IOSR Journal of Pharmacy and Biological Sciences (IOSR-JPBS)
e-ISSN:2278-3008, p-ISSN:2319-7676. Volume 13, Issue 1 Ver. III (Jan. – Feb. 2018), PP 22-28
www.iosrjournals.org

A review of literature on Targeted Drug Delivery Systems for the treatment of oropharyngeal cancer and strategies of targeting cancer

Dr. Ayesha Sameera[1], Dr. Sridhar Reddy Erugula[2], Dr.Vijay Kumar Nellore[3] Dr.M.V.S Sudhir[4], Dr. Annem Sudarshan Kumar[5], Dr.V.R.Chandrababu Pamidi[6], Dr. K.T.S.S.Rajajee[7], Dr.B.Badari Ramakrishna[8],

[1]*Senior Lecturer, Department of Oral Pathology and Microbiology, MNR Dental College and Hospital, Sangareddy,Telangana State, India.*
[2]*Senior Lecturer, Department of Oral Pathology and Microbiology, MNR Dental College and Hospital, Sangareddy,Telangana State, India.*
[3]*Senior Lecturer, Department of Oral and Maxillofacial Surgery, MNR Dental College and Hospital, Sangareddy,Telangana State, India.*
corresponding Author:Dr.Ayesha Sameera
[4]*Consultant,Oral and Maxillofacial Surgery,Sujatha Super Speciality Dental Hospital, Hyderabad, Telangana State,India.*
[6]*Senior lecturer, Department of Oral Pathology and Microbiology, GSL Dental College & Hospital, Rajahmundry, Andhra Pradesh, India*
[7]*Reader,Department of Oral and Maxillofacial Surgery, GSL Dental College & Hospital, Rajahmundry, Andhra Pradesh, India.*
[8]*Professor,Department of Pedodontics, Anil Neerukonda Institute of Dental Sciences, Visakhapatnam, Andhra Pradesh, India.*
[8]*Reader,Department of Oral Medicine and Radiology,Anil Neerukonda Institute of Dental Sciences, Visakhapatnam, Andhra Pradesh, India.*

Abstract: *Oral cancer is an aggressive cancer with a high mortality rate. Surgery, chemotherapy, and chemoradiotherapy are the conventional methods that have been used to treat oral cancers but they all come with certain level of compromise. Currently, targeted drug delivery has emerged as a promising method of delivering drugs to targeted site with increased concentration drug to the targeted cancer cells, improved efficacy of treatment which leads to administration of drug in fewer doses and hence reduced side effects. For this purpose, various drug delivery systems have been investigated and formulated. These include liposomes, microspheres, nanoparticles , nanoshells, nanorods, nanocubes, carbon nanotube, nanotubes, nanodiamonds, nanomedicine heat therapy, nanotechnology latest oncolytic agent , quantum dots, curcumin ultrasound mediated delivery and magnetic nanoparticles. The aim of a targeted drug delivery system is to have a protected localize drug interaction with the diseased tissue. The objective of this study is to present a review of targeted drug delivery systems for treatment of oropharyngeal cancers.*

Keywords: *oral cancer, therapeutics, targeted drug delivery*

Date of Submission: 13-01-2018 Date of acceptance: 30-01-2018

I. Introduction

Oral cancers are the sixth most common cancer worldwide and one of the leading causes of death worldwide and accounting for 5-6% of all cancer cases, with twice more common in males than females [1, 2]. Mostly these cancers are squamous cell carcinomas arising in oral cavity, nasal cavity, paranasal sinuses, pharynx and larynx. Tobacco, alcohol and betel quid chewing are widely the most significant risk factors for oral cancers.[3] Significantly infection with human papillomavirus (HPV) is associated with an increase oropharyngeal cancer in nonsmokers.[4] Prognosis is poor with these types of cancers with a five-year survival rate in only 50% of the cases and metastatic patients have a median survival of less than 1 year only.[5]

The standard treatment protocols for oral cavity cancers include surgical resection and radiotherapy along with adjunctive chemotherapy but owing to the complexity of the facial structures the extent of surgery will always be limited. [6] To preserve the organ function and vitality of structures researchers have focused on advanced chemotherapy or radiotherapy. However, the efficacy of conventional chemotherapy is reduced by numerous factors like nonspecific distribution, rapid clearance, drug resistance at the tumor and cellular level,

low efficiency, and toxicity. Therefore, vast efforts have been devoted to the design drugs that target cancerous cells only rather than affecting both healthy and cancerous cells unlike conventional chemotherapy.[7]

