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Review

Smart Nanocarriers as a Targeted Drug Delivery Platform for Oral Cancer Therapy: A Review of Recent Advances

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Abstract:
Nanoparticle-based smart nanocarriers are promising platforms for enhancing the therapeutic index in oral squamous cell carcinoma (OSCC). These systems are designed to detect tumour-specific signals and respond to various internal or external stimuli. The outcomes of late-stage diagnosis, high recurrence rates, and adverse effects of traditional therapy all continue to cause OSCC to induce high morbidity and mortality throughout the world. The reduced tumour selectivity, systemic toxicity, short circulation times and resistance to multiple drugs limit the activity of conventional chemotherapeutic regimens. We have recapitulated recent innovations in the ligand-directed and stimulus-responsive nanocarrier systems in OSCC, outlined tumour-microenvironmental features that could be used to obtain site-selective release, and examined preclinical data that support the key nanoparticle platforms, such as lipid, polymeric, inorganic, and biological carriers. Translational challenges, including scale-up of manufacturing, regulatory issues, and safety concerns, and suggested feasible strategies to speed clinical translation have also been discussed.

Keywords: Smart Nanocarriers; Oral Cancer; Active Targeting; Targeted Drug Delivery.

1. INTRODUCTION

1.1 Burden of Oral Cancer

OSCC is the most common oral cavity malignancy, occupying over 90% of all the tumors cases in the region [1-3]. Although there is some advancement with respect to therapy, OSCC has still been linked to high morbidity and mortality rates mainly due to the prevalence of many patients with the disease at an advanced stage of the disease. The high global incidence of it is caused by established risk factors including tobacco consumption, alcohol overuse, chewing on betel-quids, and HPV infection. The result of the treatment is often very severe functional dysfunctions – speech, swallowing, and facial expression difficulties- indicating that more sophisticated forms of therapy are necessary [1]. Treatment often involves extensive surgery and radiotherapy, resulting in functional impairment, disfigurement, and reduced quality of life [18].

1.2 Limitations:

Existing treatment regimens are limited by many acute limitations. There is no tumour selectivity of chemotherapeutic drugs, which promotes the extensive toxicity of non-tumour tissues and dose-limiting side effects [4,7]. In addition, most anticancer therapies have a limited half-life of circulation, low solubility and no or low concentration in tumour tissue. Another effect reducing the outcomes is the ability of MDR to allow the tumour cells to respond to drug-induced cytotoxicity through overexpression of efflux pumps and increased DNA repair pathways. Many chemotherapeutic agents also suffer from poor bioavailability, rapid clearance, and multi-drug resistance (MDR), limiting their efficacy [17].

1.3 The Revolution in Nanomedicine: A New Strategy.

Nanotechnology provides to a large extent, the versatile platforms which can solve most of these limitations. Nanocarriers, such as liposomes, polymeric nanoparticles, dendrimers, micelles and inorganic nanomaterials, enhance the stability of drugs, controlled and sustained release, and tumour accumulation with passive or ligand-based targeting [7, 10]. These systems will offer a significant paradigm change in the treatment of OSCC by improving the efficiency of the delivery system as well as minimizing systemic toxicity.

1.4 Scope and Aim of This Review

Based on these ideas, this review has narrowed down to smart nanocarriers, which portray stimulus-responsive behaviour, and targeted systems, which can identify OSCC-related molecular targeting. We give a systematic review of the OSCC TME, focusing on strategies, stimuli induced mechanisms, leading nanocarrier platforms, pre-clinical evidence, and critical issues connected to clinical translation. The aim is to summarise what is already known and point out the areas of potential and lack of opportunity in OSCC nanotherapy [1,4,6].

2. UNDERSTANDING ORAL CANCER TUMOUR MICROENVIRONMENT (TME).

2.1 Physiological Barriers

There are many physical barriers to successful drug delivery in the OSCC microenvironment. Thickness and fibrosis of the ECM, along with an increase in interstitial fluid pressure, inhibit the penetration of the nanoparticles and interfere with the diffusion of the drug [12,13]. These abnormalities of structure cause tremendous resistance to traditional transport of the chemotherapeutic. It is also characterised by chemical triggers (acidic pH, hypoxia), biochemical triggers (overexpressed MMPs, high glutathione levels), and vascular abnormalities that enable passive targeting via the EPR effect [21].

2.2 Chemical Triggers

The characteristic chemical gradients are frequently seen in OSCC lesions. The pH of the extracellular space is slightly acidic due to increased glycolysis and insufficient perfusion and hypoxic areas occur due to the disrupted vascular networks [8,12]. These are the desirable features of pH-responsive and hypoxia-activated nanocarriers which have been used in the release of drugs selectively in tumour tissue.

