

# A Targeted Drug Delivery System for Cancer Treatment a Novel Approach: A Review

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## REVIEW ARTICLE

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### ABSTRACT

In the recent scenario of the world there are millions of the people are suffering from the various types of cancer. To cure the cancer immunotherapy, radiation therapy, chemotherapy, surgery and hormonal therapy treatments are used. In treatment of cancer the convectional approaches are used which can adversely affect to normal cells on the body. Also, the side effects of this treatments are damage the immune system of the patient. To overcome such problems with the conventional treatment of the cancer the targeted drug delivery system is developed, in such oral delivery of drug at the particular location of tumor at perfect time with specific dosage. This review includes the development of the new targeted drug delivery system and its limitations.

**Keywords:** Cancer pathophysiology, Drug Delivery, Targeted drug delivery, anti-cancer drugs.

### 1. Introduction

Cancer is a worldwide public health problem. Despite considerable progress in its early diagnosis and treatment, successful remedy is alarmingly negligible. Cancer was thought to arise when cell growth exceeds the rate at which cells die, so that cells are dividing at an uncontrollable rate. There are more than 100 different types of cancer. Most cancers are named for the organ or type of cell in which they start. Cancer types can be grouped into three broader categories. The main categories of cancer include: Carcinoma - (cancer that begins in the skin or in tissues that line or cover internal organs), Sarcoma - (cancer that begins in bone, cartilage, muscle, blood vessels, or other connective or supportive tissue), Leukemia - (cancer that starts in blood-forming tissue such as the bone marrow and causes production of large numbers of abnormal blood cells and enter the blood).

In current anti-cancer therapy, drugs are administered through intravenous and oral route using conventional formulations like tablet, capsule and injectable. Sustained and targeted delivery of anti-cancer agents at the site of action is desired to maximize the killing effect

during the tumor growth phase and avoiding the exposure to surrounding healthy cells for reducing the toxicity. It is also desired to maintain a steady state infusion of drug into the tumor interstitium to maximize the exposure to the dividing cells that results in tumor regression. (1) Conventional oral and injectable dosage forms of anti-cancer drugs are not able to do this due to short biological half-life, narrow therapeutic index, poor oral bioavailability and formulation difficulties like poor water solubility, stability and high molecular weight. (2) In the recent past, advances in novel drug delivery system (NDDS) have resulted in use of several colloidal carriers such as liposomes, niosomes, microemulsion, nanoemulsion, microsphere and polymeric micelles for sustained and targeted delivery of anti-cancer agents. Further revolutions in nanotechnology increased the hope for rationalization in therapeutic options for rationalized delivery of anti-cancer agents with high efficacy. Development of NDDS based formulation for delivery of anti-cancer drugs is a recent topic of research in Pharmaceutical Industries. Nanoxel(R), nanoparticles based formulation for paclitaxel from Dabur and Abraxane(R), albumin based

formulation for paclitaxel from Abraxis commercial products Table 1. BioScience Inc., USA is the well-known

**Table 1.** Commercially available NDDSs for anti-cancer drugs

Drug name	Novel system	Brand name
Paclitaxel	Polymeric nanoparticles gel	Nanoxel
Doxorubicin	Liposomal injection	Doxil
Doxorubicin	PEGylated liposomal injection	Lipo-dox
Doxorubicin	PEGylated liposomal injection	Myocet
Doxorubicin	PEGylated liposomal injection	Lip-Dox
Paclitaxel	Albumin bound particles	Abraxane
Cytarabine	Liposomal injection	Depocyt

The reason behind the interest of pharmaceutical company in this area of research is due to high cost of treatment, required repeated administration for prolong period of time and exponential increase in number of cancer patients. In the present section of review of literature, we have explored the possible use of different carrier systems for sustained and targeted delivery of anti-cancer agents with their relative advantages, limitations and commercial importance. This information will help the drug delivery scientist in designing the better formulation for delivery of anti-cancer drugs.

