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Application of nanocarrier-based drug delivery system in treatment of oral cancer

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ABSTRACT

Oral cancer includes cancer of lips, oral cavity and oropharynx. Oral cancer is the sixth most life-threatening disease affecting 65% of population. The delivery of cytotoxic chemotherapeutic anticancer drugs is a challenging task due to unfavorable properties. Both synthetic chemotherapeutic agents and herbal constituents are used in treatment of oral cancer. The purpose of present article is to overcome the limitations through concept of nanotechnology and conjugation approach. Also, it will provide better therapeutic effect and sustain long life of healthy and recovered cells. Moreover, development in this area will raise opportunities for the oncologist, researchers and pharmaceutical scientists. This review summarizes the clinical findings and patents on various oral anticancer drugs for effective pharmacotherapeutics.

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KEYWORDS
Oral cancer; nanotechnology; oropharyngeal cancer; conjugation; targeted delivery

Introduction

In most of the developing countries, oral cancer is one of the major causes of increasing mortality. Not only men but women's also suffers from oral cancer with a higher risk. This is due to the increasing addictive habits and several cultural and geographical factors. Oral cancer includes cancer of lips, oral cavity and oropharynx. From 2005, every year, an article is published about the facts of oral cancer, its prevalence, mortality rate and prevention aspects. This shows that there is an alarming need to think and act on oral cancer and its scenario [1].

Oral and pharyngeal cancer is the sixth or seventh most prevalent cancer throughout the world. The global epidemiology of oral malignancies/cancers/tumors is discussed in brief by Warnakulasuriya et al. (2009) [1]. Most of the oral cancers (≥90%) originating in the tissues that line the mouth and lips and thus are oral squamous cell carcinoma (OSCC). They look very similar under the microscope and are malignant type which tends to spread rapidly. These oral malignancies are heterogeneous in nature and arise in various parts of the oral cavity due to predisposing factors, prevalence and treatment outcomes. Of all the oral cancers, cancer of lips and oral cavity are preventable [2].

Primary oral cancer is finally turned into second primary cancer of aerodigestive tract (oral cavity, pharynx and esophagus). The countries which are at higher risk of oral cancer include India, Pakistan, Bangladesh, South Africa, Asia, Thailand, Canada and Australia. In India, Chennai, Gorakhpur and Uttar Pradesh are more prone to risk of oral carcinomas, malignancies and tumors.

There are several agencies working for the prevention, care and treatment of oral cancer throughout the world [3]. Some of these are:

- National Institute for Clinical Excellence (NICE), UK,
- International Agency for Research on Cancer,
- National Institute of Health and the American Dental Association, and
- WHO Global Oral Health Programme.

Causes of oral cancer

The causes of oral cancer are well-known. It occurs mainly due to lack of hygienic conditions, consumption of tobacco and related products, alcohol consumption, certain hormonal factor and infectious agents. Awareness about drawbacks of addictive substances, educating the illiterate persons is a mandatory requirement at broader level to combat and decrease the prevalence of oral cancer in society [4].

Human papilloma virus (HPV) mainly type 16 and type 18 are known risk factors and independent causative factor for oral cancer. This is causing not only huge impact on the health of the community but also the economy of the countries. The distribution of oral cancer in the oral cavity is shown in Figure 1.

Percentage statistics and prevalence of oral cancer

Globally, India is at the highest to report prevalence of oral cancers. Every year 75,000–80,000 new cases of oral cancer

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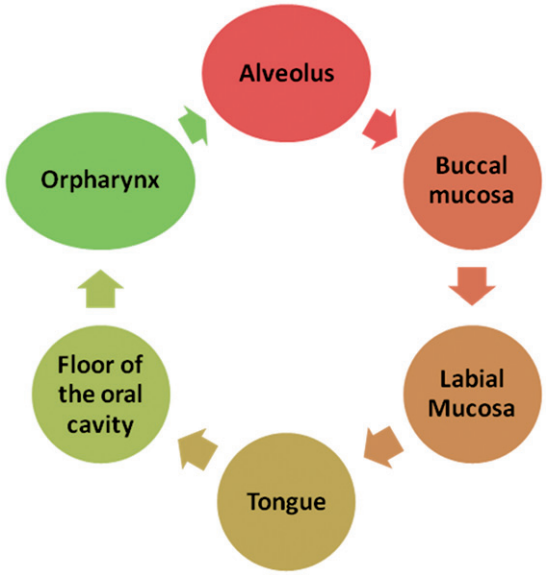


Figure 1. Distribution of oral cancer in oral cavity.

