Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(3), 1143-1149 | ISSN:2251-6727

Revolutionizing Oral Cancer Theranostics Through Microneedle Technology: A Comprehensive Insight

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(Received: 04 February 2024 Revised: 11 March 2024 Accepted: 08 April 2024)

KEYWORDS

Microneedle, local drug delivery, oral cancer, hydrogels, tumour micro-environment, hypodermic needles

ABSTRACT:

Microneedles are an intricately designed technology that aids in transdermal therapy where vaccines, drug molecules, genes, antibodies and protein compounds can be delivered locally to a part of tissue. They are highly beneficial in disease diagnostics as they are simple to use, can be self-administered, non-invasive, heal faster and provide painless treatment especially in disease conditions like cancers. Animal and human trials that explore the use of microneedle in other anatomical sites like the oral mucosa are limited. The oral mucosa houses a complex barrier mechanism with numerous commensal microbiomes that regulate the immune mechanism locally. Disease conditions like oral dysplasia affect the entire epithelial cell component and so drug delivery has to penetrate deep below the epithelial layers into the underlying connective tissue with minimal loss of drug along the path delivery. Microneedles are designed with a blend of hypodermic needles laid out on transdermal patches with a height ranging from 25 to 2,000 um and an external diameter of 30 um. Microneedles have been tested for their efficiency in drug delivery for oral cancer in a number of in vitro and in vivo studies and they have provided effective drug deposition with reduction in the tumorigenic potential. Microneedles also can be used in disease detection when they are fabricated as a biosensor. The current review explores the microneedle technology, its types, methods of fabrication, and their applications in oral cancer theranostics.

1. Introduction

The concept of using microneedle technology for transdermal drug delivery was proposed by Pistor in the 1970s. Since then, numerous improvements have occurred in fabrication methods, types of microneedles and their structural configuration. Microneedles are an intricately designed technology that aids in transdermal therapy where vaccines, drug molecules, genes, antibodies and protein compounds can be delivered locally to a part of the tissue. Microneedle therapy consists of the fabrication of a patch with small, micron-sized needles attached to it. They have been recently explored in cancer therapy where chemotherapeutic agents are loaded in them thus offering patients a painless, non-invasive therapy that overcomes various limitations of conventional treatments. Microneedles are highly beneficial in disease diagnostics apart from enabling local drug delivery. (1) They are simple to use, can be self-administered, non-invasive, heal faster and provide painless treatment, especially in disease conditions like cancers. They are employed as alternatives to hypodermic needles as they can deliver a wide range of drug molecules, and gene components to the dermal and subcutaneous layers. (2) Different structural changes have been incorporated into these microneedles to enhance their drug delivery potential with maximum permeation of macro and micro molecules. Earlier researchers have explored the use of microneedles in transdermal routes only. However, the successful use of microneedles as vaccine delivery devices has prompted researchers worldwide to explore their role in non-dermal sites too.

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JCHR (2024) 14(3), 1143-1149 | ISSN:2251-6727

The oral cavity is one of the most exposed anatomical parts to xenobiotics. The oral mucosa exhibits a defence mechanism with its complex mechanical and microbial immune barrier. It is resistant to foreign bodies and enables only limited drug permeation. (3) However, the concept of using oral mucosa as a delivery site for systemic therapeutics has been explored from time to time. For example, the delivery of nicotine through the oral mucosa for smoking cessation and the delivery of prochlorperazine for the management of nausea and vomiting has been in vogue for several years. Since certain adjuvants and vaccine antigens are macromolecular with highly water soluble, they are unable to traverse the lipid barrier of the oral mucosa efficiently. Reversible disruption of the oral mucosa is one strategy that is employed in oral mucosal vaccine delivery. (4) With the development of nanodevices and innovative fabrication technologies, microneedle devices targeting oral cancers at the cellular level are considered safe, biocompatible and non-invasive. Studies in stomatology have shown significant results in anti-tumoral therapy executed through microneedles for oral cancers and further research in nanomaterial fabrication will emerge as a promising therapeutic option for the management of oral cancers.