## 2. Pathophysiology of Cancer

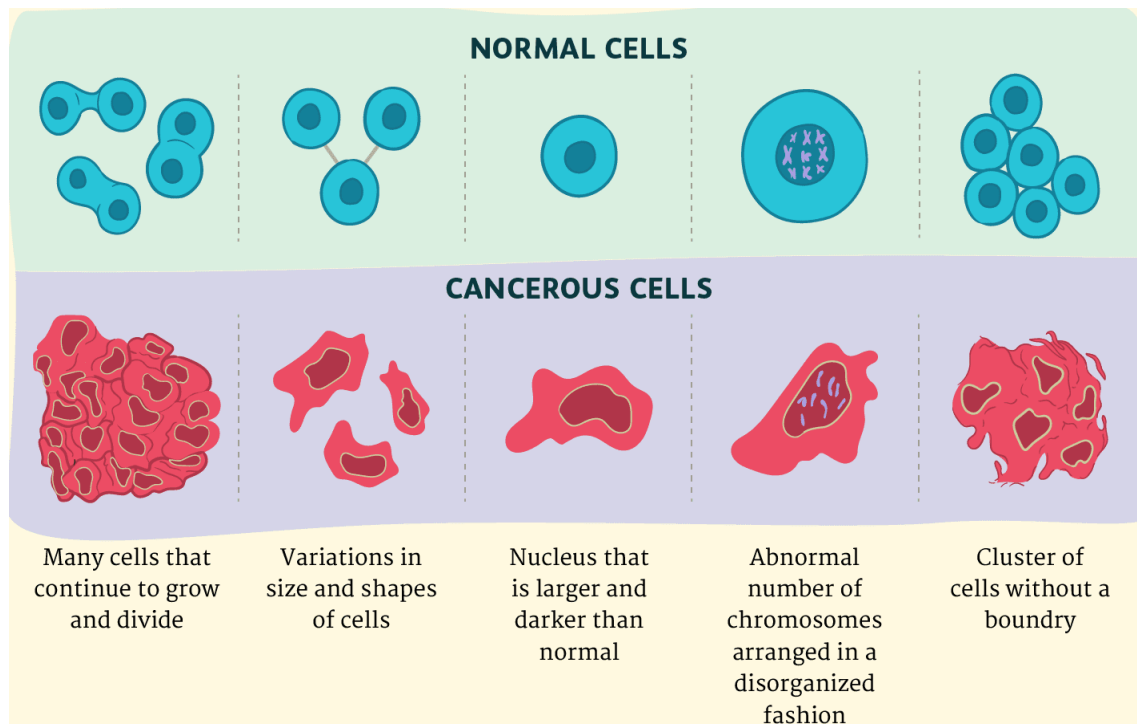
Cancer is basically a disease of failure of regulation of cell cycle. In cancer, the cells transform from normal into cancer cells mainly due to alterations in genes which regulate the cell growth and differentiation. The altered genes are divided into two broad categories. Oncogenes (*e.g.* Her 2, *c-Myc*, *etc.*) and tumor suppressor genes p53 Rb). Oncogenes are the genes which promote the cell growth and reproduction. Second class of genes inhibits the cell division. The cancerous transformation can occur through the formation of novel oncogenes, the inappropriate over expression of normal oncogenes or disabling of tumor suppressor genes. Genetic changes can occur at different levels and by different mechanisms. The gain or loss of an entire chromosome can occur through errors in mitosis. Cell division is a genetic process in which a cell passes its genes onto two daughter cells, each of which is a clone or exact of itself. Sometimes, this orderly process goes wrong, the genes in a cell may suffer a mutation or some mistakes may occur in DNA replication and recombination

during cell division. Genetic changes are more commonly by mutations, which are changes in the nucleotide sequence of genomic DNA. Large-scale mutations involve the deletion or gain of a portion of a chromosome. Genomic amplification occurs when a cell gains many copies (often 20 or more) of a small chromosomal locus, usually containing one or more oncogenes and adjacent genetic material.