Drug delivery system is a device that empowers the introduction of a therapeutic substance in the body and enhances the efficacy and safety by controlling the rate, time, and place of release of drug in the body. [8, 9] Paul Ehrlich, a microbiologist, introduced drug delivery in the form of magic bullet. [10] Targeted drug delivery system delivers a therapeutic agent for a prolonged period of time to a targeted diseased area within the body in a dosage form therefore maintains a required plasma and tissue drug level in the body and avoids damage by drug to the healthy tissue. [11] A Targeted drug delivery system is preferred over conventional drug delivery systems as it has more solubility, less drug instability, better absorption, increased half-life, require less volume of distribution, more specificity and high therapeutic index [12, 13].

II. Targeted Drug Delivery System

Targeted drug delivery means accumulation of pharmacologically active moiety at desired target in therapeutic concentration at the same restricting its access to normal cellular lining, thus minimizing therapeutic index. The drug can be targeted to virus cells, bacteria cell, parasites and intracellular sites and for this reason delivery system should be prepared in accordance with the specific properties of target cells, transport carriers / vehicles as they convey drug to specific receptors and ligands and also physically modulated components. [14]

Targeted drug delivery systems ideally should be non-immunogenic, biochemically inert (non-toxic), stable physically and chemically in vivo and in vitro conditions, controllable and predictable rate of drug release, restricted drug distribution to target cells, uniform capillary distribution and minimal drug leakage during transit .Carrier should be biodegradable or readily eliminated from the body without inducing modulation of diseased state. The delivery system should be reasonably simple, reproductive and cost effective in preparation. [15, 16]The design of potential carriers should be based on recognition sites on the surface of target cells for cell-specific drug delivery. Carriers used should be biodegradable or readily eliminated from the body without any problem. The choice of carrier system depends on target cells and drugs. [14]

Types of targeted Drug delivery systems:

Liposomes:

Liposomes are small spherical artificially designed vesicles composed of phospholipid bilayers in aqueous environment of size between 20 to10, 000 nm. These are rapidly taken up by macrophages and hence used in macrophage-specific delivery of drugs or for passive drug delivery which allow slow drug release of the drug over time into the general circulation. Cationic liposomes and lipoplexes are widely used in non-viral vector mediated gene therapy [17].

Microspheres/Microparticles:

Microspheres or microparticles are small solid spherical particles of 1 μm to 1000 μm consist of a microscopic hollow sphere. Polymeric backbone carriers have also been prepared using dextrans, ficoll, sepharose or poly-L-lysine. Post systemic administration, these quickly distribute to the target site and become internalized by the phagocytic system. Apart from selected drug delivery these have been used oral delivery of peptides and peptidomimetics [18, 19].

Nanoparticles:

Nanoparticles are smaller in size of 0.2– 0.5 μm than and have a smaller drug loading capacity. Formulation of drugs into the nanoparticles can occur at the surface of the particles or in the nucleus based on the physicochemical properties of the drug. Nanoparticles with non-modified surface can be recognized by the host immune system cleared from the circulation by mononuclear phagocyte system (MPS) significantly shortens the circulation time and leads to targeting failure. Novel nanoparticles coating with hydrophilic polymers or surfactants prevents opsonization and reduces phagocytosis. [20,21]

Nanodiamonds:

Nanodiamonds are composed of atoms in either a single or poly-crystalline arrangement with size less than 100 nanometres and these bound to doxorubicin and are encapsulated into a polymer microfilm which causes slow and sustained release over a period of 1 month. [22]

Nanotubes:

They are tubular molecule hollow cylinder made of a large number of carbon atoms which can be filled and sealed for potential drug delivery. These are helpful in identifying DNA changes associated with cancer cells. [14]

Carbon Nanotube:

Carbon nanotubes are hollow nanotubes and are formed when single or multiple graphene sheets are rolled into a shape of a cylinder. They can enter living cells without causing any cell death or damage. [22] However, they require covalent or non-covalent functionalization for the better aggregation and higher solubility. [23] Single walled carbon nanotubes (SWNTs) are a recent technological advancement for cancer treatment. SWNTs move into cells through the process of endocytosis. Radiofrequency or near infrared region (NIR) radiation are required for activation of these nanotubes which produces heat. This heat gets dispersed inside the tumor from the entire surface area of the SWNTs causing overheating, protein denaturation and eventually malignant cell death. [24]

Nano cubes:

Nanocubes have 100 crystallographic planes and hence exhibit high density. Graphitic carbon nanocubes featuring high biocompatibility and high photothermal conversion efficiency were originally synthesized by pyrolysis of the zeolitic imidazolate framework ZIF-8 and developed as a new class of photothermal agent for the treatment of human cancer cells by near-IR irradiation. [25]

Nano rods:

Nanorods are synthesized from metals or semiconducting materials with size ranging from 1–100 nm. Huang *et al*., in his study stated that conjugation of gold nanorods to anti-epidermal growth factor receptor antibodies were able to differentiate oral cancer cells from non malignant epithelial keratinocyte cells and thus are helpful in diagnosis of cancer cells. [26]

Nanoshell:

Nanoshells is made up of diblock copolymers (2060 nm) and is made by self-assembly of oppositely charged polymers to form a shell like structure.[27] Hirsch *et al*., demonstrated that silica-gold nanoshells labeled with antibodies specific to oncoprotein had shown to target and destroy the oral squamous cancer cells in a minimal invasive way. [28]

Magnetic nanoparticles:

Magnetic nanoparticles is one of the most investigated and studied systems in the field of nanotechnology. The iron oxide nanoparticles coated with oleic acid and embedded with doxorubicin and paclitaxel have shown loading efficiency up to 95%. [22]Candido *et al*., had studied the action of polyphosphate-coated magnetic nanoparticles (MNPs) on oral cancer cells and when treated with magneto-hyperthermia using MNPs had showed significant time dependent cancer regression.[28]

Curcumin ultrasound mediated delivery:

Curcumin showed both anticancer and antioxidant properties especially in low doses and performed an *in vitro* suppression of oral squamous cell carcinoma (OSCC) cell lines by ultrasound mediated delivery of curcumin microemulsions (with a mean size of 40-50 nm).The results showed the cytotoxic effects of curcumin microemulsions on OSCC-25 cells by causing damage and rupture of the cells. [29]

Quantum dots:

Quantum dots are highly sensitive at optical imaging of cancer at cellular and animal level. QDs are semiconductor nanostructures of 25 billionths of a meter in diameter and can confine electrons in three dimensions and emit light when exposed to ultraviolet radiation.[30] QDs are fluorescent nanoparticles with sizes of 2-10 nm that contain a core of 100s-1000s of atoms of group II and VI elements (e.g., cadmium, technetium, zinc and selenide) or group III (e.g., tantalum) and V elements (e.g., indium). These give rise to reactive oxygen species and thus will be lethal to the target cells.[31]

Nanotechnology Latest Oncolytic Agent :

Reitz in 2003 did a retrospective review on the universal antimicrobial effects of oligodynamic Ag^{+2}. Reitz documented that many cancer associated infections such as human immunodeficiency virus ,human herpesvirus 8, human papillomavirus and epstein-barr virus 18 ,influenza and parainfluenza viruses, and cytomegalovirus are susceptible to oligodynamic Ag^{+2}. The main advantage of silver particles is their ability to absorb, interact and destroy bacteria affecting abnormal human tissue or upregulate immune tissues and healing mechanisms.[32-35]

Nanomedicine Heat Therapy:
Similar to radiotherapy for cancer, heat therapy uses nanoparticles targeted at the cancer cells. A laser optic probe is used to direct infrared radiation through the skin, from outside the body. Current method of nanoparticle heat therapy cause minimal damage to the healthy tissue. [36]

III. 3. Strategies Of Targeting Cancer

Targeted drug delivery can occur either by active or passive targeting. Active targeting is the interactions between drug, drug carrier and the target cancer cells through specific ligand-receptor interactions.[37] Passive targeting occurs through accumulation of drug, drug-carrier system at the targeted site due to physico-chemical factors or pharmacological factors. [23]

Passive targeting:

Passive targeting mainly depends on the enhanced permeability and retention (EPR) effect of the tumor. [38] Rapid angiogenesis in tumors tends to be leaky and defective which can be easily accessible to chemotherapeutic drugs. Drugs when administered as prodrugs or inactive become highly active when exposed to the tumor environment. [23] Passive targeting can also involve other several invasive modalities for drug delivery. [39]

Tumor vascularization:

Neoangiogenesis is an important phenomenon in tumor progression as it supports tumor growth and provides a medium for dissemination of cancer cells to different parts of the body, leading to metastasis. The leaky vasculature in tumor forms a more accessible route for drugs to be delivered to the exact site. The EPR phenomenon is based on the disorderly and more permeable capillary endothelium in malignant tissue than the capillary endothelium in normal tissues and absence of tumor lymphatic drainage which results in drug accumulation within the tumor interstitium. [40, 41] If a degradable molecular carrier is coupled with chemotherapeutic agent then the concentration of the drug within the tumor tissue can reach levels 10 to 100 times higher than the administration of free drug [42]. A tumor dependent pore cutoff size of 200 nm to 2 mm was demonstrated by direct observation of tumor vasculature. [43, 44] These size ranges indicate that drug-loaded nanoparticles and liposomes may be accumulated in tumor. Park et al stated that a polymer based nanoparticles with DOX circulated in the blood for more than 3 days and accumulated in tumors *via* the EPR effect [42].

Tumor Microenvironment:

Tumor tissues have a more acidic environment (5.7-7.4) due to acidic intracellular organelles and insufficient supply of oxygen leading to hypoxia and production of lactic acid. [45] Therefore, various pH-responsive polymeric nanoparticles can be conjugated to anticancer drug to exploit the acidic environment of tumor. The pH-sensitive liposomes are stable at a physiologic pH of 7.4, but undergo degradation in tissues with less than physiological pH values like acidic environment of tumor cells to release active drug. [46] A pH-sensitive poly (vinylpyrrolidone-co-dimethyl maleic anhydride) (PVD) carrier was conjugated with doxorubicin (DOX) was synthesized by Kamada et al that can gradually release free drug in response to change in acidic pH. [47] Similarly intracellular pH-sensitive polymeric micelles can release the anticancer drug in acidic pH at lysosomes (pH 4.0–5.0) and endosomes (pH 5.0–6.0) which can increase the drug delivery efficiency to the tumor cells. [48]

Active Targeting:

Active targeting utilizes an extraordinary ligand that can recognize and bind to receptors on the surface of tumor cells. Active targeting can be achieved by ligands like antibodies, peptides and nucleic acid aptamers when conjugated with nanoparticles. [49]

Monoclonal Antibodies, Peptides and Nucleic acid Aptamers:

Monoclonal antibodies (mAb) became widespread after the discovery of hybridoma technology and are the first macromolecular ligands used for targeted delivery drug system. Recently, human immunoglobulins have been produced from transgenic mice. Combinatorial phage display libraries have become important in selecting novel protein ligands [50]. Most recently, cancer targeting antibodies was produced using live cancer patients [51, 52] and they antagonize the signal transduction pathway that leads uncontrolled growth in cancer cells. Currently studies are focused on assessing the affinity of these antibodies against the respective antigens to conjugate them with chemotherapeutic drugs like doxorubicin, methotrexate and calicheamicin. [53]

Peptides are synthetic small molecules that can be produced in large quantities without being immunogenic and are more stable than antibodies and owing to this property they have become a potent

targeting ligand. Peptides are superior to antibodies because they are small in size, low immunogenic and have higher stability. [54] Presently the development of phage display screening methods has led to isolated peptide ligands with high specificity and affinity to tumor vasculature antigens. [55]

Nucleic acid aptamers are single stranded RNA, DNA or unnatural oligonucleotides that are folded into unique structures with high affinity and specificity for the target. [56] Aptamers have a half life of minutes to hours and can be rapidly cleaned from the bloodstream due to nuclease degradation through kidneys. [57] Nanomaterial-based aptamer bioconjugates has wide variety of applications. Bagalkot *et al*. demonstrated an innovative strategy for the targeted delivery to cancer cells through an aptamer doxorubicin conjugate. [58]

Folate-Based Targeting Molecules:

Folic acid (folate) is a high-affinity vitamin commonly used as ligand for cancer targeting. It involves the attachment of folate (folic acid) to drug to form folate conjugate because of the natural high affinity of folate to the folate receptor protein (FR) which is commonly highly expressed on the surface of cancer cells. Folate-drug conjugates specifically binds tightly to the folate receptor protein (FR) on cancer cells only without causing harm to normal cells which trigger cellular uptake mediated by endocytosis. [59] Wide variety of drug delivery vehicles like liposomes, dendrimers, polymeric NPs and linear polymers can be used to conjugate with folate. Recently, dendrimer-conjugated with folate have demonstrated good *in vivo* efficacy in specific killing of cancer cells through multivalent interaction [60]. The nanoparticle conjugated with folic acid containing methotrexate has been demonstrated inhibition of cancer cell growth [61].

IV. Recent Advances

Stimuli responsive drug targeting strategies

Ultrasound Sensitive Targeting:

Ultrasound (US) is increasingly used in the delivery of therapeutic agents like chemotherapeutic agents, genetic material and proteins as it is safe and low cost imaging modality with high potential for applications in molecular imaging and targeted drug delivery [62]. Ultrasound is used to transmit energy into the body which is the key to ultrasonic-activated drug delivery. Ultrasound works through three mechanisms like, local hyperthermia, cavitation which leads to increase in the permeability of cell membranes, and the release of highly reactive free radical species [63]. A study conducted by Howard el al. on a breast cancer drug-resistant cell line by using paclitaxel in micelles of methyl capped poly(ethylene oxide)-co-poly-(L-lactide)-tocopherol with 1 MHz ultrasound at density of 1.7 W/cm2 and duty cycle of 33% resulted in increased amount of drug found in non-insonated cells.[64]

Magnetically Sensitive Targeting:

Magnetically targeted therapy uses a cytotoxic drug that is attached to a biocompatible magnetic nanoparticle carrier and are injected into the patient through the circulatory system. An external high gradient magnetic field is used to concentrate the drug carriers at a specific target site. [65]. A study conducted with doxorubicin showed that administration of magnetoliposomes with an applied external magnetic field produced four times more doxorubicin concentration in the tumor when compared to the doxorubicin alone indicating that it could effectively control the primary tumor without significant side effects [66]. A water dispersible oleic acid pluronic-coated iron oxide nanoparticle was used by Jain et al that can be conjugated with high doses of water-insoluble anticancer agents with magnetic targeting for treatment of cancer. [67]

V. Future Prospects

Cancer Nanovaccines:

Cancer nanovaccines function in the similar way like conventional vaccines. It can be designed, manufactured and introduced into the body to improve health along with cellular repairs at the molecular level. The nanovaccines are very tiny and can easily enter the cell and hence can be used in both *in vivo* or *invitro*. [36]

Hypersonic Poration:

Efficient delivery of therapeutic agents only to the cancer cell and not to normal cell is critical. A new type of chemical-free cell poration method called hypersonic poration is under trials to improve the cellular uptake. Hypersound can be generated by a piezoelectric nanoelectromechanical resonator which may directly induces shear stress and leads to molecular bombardment effects on the bilayer membranes of the cell and creates reversible nanopores improving the membrane permeability for therapeutic agents. It has a high potential in the field of therapeutic drug delivery, cell transfection, and gene therapy.[68]

VI. Conclusion

Targeted drug delivery systems in treating tumors can increase the chances of precision drug delivery. Owing to the complexity of the cellular network, drug delivery to the site of action is difficult but targeted delivery of drug is becoming one of the most promising stars in the cancer therapies. This is due to the fact that this technique has reduced the dose and the adverse effect of drug. Nanoparticle-based targeted drug delivery systems are gaining a strong foothold in cancer therapies. These have brobdingnagian potential in fulfilling the need for practical alternative cancer therapies. Further research into advanced specificity tumor targets, very efficient nanocarriers is required, along with modifications to enhance antitumor efficacy and personalized cancer therapeutic strategies.