Oral mucosa anatomy and Drug Penetration:

Microneedle drug delivery through the transdermal route is a robust and proven route that offers site-specific, targeted drug delivery for different diseases inclusive of cancer. Animal and human trials that explore the use of microneedles in other anatomical sites like the oral mucosa are limited. The oral mucosa houses a complex barrier mechanism with numerous commensal microbiomes that regulate the immune mechanism locally. The permeability factor of the oral mucosa depends on the lipid content in the upper layers of the epithelium. Below the epithelium, the suprabasal cells differentiate forming desmosome junctions with membrane-coating granules at their apical surfaces. (5) Kulkarni et al in 2009 demonstrated in their research that the epithelium and its components of the oral mucosa is the major permeability barrier. He also proved that the connective tissue provides some resistance to lipophilic materials as there is a high level of hydration in it. (6) Drug permeation across the oral epithelium is also limited by other parameters like the superficial mucus, luminally secreted and membrane-bound enzymes which cover the underlying lamina propria and deeper epithelial tissue layers. The mucus that binds to the external epithelium has a hydrogel type of structure possessing 83% water with inorganic compounds, carbohydrates, proteins and lipids. The main component of mucus is mucin which is produced by the Goblet cells of the epithelium. This mucus barrier decreases permeation of macromolecular drugs across the oral mucosal layer and it may contribute to degradation and potentially alter the concentration of drugs. (7)

Disease conditions like oral dysplasia affect the entire epithelial cell component so drug delivery has to penetrate deep below the epithelial layers into the underlying connective tissue with minimal loss of drug along the path of delivery. Microneedles are designed with a blend of hypodermic needles laid out on transdermal patches with a height ranging from 25 to 2,000 um and an external diameter of 30 um. They are created utilizing materials like metal, polymer, silicon, ceramics, titanium, glass, and sugar-like carbohydrates. They have been evaluated for their permeability in previous studies against the oral mucosa and the results have been impressive. Ma and colleagues in 2015 gave a proof of concept based on the use of microneedles coated with doxorubicin hydrochloride loaded Poly lactide co-glycolic acid (DOX-PLGA) nanoparticles against oral cancer in 3D tissue phantoms and porcine cadaver buccal tissues. The researchers stated that DOX upon release from nanoparticles rapidly diffused into the tissues and produced the required cellular toxicity and death. (8) Other studies have also stated that microneedles have demonstrated significant promise in the therapeutic management of oral cancer by their ability to facilitate precise and regulated administration of pharmaceutical agents to the malignant area within the oral cavity.

Types of Microneedles:

Microneedles comprise of few hundred micrometres squares of micro projections that resemble a honeycomb-like structure. Each projection has a dimension of 500-900 µm length, 50–250 µm wide and 1–25 µm thickness. Microneedles are classified as solid, coated, porous, dissolving type and hydrogel-forming type. (Table 1) Each of the microneedle types has a unique configuration with a unique fabrication technique which delivers the

Journal of Chemical Health Risks

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JCHR (2024) 14(3), 1143-1149 | ISSN:2251-6727

drug through a unique mechanism. Solid microneedles comprise two components embedded with a poke and patch mechanism. The first component engages in the application of the microneedle array for the opening of microscopic pores in the skin and the second component delivers the drug. Solid microneedles can deliver drugs prepared in various formulations like topical cream, gel, solution and patches. The solid microneedles penetrate the skin thus creating a series of channels that allow the drug molecules to traverse the stratum corneum layer and enter the blood capillaries to provide a systemic effect. (9)

Coated microneedles are designed to function by a coat-and-poke approach and these aid in the rapid dissolution of the coating layer of the needles. Sometimes hollow microneedles are designed to function as coated microneedles. These hollow needles have a hollow core within them with an aperture at the tip that acts as microfluidic channels. These channels disrupt the dermal layers of the skin and deliver the drug molecules through the poke-and-flow technique. The thickness of the coated solution over the needles is determined by the dosage of a drug that needs to be delivered. One of the major advantages of using hollow microneedles is rapid and sustained drug delivery. Coated microneedles performed better in previous studies as they can deliver drug molecules precisely and local tissues without drug loss or systemic side effects that can be caused due to injection fluid leakage.

Dissolving microneedles is a recently developed technology which is based on polymeric needles having a poke and release mechanism. These dissolving microneedles dissolve in body fluids like blood and they deliver the drug without leaving any residue on the skin or mucosa. Hydrogel-based microneedles are the most recently evolved type that are designed based on a poke and swell approach. They are fabricated using elaborate techniques comprising of cross-linking of polymers that have a high affinity towards water and thus swell up. The main advantage of using a hydrogel-based microneedle is the ability to deliver large doses of drugs without any drug losses. (10) Different geometric configurations like arrowheads, angled microneedles, honeycomb patterns etc., can be developed. Factors like aspect ratio, height, basal diameter, patch size and area, and needle spacing play an important role in determining the result. A high level of uniformity is needed for high throughput fabrication. This is because the skin and the mucosal layers have a certain amount of tensile strength that resists microneedles and thus these needles should have a certain degree of mechanical strength that enables effective skin penetration without breakages. Materials that have proved to be highly efficient as microneedles are microelectromechanical systems (MEMS). Other options are silicon, glass, ceramics, titanium, aluminium, etc., Biodegradable options like polymers, and hydrogels with the incorporation of 3D fabrication technology have been explored by many researchers recently. (11)