Translocation occurs when two separate chromosomal regions become abnormally fused, often at a characteristic location. Small-scale mutations include point mutations, deletions, and insertions, which may occur in the promoter region of a gene and affect its expression, or may occur in the gene's coding sequence and alter the function or stability of its protein product. Disruption of a single gene may also result from integration of genomic material from a DNA virus or retrovirus, and resulting in the expression of *viral* oncogenes in the affected cell and its descendants. Replication of the enormous amount of data contained within the DNA of living cells will probabilistically result in some errors (mutations). Complex error correction and prevention is built into the process, and safeguards the cell against cancer. If significant error occurs, the damaged cell can "self-destruct" through programmed cell death, termed apoptosis. If the error control processes fail, then the mutations will survive and be passed along to daughter cells. Some environments make errors more likely to arise and propagate. Such environments can include the presence of disruptive substances called carcinogens, repeated physical injury, heat, ionising radiation, or hypoxia. The transformation of normal cell into cancer is

akin to a chain reaction caused by initial errors, which compound into more severe errors, each progressively allowing the cell to escape the controls that limit normal tissue growth. This rebellion-like scenario becomes an undesirable survival of the fittest, where the driving forces of evolution work against the body's design

and enforcement of order. Once cancer has begun to develop, this ongoing process, termed clonal evolution drives progression towards more invasive stages. Figure 1 shows pathophysiology of cancer.



**Figure 1.** Normal cells and cancer cell difference

### 3. Problems in Conventional Delivery of Anti-Cancer Drugs

In the field of medicine, the oncology is widely growing subspecialty. There are various treatments as immunotherapy, radiation therapy, chemotherapy, surgery and hormonal therapy used to treat the cancer. However, chemotherapy treatment for cancer is mostly in use but it has many side effects. Various anti-cancer drugs are listed in Table 2. Currently, the intravenous and convectional oral routes are used for administration of the anti-cancer drug. The listed drugs in the Table 3 is marketed anti-cancer drugs convectional dosage forms. The administrative routes for this drug have significant side effects on the healthy tissues in organs because of the non-specific delivery. (3) On the other hand, oral administration of the drug delivery has potential and helps to improve patient life. Also, this method for drug

delivery are most economical and effortable but it has some limitations such as low therapeutic, poor patient compliance, short biological half-life, development of resistance and inability to achieve therapeutic concentrations at the target site. (4-5)

Another major limitation of the oral administration is the variability in bioavailability of substantial patient after taking treatment. The significant difference is observed in pharmacology effects because of the difference in absorption profile. Intravenous route also has many limitations particularly as this route delivers potentially high concentration of drug to normal tissues which results in toxicity.

Several anti-cancer agents are biologically reactive and may trigger the release of various vasoactive substances, sometimes resulting in life threatening reactions.

**Table 2** Classification of anti-cancer drugs

S. No.	Class of drugs	Examples	Therapeutic indications	Side effects	Mechanism of action
1.	Antibiotics	Dactinomycin Danorubicin Doxorubicin Idarubicin Valrubicin Bleomycin Mitomycin Plicamycin	Whilm's tumor, Rhabdomyosarcoma, solid tumors, acute leukaemia, acute non haemolytic leukaemia, non Hodgkin's lymphoma, skin cancer	Mucosal inflammation, pulmonary fibrosis	Inhibit DNA and RNA synthesis
2.	Natural Products	Vincristine,vinblastine Taxanes:Paclitaxel, Docetaxel Etoposide Taniposide Camptothecins Docetaxel	Solid tumors, childhood acute leukaemia, Wilms tumor, Lung carcinoma	Reversible myelosuppression mucositis, neurotoxicity, peripheral neuropathy and alopecia.	Disrupt microtubule apparatus Inhibit depolymerization
3.	Anti-Metabolites	Mercaptopurine Thioguanine Fludarabine Fluorouracil Cytarabine Methotrexate	Acute leukemia, Choriocarcinoma, non Hodgkin's lymphoma, colon, urinary bladder, liver and breast cancers	Chills, fever, vomiting after injection and opportunistic infections	Inhibition of thymidilate synthase Inhibition of DNA polymerase Inhibition of