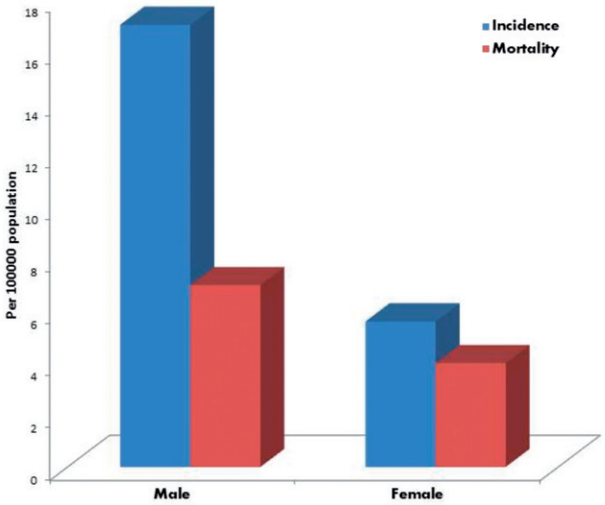


Figure 2. Incidence and mortality of oral cancer in India.

are reported. In India, 95% of the oral cancers are squamous cell carcinoma (Figure 2). According to the International Agency for Research on Cancer; the incidence of cases of oral cancer will reach more than 1.7 million in 2035. Oral Cancer is the eighth most common cancer in the world, with the highest prevalence among men. In developing countries, the incidence of oral cancer is 107,700 in males and the estimated deaths are 61,500.

Drug used for treatment of oral cancer

Both synthetic chemotherapeutic agents and herbal constituents are used in treatment of oral cancer. The synthetic drugs are administered either alone or in combination with other drugs. Some of the cytotoxic anticancer agents used in oral cancer and their marketed preparation are depicted in Table 1.

Biomarkers used in oral cancer

Although oral cavity is easy for diagnosis through visual inspection, but by this it is not possible to detect oral cancer. Thus, salivary biomarkers are used for detection. Collecting saliva is relatively easy and non-invasive as compared to the collection of blood from patient's body. These biomarkers can be small molecules or large molecules. Till today, more than 120 salivary biomarkers used for detection of oral cancer are reported in literatures. Some of them are listed in Table 2.

Oral delivery of cytotoxic drugs for treatment of oral cancer

Oral route is the most preferred route for delivery of medicaments to the body. The advantages of oral delivery are:

- Improved patient compliance
- Facilitates prolong exposure of cytotoxic drug
- Suitable for outpatients

The limitations associated with delivery of most of the cytotoxic drugs are poor solubility in aqueous fluid, low apparent permeability and poor bioavailability. To overcome these issues, nanotechnology-based novel drug delivery came into existence. Advantages of nanoparticles-based drug delivery therapy include improved therapeutic benefits, reduces side effects of the drug payloads by improving their pharmacokinetics profile, provides long circulation half-lives, improved permeation and retention effect, drug safety, and patient compliance. These nanocarriers serve as promising candidate and provide unique platform capable of replacing the conventional available chemotherapeutic treatment. In contrast, nanotechnology-based novel drug delivery already offer considerable impact on the field of drug delivery application by improving pharmacokinetics and therapeutic benefits of various drugs. It is expected that nanotechnology-based drug delivery strategies could have a significant relevant positive impact on the field of cancer vaccines [5].

