneedle application for a curcumin analogue, which is biocompatible and prevents cancer cell replication	110
8	Combination therapy	Dissolvable	904 ± 8 μm and 8 ± 2 μm, pyramidal geometry	Hyaluronic acid (HA)	10 mg of IR820 and 10 mg of p53 DNA in a 5 × 5 mm array	*In vivo* ectopic (mouse)	Successfully delivery of a gene therapy and photothermal therapy which showed high and synergistic effect on oral cancer cells	113
9		Dissolvable	800 μm in height, conical geometry	Cellulose	Cisplatin in a 9 × 9 mm array	*In vivo* ectopic (mouse)	The study successfully reduces the side effects caused by cisplatin and higher bioavailability due to the intratumoral delivery	119
10		Dissolvable	700 μm in length and 200 μm width	Polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP K30)	PEGylated DOX nanoparticles 10 × 10 mm array	*In vitro* (3D tissue phantom model)	The developed microneedle patch delivers PEGylated doxorubicin to localized oral cancers	120
11		Dissolvable	800 μm long and 300 μm, pyramidal geometry	Polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP K30)	Aza-BODIPY	*In vivo* ectopic (mouse)	Chemo-phototherapy drugs showed high synergy and low toxicity due to the administration through microneedles	122
12		Dissolvable	700 μm height and width of 280 μm, conical geometry	Hyaluronic acid (HA)	Manganese loaded carbon dots	*In vivo* ectopic (mouse)	Mn-CD loaded microneedles cause significant reduction in tumor size while overcoming the limitations such as poor stability and solubility of traditional phototherapy	124

need of mucoadhesive action to prevent back diffusion of drug. This study also highlighted the need for models to emulate mastication and deglutition along with the need for a mucoadhesive patch to prevent backflow.[129]

Based on this previous study a team prepared a backing layer in a hyaluronic acid-PVP based microneedle to reduce the effect of salivary backflow. They also determined that the designed microneedle was mucoadhesive due to the presence of PVP, the patch was observed to be mucoadhesive for over 3 h. The backing layer prepared with ethyl cellulose in practical application can be spat out by the patient in real world application.[131] Mucoadhesion in such systems primarily results from hydrogen bonding, van der Waals interactions, and polymer chain interpenetration with mucin glycoproteins. Optimizing the balance between hydrophilicity and molecular weight of polymers enhances adhesion strength while maintaining biodegradability, which is crucial for retention in the dynamic oral environment. The oral cavity provides a different challenge for microneedles. Due to the various structures present in the oral cavity, microneedles may not be able to target structures such as the gingiva and hard palate due to their varying layers and the existence of a keratinized layer. The keratinized layer consists of neutrally charged lipids like ceramides and acylceramides, causing them to be less permeable to water and water-soluble drugs. The keratinized layer also contains membrane-coating granules, which are lipid-rich and densely packed in the oral mucosa. It provides resistance from foreign agents and may cause difficulty in microneedle application, diffusion, and release.[132] From a biophysical standpoint, this lipid-dominant microstructure acts as a physical and chemical barrier that resists the penetration of both hydrophilic and large molecular-weight compounds. The high lipid order and dense protein-lipid interactions create a tortuous diffusion pathway, effectively blocking the entry of foreign agents and reducing overall permeability. To overcome this, strategies such as chemical permeation enhancers, tip-functionalized microneedles, or mechanical vibration-assisted insertion may be proposed to transiently disrupt lipid packing and improve drug flux without causing mucosal damage.

7. Future perspectives and way forward

Microneedles have already been designed and explored for therapeutic delivery, diagnosis, vaccine development and anesthesia administration, proving to be a robust and versatile system. There is already multiple microneedle systems used to detect cancer biomarkers developed in the past decade.[123] Microneedles need to be further investigated for various biomarkers detection in oral cancer diagnosis, providing a non-invasive, reliable, and easy-to-use method for cancer prevention. Microneedles have also been engineered to be integrated with electronic patches for accurate and timely dose delivery of chemotherapeutics using smartphone integration, improving patient compliance and automating the treatment process especially for geriatric patients.[133] Stimuli-responsive microneedles are designed to deliver dugs based on specific pH, enzyme, or temperature changes. They adapt to the various changes of the tumor microenvironment, facilitating drug delivery. They can also be employed to deliver targeted drugs to mitigate oral cancer.[134]

Various breakthroughs and integration of microneedles with smart electronic biosensing platforms are revolutionizing non-invasive cancer diagnosis and detection. Lab-on-the-needles is a revolutionary approach that utilizes a microneedle patch-based sensing box, which samples biomarkers from the epidermis for immediate testing. It provides rapid assessment of cytokine levels, has higher detection limits than currently available tests, and can be employed to detect oral cancer biomarkers for early detection.[135]

3D microneedles offer faster design and fabrication than other microneedles with complex geometric shapes. This also facilitates streamlining the manufacturing process and improving regulatory compliance. Due to their flexibility, 3D microneedles are a cost-effective dosage form with the same benefits as traditional microneedles in oral cancer, with faster and reproducible manufacturing, along with higher customization for precision and personalized therapy for oral cancer.[136]

8. Conclusion

Microneedles are a painless, efficient dosage form for oral cancer treatment which have been explored for both monotherapy and combination therapy. They provide minimally invasive drug delivery while reducing side effects or systemic toxicity. Tumor-specific delivery helps improve the quality of life in patients and may help oral cancer patients regain their ability to swallow, speak, and eat. They provide better mechanical stability, penetration, and can be easily self-administered by patients, unlike other transdermal dosage forms. Although microneedles have been thoroughly explored for different cancers, studies regarding microneedle drug release in the buccal mucosa still lack more detailed kinetic studies related to salivary washout and the effect of varying pH within the buccal cavity. To move forward with the clinical translation of oral microneedle devices for cancer treatment, there is a need for more consistency in the evaluation of buccal pharmacokinetics and salivary washout effects. Future studies could benefit from standardized use of validated *ex vivo* models, such as human or porcine buccal tissue, and could include the reporting of quantitative permeation parameters such as flux ($\mu g\ cm^{-2}\ h^{-1}$), permeability coefficients, and drug retention in tissue rather than percentage release. Because of the dynamic nature of the oral environment, the inclusion of simulated salivary flow rates within physiological limits (0.3–2 mL min^{-1}) may also enhance the evaluation of formulation stability, mucoadhesive force, and residence time under shear stress.[137] More regulatory guidance in the evaluation of safety and dosing will help provide more opportunities for microneedles to be pushed into the consumer market.

Author contributions

Souradeep Dutta: writing – original draft, writing – review & editing; Vaibhavi Meghraj Desai: conceptualization, writing – original draft, writing – review & editing; Pragati Ramesh Kumbhar: conceptualization, writing – original draft, writing – review & editing; Bhavini Pahuja: writing – review & editing; Yogesh Khairnar: writing – review & editing; Gautam Singhvi: validation, visualization, conceptualization, supervision.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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