**Table 3** Marketed conventional dosage forms of anti-cancer drugs

Drug	Dosage Form	Brand	Company
Busulfan	Tablet	Busulfex	Orphan drug company
Docetaxel	Injection	Taxotere	Sanofi Aventis
Vincristine	Injection	Oncovin	Genus Pharmaceuticals Limited
Tamoxifen	Tablet	Nolvadex	AstraZeneca Pharmaceuticals
Chlorambucil	Film coated	Amcil	Amronco life sciences limited
5-FU	Capsules	Fluracil	Biochem Pharmaceuticals

#### 4. Novel Drug Delivery Systems for Anti-Cancer Drug Delivery

As discussed in the above section the conventional treatment for the cancer is killing the healthy tissues in the body with cancer cells because cytotoxic agent's travel with it. Due to its side effect patient can feel unpleasant side effects such as hair loss to nausea and this treatment can damage the immune system of the patient. The development and research are ongoing on reducing the side effects of cancer treatment.

(6) One of the potential treatments is target

drug delivery system at the right pace with required amount. The new development of the targeting drug delivery the new innovations in delivering cancer therapies are the development of a technology platform which targets the therapy only to the tumor; leaving normal cells undamaged Table 4.

#### Extensive Survey on Different Approaches Reported for Sustained and Targeted Delivery of Anti-Cancer Agents

##### Nanoparticles

To compare the anti-tumor efficacy of paclitaxel loaded nano particles and delivered

intratumorally in comparison to marketed Cremophor EL based paclitaxel injection.

**Table 4** Summary of findings reported for altering the biodistribution of anti-cancer drugs

Drug Name	System	Finding	Reference
<b>Tamoxifen</b>	Nanoparticles	• Increased level of accumulation of the drug within tumor	(1)
<b>Paclitaxel</b>	Microemulsion	• Enhanced anti-tumor activity • Total inhibition of cell growth upto 144h	(7)
<b>Paclitaxel</b>	Nano particles	• Achieved larger cytotoxicity and smaller IC50 over Commercial preparation	(8)
<b>Doxorubicin</b>	Human albumin serum (HAS)-Nanoparticles	• Diminish the toxicity and overcome the problem of multi drug resistance	(9)
<b>Mitoxantrone (MTO)</b>	Nanospheres	• Found as promising carrier with altered biodistribution	(10)
<b>Docetaxel</b>	Water Emulsion system	• Enhanced accumulation of docetaxel in a model tumor • 4.5 fold increase accumulation of docetaxel in model tumor mice	(11)
<b>9-nitro-camptothecin (9-NC)</b>	Folate-conjugated polymer micelles	• 3.7 to 17.0 times increased killing ability shown by formulated preparation than free drug in various cell lines	(12)
<b>5-Fluorouracil (5-FU)</b>	Niosomes	• 4 to 8 folds enhanced drug penetration	(13)

It was found that developed nanoparticles sustained the drug release, increased cellular concentration and enhanced anti-tumor efficacy of paclitaxel compared to marketed formulation. (14-15)

To prepared paclitaxel loaded polymeric nanoparticles with an aim to achieve targeted delivery of paclitaxel. Nanoparticles were developed by using biodegradable methoxy poly(ethylene glycol)-poly-( $\epsilon$ -caprolactone) (MPEG-PCL) diblock copolymer. Paclitaxel loaded nanoparticles had shown very high entrapment efficiency above (95%) and sustained release during *in vitro* experiments. The maximum tolerated dose (MTD) of paclitaxel loaded nanoparticles after single dose in Balb/c mice was above 80 mg PTX/kg body weight (b.w), which was 2.6-fold higher than that of Taxol(R) (30 mg paclitaxel/kg b.w). The higher concentration of paclitaxel found in tumor tissue in paclitaxel loaded nanoparticles administered group in comparison to taxol treated group. It was concluded that nanoparticles based paclitaxel formulation is good alternative to conventional

formulation for controlled delivery of paclitaxel. (16)

Studied the efficiency of doxorubicin loaded iron oxide nanoparticles in comparison to doxorubicin drug solution. The results indicated that doxorubicin nanoparticles were readily taken up by drug resistant cells and greater reduction in cell viability was found than cell treated with doxorubicin solution. The results suggest that doxorubicin nanoparticles could improve the efficiency of chemotherapy. (17)