Advancement in novel drug delivery system for oral cancer

Liposomes

Liposomes are concentric vesicles in which an aqueous volume is enclosed by membranous lipid bilayer. They entrap hydrophilic drug in the aqueous phase and hydrophobic drug in the lipid bilayer and retain drugs in route to their destination. Most of the cytotoxic agents are loaded into liposomes for treatment of cancer. Literatures report that cationic liposomes are suitable and efficient for gene delivery in oral cancers. The effect of poly cationic liposomes was investigated on H357 human OSCC cells and successful results were obtained. Moreover, the use of photodynamic therapy mediated by a liposomal formulation is also effective for treatment of chemically induced oral cancer. Earlier liposomes were used as potential carrier for targeted delivery to the pilosebaceous unit but now-a-days PEGylated, conjugated and charged liposomes have proved to be more efficient in treatment of oral cancer [6]. In year 2014 Heber et al. [7], discussed the application of boron neutron capture therapy

Table 1. Chemotherapeutic agents used in treatment of oral cancer.

Name of drug	Category	Route of administration	Marketed preparation
Cetuximab	Monoclonal antibody	Parenteral	Erbitux®
Cisplatin	Platinum containing alkylating agent	Parenteral	Platinol®, Platinol®-AQ
Docetaxel	Anti-mitotic chemotherapeutic agent	Parenteral	Taxotere®
Fluorouracil	Pyrimidine analogue	Topical and parenteral	Adrucil (IV), Carac (topical), Efudex and Efudix (topical)
Methotrexate	Antimetabolites	Oral and parenteral	Methex®

Table 2. Potential salivary biomarkers used for detection of oral cancer.

Type of salivary biomarker	Examples
Inorganic compounds	Na, Ca, F, Mg
Proteins and peptides	α-Amylase, IL-1, IL-6, IL-8, MMP-2, MMP-9, IGF-1, IL-1β
DNA and RNA	P53 gene codon 63, S100P, SAT
Metabolomic compounds	Amino acids-like tyrosine, alanine, serine, valine, phenylalanine
Miscellaneous	Telomerase activity

Na: sodium chloride; Ca: calcium; F: fluorine; Mg: magnesium; IL: interlukine, MMP: matrix metalloproteinase; IGF: immunoglobulin factor; SAT: satellite.

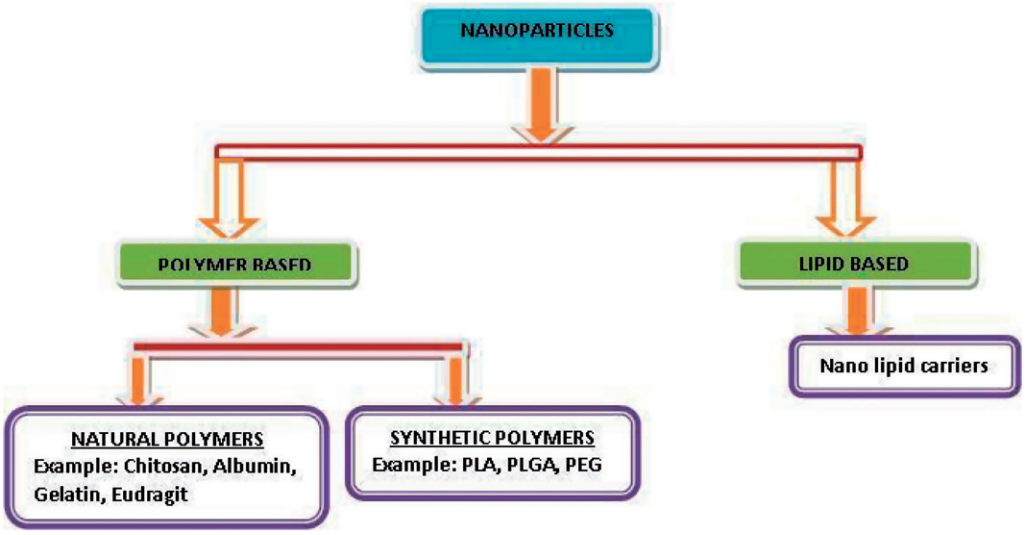


Figure 3. Types of nanoparticles.

(BNCT), which was mediated by liposomes. Liposomes were composed of ^{10}B-enriched polyhedral borane and carborane derivatives and were utilized for the treatment of head and neck cancer using hamster cheek pouch oral cancer model [7].