References

[1]. Siegel, R. L.; Miller, K. D.; Jemal, A. Cancer statistics, 2016. Ca−Cancer J. Clin. 2016, 66, 7−30.
[2]. Ferlay J, Shin HR, Bray F. et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010;127:2893–917.
[3]. Hashibe M, Brennan P, Benhamou S. et al. Alcohol drinking in never users of tobacco, cigarette smoking in never drinkers, and the risk of head and neck cancer: Pooled analysis in the international head and neck cancer epidemiology consortium. Journal Of the National Cancer Institute. 2007;99:777–89.
[4]. D'Souza G, Kreimer AR, Viscidi R. et al. Case-control study of human papillomavirus and oropharyngeal cancer. N Engl J Med. 2007;356:1944–56.
[5]. Carvalho AL, Nishimoto IN, Califano JA. et al. Trends in incidence and prognosis for head and neck cancer in the United States: a site-specific analysis of the SEER database. Int J Cancer. 2005;114:806–16.
[6]. Murphy BA, Gilbert J, Ridner SH. Systemic and global toxicities of head and neck treatment. Expert Rev Anticancer Ther. 2007;7:1043–53.
[7]. Lango MN. Multimodal treatment for head and neck cancer. Surg Clin North Am. 2009;89:43–52.
[8]. Khan DR .The use of Nanocarriers for Drug Delivery in Cancer Therapy. J Cancer Sci Ther. 2010; 2: 058-062.
[9]. Gautami.J. Targeted Drug delivery systems. Research and Reviews: Journal of Pharmaceutics and Nanotechnology. 2015;3 (1):25-31.
[10]. Strebhardt K, Ullrich A. Paul Ehrlich's magic bullet concept: 100 years of progress. Nat Rev Cancer. 2008;8:473–480.
[11]. Muller RH, Keck CM; Challenges and solutions for the delivery of biotech drugs-a review of drug nanocrystal technology and lipid nanoparticles. Journal of Biotechnology, 2004; 113 (1–3): 151-170.
[12]. Vyas SP, Khar RK; Basis of targeted Drug Delivery. In Targeted and controlled Drug Delivery, CBS Publishers and Distributors Reprint, 2008: 42-46, 74.
[13]. Mark SW, Torchilin, Vladimir P; Drug delivery systems. AccessScience, McGraw-Hill Companies, 2011.
[14]. Bhargav E, Madhuri N. Targeted Drug delivery-A review. WJPPS. 2013;3(1):150-9.
[15]. Won R; Method for delivering an active ingredient by controlled time release utilizing a novel delivery vehicle which can be prepared by a process utilizing the active ingredient as a porogen, Patent No 4690825 US: 1987.
[16]. Mastrobattista E, Koning GA, Storm G; Immunoliposomes for the targeted delivery of antitumor drugs. Advance Drug Delivery Reviews, 1999; 10:40(1-2):103-127.
[17]. Torchilin VP; Multifunctional nanocarriers. Advance Drug Delivery Reviews, 2006; 58(14):1532-1555.
[18]. Farah RA, Clinchy B, Herrera L, Vitetta ES; The development of monoclonal antibodies for the therapy of cancer.Critical Reviews In Eukaryotic Gene Expression, 1998;8: 321–356.