To developed the nanoparticles that facilitate intracellular delivery of nanoparticles within the tumor. Hydrophobically modified glycol chitosan nanoparticles conjugated with interleukin-4-receptor (IL-4R) binding peptides were developed and were tested in mice bearing positive tumors. The results indicated enhanced cellular uptake of nanoparticles in tumors in comparison to conventional approach. (18) Developed natural polymer based etoposide loaded nanoparticles attached with folic acid as ligand. These nano particles found more effective on HeLa cell

line than etoposide loaded plain nanoparticles and shown more potential as a targeted cancer therapy. (19)

To prepared tyrosine derived nanospheres loaded with paclitaxel and evaluated the toxicity and efficacy of this drug delivery system in comparison to Cremophor EL based marketed formulation. The results of this study suggested that nanospheres based formulation significantly increased the maximum tolerated dose and enhanced anti-tumor efficacy in tumor breast cancer cell lines. (20)

The above studies suggested that nanoparticles for drug delivery of anti-cancer drugs are a useful approach to provide site specific and controlled release of drug at the target tumor site which ultimately improves the efficiency of chemotherapy at lower dose.

### Emulsion systems

To prepared paclitaxel micro emulsion containing reduced amount of Cremophor EL and evaluated pharmacokinetics, biodistribution and *in vivo* anti-tumor efficacy. The antitumor efficacy of the paclitaxel microemulsion in OVCRA-3 and A 549 tumor-bearing animals was similar to that of paclitaxel marketed formulation. The incidence and degree of allergic reactions exhibited by the paclitaxel microemulsion group, with or without premedication, were significantly lower than those in the paclitaxel injection group. (21)

To prepared the Vinorelbine-loaded lipid emulsion (VLE) and compared its toxicity and its anti-tumor efficiency in comparison to conventional marketed formulation. VLE significantly reduced the toxicity in comparison to marketed formulation. Comparable anti-tumor efficiency was also obtained in comparison to marketed formulation.

To developed hydroxylcamptothecin (HCPT) loaded emulsion spun fibers and evaluated anti-tumor efficiency by *in vitro* and *in vivo* method. *In vitro* cytotoxicity tests on HCPT-loaded electrospun fibers indicated over 20 times higher inhibitory activity against HepG2 cells than free HCPT. Similarly, HCPT-loaded fibers indicated superior *in vivo* antitumor activities and fewer side effects than free

HCPT. The above results demonstrate the potential use of emulsion electrospun fibers as drug carriers for local treatment of solid tumors. (22)

The above studies suggested that emulsion systems are safer to administer and easier to prepare but some problems such as difficulty in particle size reduction and low entrapment efficiency limit the application of emulsion systems in drug delivery.

### Polymeric micelles

Polymeric micelles are currently recognized as one of the most promising modalities of drug carriers. (23-24) Polymeric micelles have a unique core-shell structure, in which an inner core serving as a nano container of hydrophobic drugs surrounded by an outer shell of hydrophilic polymers, such as poly (ethylene glycol) PEG, and have demonstrated longevity in the bloodstream and effective tumor accumulation after their systemic administration. (25-26)

To prepared Docetaxel-loaded methoxy-poly(ethylene glycol)-*block*-poly(*d, l*-lactide) (m PEG-PDLLA) micellar formulation and its pharmacokinetics, efficacy, and toxicity were evaluated in comparison with marketed paclitaxel formulation Taxotere® in preclinical studies. Results of study indicated that prepared micellar formulation reduces side effects while retaining anti-tumor efficiency in cancer patients in comparison to Taxotere®. (27)

The above studies indicated that polymeric micelles are good colloidal nanocarriers for the targeting of poorly water soluble drugs. Due to their hydrophilic shell and small size they can accumulate in tumoral tissues.

### Solid lipid nanoparticles (SLN)

To prepared and investigated tumor targeting potential of surface tailored solid lipid nanoparticles (SLNs) loaded with anti-cancer drug doxorubicin. Results revealed that formulation exhibited a biphasic pattern characterized by initial rapid release of the drug followed by slow and prolonged release. Significantly higher cytotoxicity of doxorubicin loaded SLNs found in comparison to doxorubicin drug solution in A549 cell line.