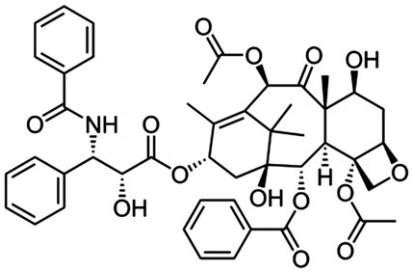
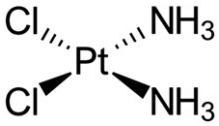
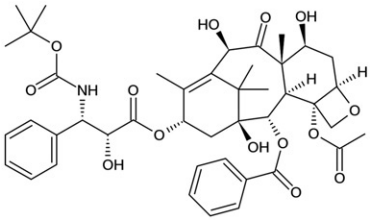
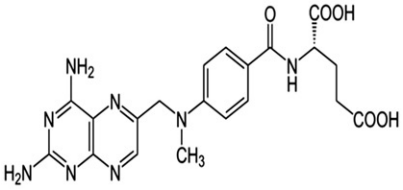
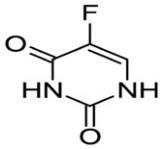
Niosomes

Niosomes are non-ionic surfactant vesicles formed by self-assembly of hydrated surfactant monomers. They have a bilayer structure and can entrap both hydrophilic and lipophilic drugs in aqueous layer and vesicular membrane. Niosomes as drug delivery carriers can overcome the drawback of severe side effects and lesser therapeutic effects associated with antineoplastic agents or with the chemotherapy of cancer [8]. Charged niosomes (negatively charged) of paclitaxel showed slow drug release, enhanced stability, reduced toxic side effects and provided efficient oral delivery [9]. Similarly, 5-fluorouracil was also loaded into niosomes and evaluated for its pharmacological action against actinic keratosis and non-melanoma skin cancer [10]. These drugs are also used in treatment of oral cancer. So, it would be worthy to investigate the potential of niosomes in treatment of oral cancer.

Nanoparticles

Nanoparticles are solid colloidal particles composed of natural, synthetic or semi-synthetic polymers with size ranging from 1 to 1000 nm. Types of nanoparticles are shown in Figure 3. Solid lipid nanoparticles (SLNs) are a class of colloidal carrier system that possesses advantage of easy preparation and cheaply available ingredients for their production. These SLNs have higher dispersibility in water and can provide controlled particle size with an extended drug release. Paclitaxel, a prominent anticancer agent is relatively insoluble in water and is associated with serious toxicities and hypersensitivity reactions [11,12]. To overcome this limitation, Gelderblom et al., 2001 [13], Kloover et al., 2004 [14] and Lu et al., 2007 [15] prepared polymeric nanoparticles of paclitaxel. These polymeric nanoparticles were more efficient as compared to pure drug. Moreover, albumin nanoparticles of paclitaxel have also been prepared and evaluated for anticancer activity [16]. Similarly, polymeric nanoparticles of

Table 3. Examples of various nanocarriers used in oral cancer.

Name of drug and its structure	Polymer	System	Purpose	References
Paclitaxel 	Albumin	SLNs	Improvement of therapeutic efficiency	[27–29]
	Eudragit	Polymeric nanoparticles	Enhanced drug delivery, improvement in pharmacokinetic properties	
	CDs	Polymeric nanoparticles	Increased drug-loading capacity	
	PLGA-PEG	Polymeric nanoparticles	Targeted lymphatic delivery	
		Niosomes	Slow drug release with reduced toxic side effects	
		NLCs	Targeted drug delivery	
Cisplatin 	PEG-poly Glutamic acid copolymer	Polymeric nanoparticles	Treatment of carcinoma	[30]
	Cyclodextrin	Inclusion complex	Increase in solubility, improvement in dissolution rate and reduction of toxicity	
		Dendrimers	Targeted drug delivery	
Docetaxel 	PLA-PEG block polymer	Polymeric nanoparticles	Targeted drug delivery	[31,32]
	CDs	Polymeric nanoparticles	Increased solubility and prolonged release	
Methotrexate 	PLA-PEG block polymer	Polymeric nanoparticles	Enhanced anti-tumor activity	[33,34]
	Cyclodextrin	Inclusion complex	Enhancement of aqueous solubility and bioavailability	
	Cyclodextrin	Niosomes	Increased entrapment efficiency and solubility	
5-Fluorouracil 	PVA	Microspheres	Enhanced anti-tumor activity	[35]
	Cyclodextrin	Inclusion complex	Enhancement of Solubility	