[19]. Köhler G, Milstein C; Continuous cultures of fused cells secreting antibody of predefined specificity. 1975;Nature,256: 495-497.
[20]. Muller RH, Maassen S, Weyhers H. et al. Phagocytic uptake and cytotoxicity of solid lipid nanoparticles (SLN) sterically stabilized with poloxamine 908 and poloxamer 407. J Drug Target. 1996;4:161–70.
[21]. Bhadra D, Bhadra S, Jain P. et al. Pegnology: a review of PEG-ylated systems. Pharmazie. 2002;57:5–29.
[22]. Jain N, Jain R, Thakur N, Gupta BR, Jain DK, Banveer J, *et al*. Nanotechnology: A safe and effective drug delivery system. AJPC 2010;3:159-65.
[23]. Barakat NS, Taleb DA, Salehi AS. Target nanoparticles: An appealing drug delivery platform. J Nanomed Nanotechnol 2012;S4:2-9.
[24]. Broadwith. Are Nanotubes the Future for Radiotherapy? Available from: http://www.rsc.org/chemistryworld/News/2010/September/01091001.asp.
[25]. Chen W, Zhang X, Ai F, Yang X, Zhu G, Wang F. Graphitic Carbon Nanocubes Derived from ZIF-8 for Photothermal Therapy. Inorg Chem. 2016. 20;55(12):5750-2.
[26]. Huang X, El-Sayed IH, Qian W, El-Sayed MA. Cancer cells assemble and align gold nanorods conjugated to antibodies to produce highly enhanced, sharp, and polarized surface Raman spectra: A potential cancer diagnostic marker. Nano Lett 2007;7:1591-7.
[27]. Hirsch LR, Stafford RJ, Bankson JA, Sershen SR, Rivera B, Price RE, *et al.* Nanoshell-mediated near-infrared thermal therapy of tumors under magnetic resonance guidance. Proc Natl Acad Sci U S A 2003;100:13549-54.
[28]. Candido NM, Calmon MF, Taboga SR, Bonilha JL, Santos MC, Lima EC, *et al*. High efficacy in hyperthermia-associated with polyphosphate magnetic nanoparticles for oral cancer treatment. J Nanomed Nanotechnol 2014;5:1-11.
[29]. Lin HY, Thomas JL, Chen HW, Shen CM, Yang WJ, Lee MH. *In vitro* suppression of oral squamous cell carcinoma growth by ultrasound-mediated delivery of curcumin microemulsions. Int J Nanomedicine 2012;7:941-51.
[30]. Gao X, Yang L, Petros JA, Marshall FF, Simons JW, Nie S. *In vivo* molecular and cellular imaging with quantum dots. Curr Opin Biotechnol 2005;16:63-72.
[31]. Medintz IL, Uyeda HT, Goldman ER, Mattoussi H. Quantum dot bioconjugates for imaging, labelling and sensing. Nat Mater 2005;4:435-46.
[32]. Fields CB. Method for treating blood borne viral pathogens such as immunodeficiency virus. United States Patent No. 6,066,489. [2000 May 23].
[33]. Kuck D, Lau T, Leuchs B, Kern A, Müller M, Gissmann L, *et al*. Intranasal vaccination with recombinant adeno-associated virus type 5 against human papillomavirus type 16 L1. J Virol 2006;80:2621-30.
[34]. Serraino D, Piselli P, Angeletti Cl, Scuderi M, Ippolito G, Capobianchi MR. Infection with Epstein-Barr virus and cancer: An epidemiological review. J Biol Regul Homeost Agents 2005;19:63-70.