Mechanism of Fabrication:

There are many techniques of fabrication employed in manufacturing the microneedles. Each technique guarantees a specific set of outcomes depending on which microneedle can be utilized. Solid microneedles are synthesized using laser ablation, 3D printing, dry and wet etching, electroplating and micro-moulding. Coated microneedles are developed from solid microneedles which are rolled, dipped or sprayed. Hollow microneedles can be developed by micropipette pulling, isotropic or reactive ion etching, wet chemical etching, and laser micromachining etc., Dissolvable microneedles are fabricated by negative moulding. The drug-releasing potency differs based on the type of microneedles and their synthesizing process. The versatile platform of different types of microneedles holds promise for medication delivery, as they are intended to transport both big and small medicinal molecules, heavy protein molecules, genes, antibodies, and nanoparticles. (12)

Microneedles in Oral cancer Therapy and Diagnosis:

Though the microneedle technology was developed and patented in the 1970s, sufficient research in the field was missing due to the lack of engineering methods and lack of material science. In the 21st century, there has been a boom in research works based on microneedle arrays, especially in the tumour microenvironment. (Table 2) Lan et al developed a microneedle-mediated transdermal delivery system loaded with lipid-coated cisplatin nanoparticles. There was enhanced drug solubility with an apoptotic index of 58.6% and high cytotoxicity in tumour cells. Personal disease trackers like biosensors are developed using microneedle arrays using which

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JCHR (2024) 14(3), 1143-1149 | ISSN:2251-6727

cancer biomarkers like nitric oxide, tyrosine kinase, and vascular endothelial growth factor can be detected using electrochemical sensors. There is overexpression of nitric oxide synthase in the early stages of cancer as it promotes angiogenesis in the cancer cells. The disease progression can be detected using microneedle arrays working as biosensors and their diagnostic property has been tested in several animal models and clinical trials. (13)

A relatively new systemic therapy option that has emerged in the treatment of advanced HNSCC is immunotherapy using immune checkpoint inhibitors (ICIs) like anti-PD-1 and anti-CTLA-4 antibodies etc., The anti-tumour activity of these agents demonstrated in clinical trials has paved the way for numerous researchers to consider ICI therapy worldwide. However, it is interesting to note that the administration of ICI through a microneedle array has been successful in several trials. In a previous study done by Gilardi et al, local drug delivery using soluble microneedles was used in tobacco signature murine head and neck squamous cell carcinoma models. The researchers state that both systemic and local anti-CTLA-4 therapy through microneedles showed >90% tumour response in the tumour microenvironment. This tumour response can be attributed to the fact that microneedles stimulate the local immune response by administering the drugs near neutrophils, Langerhans, dendritic cells and other cellular components that are seen deep within the skin and mucosa. (14) Manimaran et al in 2023 fabricated a photosensitizer-loaded dissolvable microneedle patch for photodynamic therapy in oral carcinoma. The photosensitizer studied was indocyanine green (ICG). The microneedle patch was made using sodium carboxymethyl cellulose and sodium alginate and the same was evaluated in porcine buccal mucosa. The technique achieved a penetration of 300 µm within the buccal mucosa and led to a decrease in the tumour volume. (15) Microneedle-based systems have robust technical abilities that work effectively when used for photodynamic therapy, immunotherapy, photothermal therapies and other treatments against tumoral cells. The safety profile and drug effectiveness derived from using microneedles have been evaluated in several studies. Xu et al in 2021 stated that when microneedles are coated with drug-loaded nanoparticles, regulated and sustained drug delivery is possible. Several authors state that utilizing microneedles in antitumoral therapy provides accurate deposition of drug concentrations through spatial and temporal manipulation of drug release mechanisms. The adverse effects on the surrounding healthy cellular environment are kept very minimal. (16)