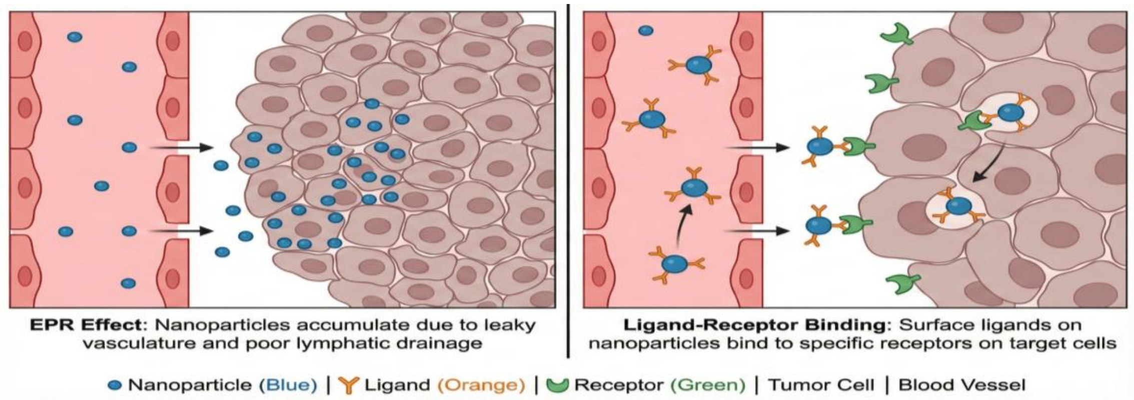
2.3 Biochemical Triggers

The biochemical character of OSCC high protein proteolytic enzymes (MMP-2, MMP-9) that are essential to invasiveness and metastasis are expressed. Also, cancerous cells are characterized by an increase in the level of GSH intracellularly, which provides a reducing environment that facilitates the activation of redox-reactive nanocarriers [3,8,13]. These stimuli allow the nanocarriers to be designed specifically to be stable in the circulation but collapse or land the drugs when internalised by the tumour cells.

2.4 Vascular Abnormalities and the EPR Effect.

OSCC vasculature is usually anomalous and leaky, which contributes to the increased extravasation of nanoparticles through the so-called Enhanced Permeability and Retention (EPR) effect [2,7]. Nevertheless, the EPR effect size is not universal across patients and locations of tumours, but the necessity of active targeting interventions encourages this trend.

3. TARGETING STRATEGIES FOR ORAL CANCER



EPR Effect: Nanoparticles accumulate due to leaky vasculature and poor lymphatic drainage

Ligand-Receptor Binding: Surface ligands on nanoparticles bind to specific receptors on target cells

Figure representing passive and active targeting respectively

3.1 *Passive Targeting*

Passive targeting is based more on the EPR effect, whereby nanoparticles of the correct size and properties on its surface preferential accumulation in tumour tissue can be achieved without ligand modification [2,9]. PEGylation is widely used to increase circulation length and passive uptake. Passive targeting exploits the leaky vasculature and impaired lymphatic drainage of tumours to accumulate nanocarriers via the EPR effect [20].

3.2 *Active Targeting*

Active targeting increases selectivity, such that ligands that bind specific receptors that are overexpressed on OSCC cells are attached.

- *EGFR Targeting*

EGFR is actively expressed in the OSCC being among the consequential preferential receptors. During the tumour internalisation, nanocarriers conjugated with the EGFR-specific antibodies or peptides, significantly enhance the internalisation of the nanocarrier by the tumour [1,4].

- *CD44 Targeting*

OSCC has cancer stem cell populations that are linked with CD44. Targeting using hyaluronic acid has been demonstrated to have increased penetration and selectivity of these CD44-rich populations [3,7].

- *Folate Receptor Targeting*

Folic acid is also commonly used as a ligand because of its simplicity and high binding ability of the folate receptors that are expressed in a number of different OSCC types [9,14,29].

- *Filtering of Transferrin Receptor*

The need of the cancer cells for iron, which is high due to their high metabolism rates justifies the efficacy of transferrin-functionalised nanocarriers, which have the advantage of effective absorption in OSCC tissues [13,19].

- *Emerging Targeting Ligands*

New targets, including c-Met and PD-L1, are emerging and can aid even more advances in precision nanomedicine [6, 10].

4. SMART DELIVERY: STIMULI-RESPONSIVE NANOCARRIER.

4.1 Internal Stimuli

- *pH-Responsive System*

SMART carriers, which include acid-labile linkers or polymers that are sensitive to protons, react to the acidic OSCC environment to enable the release of sites to occur [8,12].

- *Redox-Responsive Systems*

Disulfide-conjugated nanocarriers are also stable in an extracellular environment, but fast to release their cargo in GSH-rich tumour cells [3,7].

- *Enzyme-Responsive Systems*

The MMP cleavable peptide sequences allow non-carriers to utilize higher protease expression in OSCC to promote increased drug targeting [8,12].

4.2 **External Stimuli**

- *Light-Responsive Nanocarriers*

These are photodynamic and photothermal systems, again particularly convenient due to the accessibility of OSCC tumours to the surface [4,10].

- *Ultrasound-Responsive*

Focused ultrasound induces carrier disruption [22].