The biodistribution profile exhibited that SLNs were able to deliver a higher concentration of doxorubicin in tumor mass. (28)

To prepare solid lipid nanoparticles loaded with a promising chemo preventive drug Resveratrol. The results indicated that intracellular delivery of drug significantly increased with this carrier system in comparison to drug solution and finally enhanced cytostatic effect was obtained. (29)

Administration of anti-cancer drugs by using solid lipid nanoparticles is a promising approach. Many problems in the administration of anti-cancer drugs like non target organ toxicity, pitiable specificity and high incidence of drug resistant tumor cells are at least partially overcome by delivering anti-cancer drugs by using solid lipid nanoparticles.

### Liposomes

To prepared liposomes containing histone deacetylase inhibitors (HDACi) and optimized the formulation. They have evaluated the cell viability of developed formulation in breast cancer cell lines SKBR3 and MCF-7 by administering without drug loaded liposomes and drug loaded formulation. The observed results indicate that no cytotoxicity of unloaded liposomes and altered breast cancer cell viability found with drug loaded liposomes in comparison to drug solution. (30)

To optimized the liposomes for the administration of mitoxantrone (MTO) with the aim to improve the therapeutic effect of drug. The anti-cancer activity was evaluated in peritoneal carcinomatosis model. This system exhibited the strongest binding affinity for MTO, the highest anti-cancer activity and the lowest toxicity. This cardiotoxicity of MTO was significantly reduced in comparison to drug solution. (31)

To prepare the RGD grafted docetaxel liposomes and evaluated *in vitro* cytotoxicity, mechanism of cell death, *in vivo* pharmacokinetic and biodistribution behavior of formulation. The results indicated sustained intracellular release of drug from liposomal system with site specific distribution of drug to tumor and enhanced anti-tumor activity. (32,33)

To synthesized a novel polyethylene glycol-phosphatidylethanolamine (PEG-PE) conjugate with the Triphenylphosphonium (TPP) group attached to the distal end of the PEG block (TPP-PEG-PE). This conjugate was incorporated into the liposomal lipid bilayer, and the modified liposomes were studied for their toxicity, mitochondrial targeting, and efficacy in delivering paclitaxel (PTX) to cancer cells. PTX-loaded TPP-PEG-L demonstrated enhanced PTX-induced cytotoxicity and anti-tumor efficacy in cell culture and mouse experiments compared to PTX-loaded conventional liposomes. (34)

The above studies in which liposomal drug delivery systems were studied indicated that this approach has provided an opportunity to enhance the therapeutic efficiency of drugs by altering their solubility and biodistribution. Some studies suggested that liposomal systems significantly increased the cytotoxicity of the anti-cancer drugs when administered by using liposomes. (35, 36)

### 5. Conclusions

Novel drug delivery systems of anti-cancer drugs will alter the pharmacokinetic properties of drug accompanied by elimination or reduction of nonspecific toxicities typically associated with chemotherapy. They will provide versatile and straight forward approach for improving the physiological and pharmacological responses of the drug and overcome the problem of drug solubility. With use of novel drug delivery systems, it is possible to reduce the dose of drug and at the same time cost of cancer chemotherapy. Novel approaches to cancer treatment not only supplement the conventional chemotherapy and radiotherapy but also prevent damage to normal tissues and prevent drug resistance.

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### Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