[35]. Lansdown AB. Microbial multidrug resistance (mdr) and Oligodynamic silver. J Wound Care 2002;11:125-30.
[36]. Alok A, Panat S, Aggarwal A, Upadhyay N, Agarwal N, Kishore M. Nanotechnology: A boon in oral cancer diagnosis and therapeutics. SRM J Res Dent Sci 2013;4:154-60.
[37]. Bae YH, Park K. Targeted drug delivery to tumors: Myths, reality and possibility. J Control Release 2011;153:198-205.
[38]. Mitra S, Maitra A. Nanoparticulate carriers in drug delivery and targeting. PINS 2002;4:349-66.
[39]. Saini, R. K., R. Chouhan, L. P. Bagri, and A. K. Bajpai. 2012. Strategies of Targeting Tumors and Cancers. *J. Can. Res. Updates.* **1**: 129–152.
[40]. Iyer A, Khaled G, Fang J, Maeda H. Exploiting the. Drug Discov Today 2006; 11: 812-18.
[41]. Smith AM, Dave S, Nie S, True L, Gao X. Multicolor quantum dots for molecular diagnostics of cancer. Expert Rev Mol Diagn 2006; 6(2): 231-44.
[42]. Park JH, Kwon S, Lee M, *et al*. Self-assembled. Biomaterials 2006; 27: 119-26.
[43]. van Vlerken LE, Duan Z, Seiden MV, Amiji MM. Multidrug resistant. Cancer Res 2007; 67(10): 4843-50.
[44]. Park JH, Lee S, Kim JH, Park K, Kim K, Kwon I.C. Polymeric nanomedicine. Prog Polym Sci 2008; 33: 113-37.
[45]. Iessi E, Marino ML, Lozupone F, Fais S, Milito AD. Tumor acidity. Cancer Therapy 2008; 6: 55-66.
[46]. Wang X, Yang L, Chen Z, Shin, DMCA. Application of. J Clin 2008; 58: 97-110.
[47]. Kamada H, Tsutsumi Y, Yoshioka Y, *et al*. Design of a pH Sensitive. Cancer Res 2004; 10: 2545-50.
[48]. Bae Y, Nishiyama N, Fukushima S, Koyama H, Yasuhiro M, Kataoka K. Preparation and biological. Bioconjug Chem 2005; 16: 122-30.
[49]. Deepak K, Deepti J, Vivek S, Rajendra K, Patil A. Cancer therapeutics, opportunities, challenges and advances in drug delivery. JAPS 2011;1:01-10.
[50]. McWhirter JR, Kretz-Rommel A, Saven A, *et al*. Antibodies selected. Proc Natl Acad Sci USA 2006; 103: 1041-46.
[51]. Singh R, Lillard Jr JW. Nanoparticle-based. Exp Mole Patho 2009; 86: 215-23.
[52]. Krag DN, Shukla GS, Shen GP, *et al*. Selection of Tumor binding. Cancer Res 2006; 66(15): 7724-33.
[53]. Brissette R, Prendergast JK, Goldstein NI. *et al.* Dentification of cancer. Curr Opin Drug Disc 2006; 9: 363-69.
[54]. Newton JR, Kelly KA, Mahmood U, *et al. In vivo* selection. Neoplasia 2006; 8: 772-80.
[55]. Saveanu A, Jaquet P, Gunz G, *et al.* Somatostatin and Dopamine-Somatostatin. Neuroendocrinology 2006; 83: 258-63.
[56]. Xiao Z, Frieder J, Teply BA, Farokhzad OC. Aptamer Conjugates: Emerging Delivery Platforms for Targeted Cancer Therapy in Drug Delivery in Oncology: From Basic Research to Cancer Therapy 2012; 1263-1281.
[57]. Nimjee SM, Rusconi CP, Harrington RA, Sullenger BA. The potential of aptamers. Trends Cardiovasc Med 2005; 15: 41-5.
[58]. Bagalkot V, Farokhzad OC, Langer R, *et al*. An Aptamer- Doxorubicin. Angew Chem Int Ed 2006; 45(48): 8149-52.
[59]. Gupta M, Sharma V; Targeted drug delivery system: A Review. Research Journal of Chemical Sciences, 2011; 1:134-138.
[60]. Leroueil PR, Hong S, Mecke A, *et al*. The Binding Avidity. Chem Biol 2007; 14: 107-15.
[61]. Kairemo K, Erba P, Bergstrom K, Pauwels EKJ. Nanoparticles in Cancer. Curr Radio pharmaceu 2008; 1: 30-36.
[62]. Bordan MA, Sarantos MR, Stieger SM, Simon SI, Ferrara KW, Dayton PA. Ultrasound radiation. Mol Imaging 2006; 5(3): 139-47.
[63]. Blanco E, Kessinger CW, Sumer BD, Gao J. Multifunctional micellar. Exp Biol Med 2009; 234: 123-31.
[64]. Howard B, Gao A, Lee SW, Seo MH, Rapoport N. Ultrasound-enhanced. Am J Drug Deliv 2006; 4: 97-104.
[65]. Kubo T, Sugita T, Shimose S, Nitta Y, Ikuta Y, Murakami T.Targeted systemic. Int J Oncol 2001; 18(1): 121-5.
[66]. Kubo T, Sugita T, Shimose S, Nitta Y, Ikuta Y, Murakami T. Targeted delivery. Int J Oncol 2000; 17(2): 309-15.
[67]. Jain TK, Morales MA, Sahoo SK, Leslie Pelecky DL, Labhasetwar V. Iron Oxide. Mol Pharmaceutics 2005; 2(3): 194-205.
[68]. Z. Zhang, Y. Wang, H. Zhang, *et al.* Hypersonic Poration: A New Versatile Cell Poration Method to Enhance Cellular Uptake Using a Piezoelectric Nano-Electromechanical Device. Small 2017; 13: 1602962-71.

IOSR Journal of Pharmacy and Biological Sciences (IOSR-JPBS) is UGC approved Journal with Sl. No. 5012, Journal no. 49063.

Dr. Ayesha Sameera "A review of literature on Targeted Drug Delivery Systems for the treatment of oropharyngeal cancer and strategies of targeting cancer." IOSR Journal of Pharmacy and Biological Sciences (IOSR-JPBS) 13.1 (2018): 22-28.