Chemotherapy is a novel treatment strategy that uses endogenously abundant hydrogen peroxide in a tumour environment that kills cancer cells by producing toxic hydroxyl radicals through the "Fenton reaction". Zhao et al in 2023 developed a polyvinyl alcohol (PVA) based microneedle patch loaded with FE3O4 nanoparticles and vitamin C for treatment against oral squamous cell carcinoma in mice. The study proved good in vitro solubility, puncture ability and drug release resulting in high anti-tumoral activity. (17) Another study was conducted by Matta et al in which a dissolvable microneedle matrix array was developed using sodium carboxymethyl cellulose, sodium alginate and PEG 400 composite. This patch was evaluated for its mechanical and chemical properties after which 5-fluorouracil (5 FU) was delivered in tumour-induced porcine buccal mucosa. Results were satisfactory and the authors stated that dissolvable microneedle patches are effective in localized drug delivery of chemotherapeutic agents to treat oral carcinoma. (18)

The use of microneedles in anti-cancer therapy presents with several benefits, including greater therapeutic efficacy, minimal side effects, and improved patient adherence. Hydrogel-forming microneedles have proved to be one of the best options for tumoral drug delivery owing to their ability to penetrate the stratum corneum, secure tissue adhesion and enable transmucosal drug delivery. Polymers like polyvinyl alcohol and polyvinyl pyrrolidone are crosslinked with tartaric acid and its derivatives for incorporating therapeutic agents. Biodegradable hydrogels like gelatin methacryloyl and hyaluronic acid hydrogels are currently being explored for their non-toxic and degradable nature. Microneedle patches especially in painful conditions like oral cancer can offer painless drug delivery with non-invasive, self-administering options for patients thus increasing patient compliance. (19) More research in this domain is needed to harness the potential of microneedle technology for treating oral cancer, as well as to assess its effectiveness in clinical environments.

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JCHR (2024) 14(3), 1143-1149 | ISSN:2251-6727

Conclusion:

The microneedle delivery platform has high diagnostic and therapeutic advantages over conventional methods or controls, including improved tumour screening and visualization, precise tumour targeting and reduced toxicity to the surrounding non-cancerous tissues. Microneedles improve drug solubility and maximize distribution leading to better absorption and uptake in the tumour microenvironment. Though there is high potential in this technology, there is only limited research in treating oral cancer. Modern drug delivery technologies are not fully utilized as treatment modalities for oral cancer and this demands the need for future research and exploration in this intriguing area. There is constant research in the field of nanomedicine and oncology that promises to transform oral cancer care providing precise, efficient, patient-centric therapeutic interventions.

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Table 1: Types of Microneedles

Sno	Type	Fabrication Method	Advantages
1.	Solid	Micro molding, Wet etching, lithography, metal injection molding, laser machining	Good drug loading, mechanical strength, physical stability
2.	Coated	Micromolding (thermal), centrifugal lithography	Mechanical strength
3.	Hollow	Deep reactive ion etching	Accurate dose and constant flow rate
4.	Dissolving	Micro molding, droplet born air blowing, centrifugal lithography	Low-cost production, controlled drug release
5.	Hydrogels	Photolithography, micro molding, casting, electrospinning	No residue after application, controlled drug release and reasonable drug loading possible

Table 2: Brief summary of recent in-vitro and in-vivo studies done using microneedle technology

Sno	Microneedle	Therapeutic agent	Type of Array	Type of study	Type of cancer	Name of cell line	Animal Model	Reference
1	Dissolvable microneedle	Anti-CTLA 4-antibody. CD-8 depletion antibody	Polyvinylpyrrolidone (PVP) polymeric matrix	In vivo	Head and neck squamous cell carcinoma	tobacco-signature murine HNSCC	Mouse model	Gilardi et al, 2022
2	Dissolvable microneedle	Fe3O4 nanoparticles (NPs) and vitamin C (VC)	polyvinyl alcohol (PVA)-based	In vitro	Oral squamous cell carcinoma	HUVECs and HN30 cells	-	Zhao et al, 2023
3	Dissolvable microneedle	curcumin nanodrugs (Cur-NDs) and	Hyaluronic acid microneedle	In vitro	Human tongue squamous	Human tongue squamous	-	Xi et al, 2022

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		photothermal trigger agent new indocyanine green (IR820)			carcinoma cells	carcinoma cells		
4	Dissolvable microneedle	5-fluorouracil (5FU)	Sodium carboxymethyl cellulose, sodium alginate, and PEG 400 based array	In vitro	Oral squamous cell carcinoma	Porcine buccal mucosa	-	Matta et al, 2023
5	Mucoadhesive microneedle patch	Triamcinolone	Polydimethylsiloxane microneedle	In vitro	Oral submucous fibrosis	mouse embryonic fibroblastic cell line	-	Cheng et al, 2023