PLGA: poly(lactic-co-glycolic acid); PEG: polyethylene glycol; PLA: polylactic acid; PVA: polyvinyl alcohol.

cisplatin, docetaxel, fluorouracil and methotrexate have been prepared using polymers such as albumin, chitosan, Eudragit and PLGA [17]. However, their potential for oral cancer has not been evaluated. In future, it will be helpful and beneficial to explore the pharmacological activity of these cytotoxic anticancer agents for treatment of oral cancer using *in vitro* and *in vivo* models [18,19].

Nanolipid carriers

Oral formulations such as gel, rinses and injections used for mucosal delivery mainly consist of aqueous vehicle. However, BCS Class II and IV drugs which are associated with poor aqueous solubility can be delivered by nanolipid carriers wherein the lipid-based nanoparticles can penetrate the superficial and deeper layer of connective tissue in the intact normal epithelium of a person suffering from sarcoma and carcinoma of oral cavity [20,21]. The use of lipid-based nanoparticles for controlled delivery of anticancer chemotherapeutic agents allows the enhancement of their therapeutic efficiency. These colloidal drug carriers provides protection against *in vivo* degradation; also the patient's comfort is also increased by avoiding the repetitive bolus injection or the use of perfusion pumps and thus leading to a better drug pharmacokinetics. It has been established that passive targeting of solid neoplasm by systemically drug carriers administration can be achieved if particles has long-circulating properties and adequate particle size for optimal extravasion at tumoral sites, i.e. in the range of 50–200 nm. The limitations of SLNs are overcome for their use in development of delivery system, by nanostructured lipid carriers (NLCs). NLCs are prepared by mixing solid lipids with various chemically

Table 4. Some patents in the area of oral anticancer drugs for oral therapeutics.

Patent number	Assignee	Year	Therapeutic agent	Disease	Invention	Reference
WO2016020697 A1	Cipla Limited, King, Lawrence	2016	–	Cancer	Disclosed the development and composition for polymeric NPs used for the treatment of cancer	[36]
US9393201 B2	JW Pharmaceutical Corporation	2016	Oxaliplatin	Cancer	Investigation disclosed the composition and development method for oxaliplatin-loaded nanoparticle by emulsification method for oral administration	[37]
WO2015023797 A9	Northwestern University	2015	–	Cancer	Reported the NLCs comprising lipid layer with lipoprotein which showed the potential in the drug delivery application for the treatment of cancer, infectious disease, vascular disease	[38]
US20150140109 A1	Unichempharm Ltd, Oy Filana Ltd	2015	Docetaxel	Cancer	Disclosed the therapeutic activity and the composition of docetaxel-loaded biodegradable nanoparticle. It comprising PLGA, serum albumin and D-mannitol for the development of NPs and it suggested for development of enterosoluble tablets, capsules granules, powder, or in any other peroral form.	[39]
US9023395 B2	University of North Texas Health Science Center at Fort Worth	2015	–	Cancer	Disclosed the composition and development method for the polymeric NPs for controlled drug delivery application. It comprising use of biodegradable polymer along with stabilizing agents noncovalently linked with space electrophilic compound which react with nucleophilic agent on the site of action and place the targeting agent on the outside surface of a biodegradable nanocarrier for the effective treatment.	[40]
US 8,911,786 B2	Abraxis Bioscience, LLC, Los Angeles, CA, USA	2014	Rapamycin	Cancer	Disclosed the method of treatment, stabilizing, preventing, and improvement in the treatment of cancer by using rapamycin-loaded NPs.	[41]
US8784895 B2	Northwestern University	2014	Gold, silver, iron oxide	Cancer, bacterial infections	Investigation comprising metallic nanoparticle of 1–100 nm coated with polydopamine. Gold, silver or iron oxide was used as metallic therapeutic agent. Other agents also bound on it such as ligands, antibodies or imaging agents. These NPs revealed the use in the effective treatment of cancer, bacterial infections and as a diagnostic imaging.	[42]
WO2013171382 A1	Oy Filana Ltd	2013	Docetaxel	Cancer	Disclosed the therapeutic activity of docetaxel-loaded NPs comprising PLGA, serum albumin and D-mannitol. The prepared NPs were proposed for development of enterosoluble tablets, capsules granules powder.	[43]
EP2648760 A2	The Johns Hopkins University	2013	Curcumin, doxorubicin	Cancer	Invented the polymeric nanoparticle loaded with curcumin and doxorubicin along with modified shell surface to overcome the multidrug resistance to cancer chemotherapeutics and treatment-related systemic toxicity. The shell surface modification were done by using NIPAAM, AA and one vinyl monomer were chosen from the group of vinyl acetate, 4-vinyl benzoic acid, methylmethacrylate, vinylmethacrylate, N-vinylpyrrolidone, N-vinyl piperidone, N-vinyl caprolacum, N-vinyl carbazole, and styrene. While NIPAAM, the AA, and the vinyl monomer are taken in the molar ratios of 50–70:10–30:10–30. These finding revealed that NPs effectively overcome multidrug resistance and ameliorate cardiomyopathy *in vivo*	[44]
US8242165 B2	Creighton University	2012	Gemcitabine, taxanes, hydrophobic agents	Cancer	Disclosed the composition and preparation method of mucoadhesive NPs. These NPs comprising therapeutic agent along with glyceryl monooleate or monolinoleate (or other mono fatty acid ester)	[45]