## References

1. Shenoy D, Little S, Langer R, Amiji M. Poly(ethylene oxide)-modified poly(beta-amino ester) nanoparticles as a pH-sensitive system for tumor-targeted delivery of hydrophobic drugs: part 2. In vivo distribution and tumor localization studies. *Pharmaceutical research*. 2005; 22(12): 2107-14.
2. Jain RK. Barriers to drug delivery in solid tumors. *Scientific American*. 1994;271(1):58-65.
3. Bhatt P, Vhora I, Patil S, Amrutiya J, Bhattacharya C, Misra A, et al. Role of antibodies in diagnosis and treatment of ovarian cancer: Basic approach and clinical status. *Journal of Controlled Release*. 2016;226:148-67.
4. Lowenthal RM, Eaton K. TOXICITY OF CHEMOTHERAPY. *Hematology /Oncology Clinics*. 1996; 10(4):967-90.
5. Ruggeri B, Zhang SY, Caamano J, DiRado M, Flynn SD, Klein-Szanto AJ. Human pancreatic carcinomas and cell lines reveal frequent and multiple alterations in the p53 and Rb-1 tumor-suppressor genes. *Oncogene*. 1992;7(8):1503-11.
6. Yewale C, Baradia D, Patil S, Bhatt P, Amrutiya J, Gandhi R, et al. Docetaxel loaded immunonanoparticles delivery in EGFR overexpressed breast carcinoma cells. *Journal of Drug Delivery Science and Technology*. 2018;45:334-45.
7. Esposito M, Kang Y. Targeting tumor-stromal interactions in bone metastasis. *Pharmacol Ther*. 2014;141(2):222-33.
8. Feng Y, Sun B, Li X, Zhang L, Niu Y, Xiao C, et al. Differentially expressed genes between primary cancer and paired lymph node metastases predict clinical outcome of node-positive breast cancer patients. *Breast cancer research and treatment*. 2007;103(3):319-29.
9. Dreis S, Rothweiler F, Michaelis M, Cinatl J, Jr., Kreuter J, Langer K. Preparation, characterisation and maintenance of drug efficacy of doxorubicin-loaded human serum albumin (HSA) nanoparticles. *International journal of pharmaceutics*. 2007;341(1-2):207-14.
10. Lu H, Ouyang W, Huang C. Inflammation, a key event in cancer development. *Molecular cancer research : MCR*. 2006;4(4):221-33.
11. Yanasarn N, Sloat B, Cui Z. Nanoparticles Engineered from Lecithin-in-Water Emulsions As A Potential Delivery System for Docetaxel. *International journal of pharmaceutics*. 2009; 379: 174-80.
12. Park C, Youn H, Kim H, Noh T, Kook YH, Oh ET, et al. Cyclodextrin-covered gold nanoparticles for targeted delivery of an anti-cancer drug. *Journal of Materials Chemistry*. 2009;19(16):2310-5.
13. Cosco D, Paolino D, Muzzalupo R, Celia C, Citraro R, Caponio D, et al. Novel PEG-coated niosomes based on bola-surfactant as drug carriers for 5-fluorouracil. *Biomedical microdevices*. 2009; 11(5):1115-25.
14. Chakravarthi S, Robinson D, De S. Nanoparticles Prepared Using Natural and Synthetic Polymers. 2007. p. 51-60.
15. P. Patel et al. Surface Modification of Nanoparticles for Targeted Drug Delivery. In *Surface Modification of Nanoparticles for Targeted Drug Delivery*, Cham: Springer International Publishing. 2019:19-31.
16. Grenha A. Chitosan nanoparticles: a survey of preparation methods. *Journal of Drug Targeting*. 2012; 20(4):291-300.
17. Kievit FM, Zhang M. Surface engineering of iron oxide nanoparticles for targeted cancer therapy. *Accounts of chemical research*. 2011; 44(10):853-62.
18. Kim SK, Foote MB, Huang L. The targeted intracellular delivery of cytochrome C protein to tumors using lipid-apolipoprotein nanoparticles. *Biomaterials*. 2012; 33(15):3959-66.
19. Kılıçay E, Demirbilek M, Türk M, Güven E, Hazer B, Denkbaz E. Preparation and characterization of poly(3-hydroxybutyrate-co-3-hydroxyhexanoate) (PHBHHX) based nanoparticles for targeted cancer therapy. *European journal of pharmaceutical sciences: official journal of the European Federation for Pharmaceutical Sciences*. 2011; 44: 310-20.
20. Goyal R, Macri LK, Kaplan HM, Kohn J. Nanoparticles and nanofibers for topical drug delivery. *J Control Release*. 2016;240:77-92.
21. He L, Wang GL, Zhang Q. An alternative paclitaxel microemulsion formulation: hypersensitivity evaluation and pharmacokinetic profile. *International journal of pharmaceutics*. 2003; 250(1):45-50.
22. Luo X, Xie C, Wang H, Liu C, Yan S, Li X. Antitumor activities of emulsion electrospun fibers with core loading of hydroxycamptothecin via intratumoral implantation. *International journal of pharmaceutics*. 2012;425(1):19-28.
23. Nagaich DU, Deepak P, Sharma A, Gulati N, Chaudhary A. POLYMERIC MICELLES: POTENTIAL DRUG DELIVERY DEVICES. *Indonesian Journal of Pharmacy*. 2013;24:223-38.
24. Aliabadi HM, Lavasanifar A. Polymeric micelles for drug delivery. *Expert opinion on drug delivery*. 2006;3(1):139-62.
25. Nishiyama N, Okazaki S, Cabral H, Miyamoto M, Kato Y, Sugiyama Y, et al. Novel cisplatin-incorporated polymeric micelles can eradicate solid tumors in mice. *Cancer research*. 2003;63(24):8977-83.
26. Bae Y, Jang WD, Nishiyama N, Fukushima S, Kataoka K. Multifunctional polymeric micelles with folate-mediated cancer cell targeting and pH-triggered drug releasing properties for active intracellular drug delivery. *Molecular bioSystems*. 2005;1(3):242-50.
27. Kulthe S, Choudhari Y, Inamdar N, Mourya VK. Polymeric Micelles: Authoritative Aspects for Drug