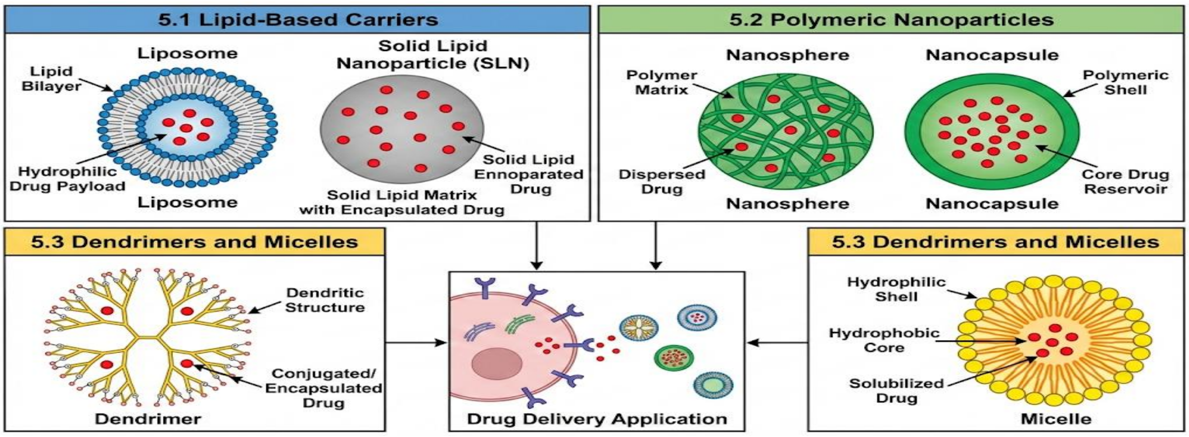
- *Thermo-Magnetic-Responsive Systems.*

These carriers have spatial and temporal control over drug release, and incorporate imaging or hyperthermia effects to enhance their therapeutic effects [6-8, 13].

5. SMART NANOCARRIER PLATFORMS AND PRECLINICAL EVIDENCE

What are “SMART” nanocarriers?

Smart nanocarriers are nanoparticulate delivery vehicles (usually 10-500 nm) engineered to respond to particular biochemical or physical stimuli to obtain controlled delivery of drugs. They overcome the drawbacks of the traditional nanocarriers like premature discharging of drugs, nonspecific dispersion, and resistance to multiple drugs; they permit controlled delivery via enhanced permeability and retention, or active targeting (EPR) effects [1].



5.1 Lipid-Based Carriers

Lipid-based carriers are better biocompatible, controlled, and have greater targeting ligand compatibility, e.g., liposomes, SLNs, and NLCs. Functionalised liposomes have also been reported to have great antitumour activity in models of OSCC [1,4,5].

5.2 Polymeric Nanoparticles

Controlled drug release, mucoadhesion, and enhanced cellular uptake are achieved in polymeric nanocarriers that include PLGA and chitosan nanoparticles [2,3,12].

5.3 Dendrimers and Micelles

These nanosystems permit multivariate adjustment and dual or stimuli-reactant discharge with fantastic accuracy [7,14].

5.4 Inorganic Nanoparticles

A significant improvement in photothermal therapy is the use of gold nanoparticles. Now we are witnessing a massive increase in effectiveness. Silica and magnetic nanoparticles, on the other hand, are useful as they assist in imaging and treatment simultaneously [4,6,13]. Gold and silica nanoparticles serve as effective platforms for PTT/PDT and theranostic applications in oral cancer [23].

5.5 Emerging Platforms

AI-generated nanocarriers, exosomes, and nanogels sound promising as an emerging platform for the therapy. They are biocompatible, strike at a target with much precision, and their design can be modified to fit various application requirements [10,16].

6. DIFFICULTIES AND FUTURE PROSPECTS.

6.1 Challenges

The transition process between the lab and the real clinical environment is no simple task. We face issues dependent on the mouth cavity, concerns on long-term safety, limits on expanding complicated nanostructures, tumor heterogeneity, and regularly shifting regulatory policies that keep us on our toes [5-12,14,15].

6.2 Future Directions

Personalised nanomedicine, which includes carrier design based on patient-specific tumor biomarkers [24]. Combination therapy, theranostic nanocarriers performing imaging and treatment in a single category, and AI-coded adjustments to make nanoparticles smarter and more efficient are the hot topics out there [3,6,10,16].

CONCLUSION

Targeted delivery and smart activation are brought together by Smart nanocarriers, and thus OSCC therapy will have a sophisticated advantage. Although the preclinical evidence is promising, their popular implementation will require us to deal with biological, manufacturing, and regulatory complexities. These Smart nanocarriers have the potential to completely change the approach towards the treatment of oral cancer with further interdisciplinary studies and technological advancements [1-16]. Smart nanocarriers represent a paradigm shift in oral cancer therapy, enabling precise targeting and controlled drug release [25]. Preclinical studies demonstrate enhanced efficacy and reduced toxicity, yet significant translational challenges persist [26]. Interdisciplinary collaboration and continued innovation are essential to bridge the gap from bench to bedside [27]. With advances in personalised design, theranostics, and AI, smart nanomedicines hold great promise for revolutionising OSCC treatment [28].

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