(*continued*)

Table 4. Continued

Patent number	Assignee	Year	Therapeutic agent	Disease	Invention	Reference
					and chitosan as a mucoadhesive natural polymer. Investigation also disclosed the technique of pharmacotherapy for breast, pancreatic, colon, prostate, and other cancers by parenterally, or administering such NPs.	
WO2011034394 A2	Choongwae Pharma Corporation	2011	Oxaliplatin	Cancer	Disclosed the oxaliplatin-loaded NPs comprising solid lipid and surfactant missed in cosolvent and removed the solid lipid and cosolvent using supercritical fluid gas technology for oral application in the treatment of cancer	[46]
WO2007108618 A1	–	2007	–	Cancer	Reported the anticancer drug-loaded NPs comprising organic chelating polymer along with biologically active metals for improvement of drug permeation and retention. Results showed that prepared NPs showed promising nanocarrier for cancer therapy along with EPR effect. Additionally, invention disclosed the aqueous soluble organometallic particles with anticancer potential via the EPR effect.	[47]
WO2007086651 A1	–	2007	–	Cancer	Developed drug-loaded hydrophobic bile acid- conjugated hydrophilic chitosan oligosaccharide nanoparticles along with high drug-loading capacity. The result showed that NPs exhibits excellent cytotoxicity potential against cancer cells along with controlled drug-release pattern. The prepared NPs showed potential nanocarrier for cancer chemotherapy.	[48]
CA2513759 A1	The Research Foundation of State University of New York	2004	–	Cancer	Disclosed the method and compositions for photodynamic medication. It comprising therapeutic agent or dye enclapsulated ceramic NPs developed by micellar composition of the dye. Thereafter, it precipitated by using alkaline hydrolysis and these NPs were isolated by dialysis. The prepared NPs were found to be spherical, highly monodispersed and stable in aqueous vehicle. Irradiation with light of suitable wavelength of the photosensitizing drug entrapped inside nanoparticles exhibited the development of singlet oxygen, and these NPs showed potential in the treatment of cancer.	[49]
US005399363A	Eastman Kodak Company, Rochester, NY	1995	–	Cancer	Invented the dispersible particles comprising anticancer drug with surface modifier having particle size <1000 nm. The formulation exhibited improved therapeutics profile with established safety parameters administered via IV bolus injection	[50]