- Delivery. Designed Monomers and Polymers. 2012;15.
28. Jain A, Agarwal A, Majumder S, Lariya N, Khaya A, Agrawal H, et al. Mannosylated solid lipid nanoparticles as vectors for site-specific delivery of an anti-cancer drug. *J Control Release*. 2010;148(3):359-67.
  29. Teskac K, Kristl J. The evidence for solid lipid nanoparticles mediated cell uptake of resveratrol. *International journal of pharmaceutics*. 2010;390(1):61-9.
  30. Raouane M, Desmaële D, Urbinati G, Massaad-Massade L, Couvreur P. Lipid Conjugated Oligonucleotides: A Useful Strategy for Delivery. *Bioconjugate Chemistry*. 2012;23(6):1091-104.
  31. Ezzati Nazhad Dolatabadi J, Valizadeh H, Hamishehkar H. Solid Lipid Nanoparticles as Efficient Drug and Gene Delivery Systems: Recent Breakthroughs. *Adv Pharm Bull*. 2015;5(2):151-9.
  32. Naik S, Patel D, Chuttani K, Mishra AK, Misra A. In vitro mechanistic study of cell death and in vivo performance evaluation of RGD grafted PEGylated docetaxel liposomes in breast cancer. *Nanomedicine: nanotechnology, biology, and medicine*. 2012; 8(6):951-62.
  33. Lalani RA, Bhatt P, Rathi M, Misra A. Abstract 2063: Improved sensitivity and in vitro efficacy of RGD grafted PEGylated gemcitabine liposomes in RRM1 siRNA pretreated cancer cells. *Cancer research*. 2016;76(14 Supplement):2063.
  34. Biswas S, Dodwadkar NS, Deshpande PP, Torchilin VP. Liposomes loaded with paclitaxel and modified with novel triphenylphosphonium-PEG-PE conjugate possess low toxicity, target mitochondria and demonstrate enhanced antitumor effects in vitro and in vivo. *J Control Release*. 2012;159(3):393-402.
  35. Bhatt P, Lalani R, Vhora I, Patil S, Amrutiya J, Misra A, et al. Liposomes encapsulating native and cyclodextrin enclosed paclitaxel: Enhanced loading efficiency and its pharmacokinetic evaluation. *International journal of pharmaceutics*. 2018; 536(1):95-107.
  36. Bhatt P, Lalani R, Mashru R, Misra A. Abstract 2065: Anti-FSHR antibody Fab' fragment conjugated immunoliposomes loaded with cyclodextrin-paclitaxel complex for improved in vitro efficacy on ovarian cancer cells. *Cancer research*. 2016;76(14 Supplement):2065.