NPs: nanoparticles; NIPAAM: N-isopropylacryl amide; AA: acrylic acid; EPR: enhanced permeation and retention.

different liquid lipids/oils. The advantage of NLCs include biocompatibility, sterility, scale up, and protection of incorporated active ingredients against chemical degradation. One of the most prominent examples is the NLCs of paclitaxel which is used for successful and effective treatment of carcinoma and sarcoma including tumors. The cholesterol-based paclitaxel-loaded NLCs were prepared by solvent emulsification–diffusion method using poloxamer 188 and oleic acid [22]. These NLCs provide targeted delivery without any side effects associated with cremophor EL-containing formulations. Thus, NLCs as carriers can provide targeted and intracellular drug delivery of various antineoplastic agents [23].

Besides synthetic drugs, herbal bioactives phytoconstituents are also effectively used for treatment of oral cancers. Most widely used herbal constituents are genistein, curcumin, quercetin, naringenin and eugenol.

Cyclodextrins

Cyclodextrins (CD) are family of water-soluble cyclic oligosaccharides obtained by enzymatic degradation of starch. They are versatile multifunctional excipients used in drug delivery. They are regarded as safe to be delivered by all possible routes [24]. They have advantages of increasing, enhancing, and modifying the poor physicochemical properties of drugs like solubility, stability, bioavailability, dissolution, bitter taste, incompatibility, pharmacokinetic parameters, therapeutic efficiency and pharmacological activity, side effects, adverse and

toxic effects. Almost all the drugs have been complexed with β-cyclodextrin and their hydrophilic and polymerized derivatives like HP-β-CD, RM-β-CD, and Epi-β-CD. These CDs are cage-like structure which incorporates the drug molecule inside their cavity through complexation. Most of the drugs like 5-FU, docetaxel, cisplatin, methotrexate and paclitaxel have been complexed with CDs to improve their therapeutic efficiency [25,26].

Other carriers

Besides nanocarriers, other vesicular carriers are used for drug delivery. Polymeric micelles of paclitaxel, microspheres of 5-FU, and dendrimers of cisplatin are reported in literature for treatment of cancer. Some examples of nanocarriers used in treatment of oral cancer are listed in Table 3. Table 4 showed some patented nanocarrier-based drug delivery for oral anticancer drugs.

Dosage form

For efficient delivery of drugs, it should be available in suitable dosage form. Oral dosage forms like tablet, capsule, suspension, syrup, solution, etc. are most widely preferred dosage form due to their advantages and ease. Conventional available oral dosage form can be modified or replaced by incorporating nano/microcarriers encapsulation into solid dosage form. These have proved to be better than the conventional products available in markets. Still, we can modify these novel products by utilizing several new concepts of dual approach of CDs and nanotechnology in single delivery system. Moreover, the concept of conjugation or binding of drugs with ligand and receptor and then loading into carrier, thereby dosage form designing will be fruitful for achieving targeted or site-specific delivery.

Chemotherapeutics agents mainly used for the treatment of oral cancer are listed in Table 3. These drugs are available in conventional oral dosage form i.e. in the form of oral pills, tablets, capsules, etc. Besides, oral-route semisolid dosage form especially gels and creams are available for application in the affected area. But, with the advancement in technology, now-a-days nano-based formulations are developed for efficient drug delivery. These nano-based formulations are available in all the dosage forms i.e. solid, semisolid, liquid and parenteral dosage [51].

Conclusion

The first and foremost goal of cancer treatment is to kill all the cancer cells without affecting or destroying the healthy cells. This will be possible by achieving the targeted and site-specific delivery of chemotherapeutic drugs in the body to achieve the maximum therapeutic potential. In this context, carrier-mediated delivery systems will emerge as a unique and potential alternative for overcoming the limitations associated with drugs and conventional formulations. Further studies on *in vitro* and *in vivo* animal models will provide practical applications thereby correlating the pharmacokinetic and pharmacodynamic parameters and elucidating the exact dose of drug and ideal release mechanism for treatment of cancer-like life-threatening disease both on molecular and cellular levels.

Disclosure statement

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