NANOCARRIERS FOR CANCER-TARGETED DRUG DELIVERY: REVIEW AND CHALLENGES

Kanchan Ravindra Lolage¹*, Pushkaraj Rajendra Wagh¹,²*

¹Bachelor of Pharmacy, ²Master of Pharmaceutical Sciences

¹Department of Pharmaceutics,

¹MVP’s College of Pharmacy, Gangapur Road, Nashik, Maharashtra, India.

Abstract

From the past decade, researchers have seen the potential application of nanotechnology in the field of cancer-targeted drug delivery. Nanoparticle-based chemical moieties such as polymeric based nanoparticles, dendrimers, polymersomes, liposomes, nano micelles, metal nanoparticles, carbon nanotubes (CNTs), etc. Due to their exclusive properties such as tunable surface chemistry, ability to penetrate cells, stimuli-sensitization they could be designed as per the targeted tissue or cells of the tumor. This review provides an insight into the development of nanomedicine with the help of different nanocarriers for cancer/tumor-targeted drug delivery. But apart from having desired flexibility in the development of nanocarrier based drug compound, it has some drawbacks/challenges. The review will also discuss the same.

Keywords: nanoparticles, drug carriers, cancer treatment, drug delivery, nanotechnology.

1. Introduction

The use of nanomedicines in the field of medicine has been investigated for the targeted delivery of drugs in various diseases. The main goal of nanomedicine is to overcome the drawbacks caused by the conventional dosage forms. Nanocarriers have unique properties such as nanoscale size, high surface-to-volume ratio, and favorable physicochemical characteristics. They have the potential to modulate both the pharmacokinetic and pharmacodynamic profiles of drugs, thereby enhancing their therapeutic index. Loading of drugs into nanocarriers can increase in vivo stability, extend a compound's blood circulation time, and allow for controlled drug release. Thus, nanomedicine compounds can alter the biodistribution of drugs by allowing them to accumulate preferably at the tumor site. This phenomenon is known as the enhanced permeability and retention effect (EPR). ¹ A wide range of nanomaterials based on organic, inorganic, lipid, protein, or glycan compounds as well as on synthetic polymers have been employed for the development of new cancer therapeutics (Fig. 1)

2. Key principles of NC based drug delivery system

1. Nanoparticles may help to overcome problems of solubility and chemical stability of anti-cancer drugs. Poor water solubility limits the bioavailability of a compound and may hamper the development of anti-cancer agents identified during early drug screens. ²
2. Nanocarrier can protect anti-cancer compounds from biodegradation or excretion thus influencing the pharmacokinetic profile of a compound.

3. Nanotechnology can help to improve the distribution and targeting of anti-tumor medication. The distribution of anti-cancer drugs is defined by their physicochemical properties and is limited by drug penetration into tumor tissue.  

4. Nanocarriers can be designed to release their payload upon a trigger resulting in stimuli-sensitive nanomedicine therapeutics. 

5. Targeted nanomedicine therapeutics may decrease the resistance of tumors against anti-cancer drugs.

3. Nanocarriers

3.1 Liposomes

Liposomes are composite self-assembled colloidal vesicles having a lipid bilayer. Liposomes usually consist of amphiphilic phospholipids but may also include other lipids as well. The types of liposomes are unilamellar or multilamellar depending upon the number of bilayer. Liposomes have exclusive physicochemical properties which help them to circulate for a longer time in blood, it can then be conjugated to compounds like PEG to form stealth liposomes with easily tunable surface charge along with tunable particle size. Liposomes can be converted to immunoliposomes where anti-body or anti-body fragment could be attached to the surface, thereby increasing the anti-tumor activity of the drug and eliminating the toxicity of the free drug. Despite all the promising advantages, liposomal drug delivery has some limitations like low drug loading capacity, oxidation of phospholipids, low industrial reproducibility, etc. Still, some formulations that are in clinical trials include Lipoplatin, Stimuvax, liposomes containing cytarabine and daunorubicin and many more. And FDA approved formulations include DOX as API along with liposomes having different composition and MXT, PCX as API.

3.2 Dendrimers

The term dendrimer is derived from the Greek word, “dendron” meaning tree-like and “mer” means part. They are highly branched polymeric macromolecules with well-defined uniform shapes and sizes. Their basic structure consists of branched repeating units along with terminal groups that provide surface chemistry and a central core. Tomalia and coworkers synthesized and characterized the first dendritic family as a polyamidoamine (PAMAM) dendrimers in the 1980s. Dendrimers having nanostructure have shown to pass the biological membrane. Due to this property functionalization of it is carried out such as PEGylation, acetylation, with the use of vitamins, peptides, antibody, aptamer, with lipids, etc. Also thermo-responsive dendrimer, enzyme-responsive dendrimers have been developed. Various other studies showed that functional dendrimers have a better anti-tumor effect. But regardless of their potential as a better therapeutic drug delivery system, they cause toxicity, hemolysis and interaction with the cellular membrane.

3.3 Metal Nanoparticles

Metal nanoparticles are nanocomposite structures made up of polymer matrix along with metal nanoparticle( Au, Cu, Pd, Pt, Ag, Fe, and Ni ) dispersed in it. A study conducted by stated that chitin-silver based nanoparticles showed an
anti-tumor effect in human breast cancer (MCF-7) cells. Another study showed that by surface modification of TiCO₂ NPs by NH₃, increased the cytotoxic effects of the Ti-CO₂.

3.4 Carbon Nanotubes

Carbon Nanotubes are essentially tubes made of carbon with a diameter measured in nanometers. They could be single-walled carbon nanotubes (SWCNTs) or multi-walled carbon nanotubes (MWCNTs). The use of carbon nanotubes for the treatment of cancer is based on the fact that they are able to penetrate into the tumor tissues due to their dimensions. Mostly, hydrophobic drugs can be loaded into the CNTs thanks to their non-covalent stacking. Docetaxel (DTX) loaded, folic acid (FA), Polyethylene glycol. (PEG) conjugated MWCNTs arrested cell death in the G2 phase of MCF-7 cells. In another study, Paclitaxel (PTX) was conjugated with lipid docosanol and functionalized with CNTs, along with conjugation of folic acid to it. The prepared formulation FA-SWCNT-lipid-PTX showed improved drug efficacy in comparison to free drugs. Cisplatin, Pt-based anti-cancer drug when conjugated with CNT (MWCNT), showed greater inhibition of urinary bladder cancer cells as compared to unfilled MWCNTs.

3.5 Polymeric based nanoparticles

Polymeric nanoparticles are conjugated nanoparticle system, made up of drug of interest encapsulated in the hydrophobic core of the particle system surrounded by a hydrophilic coating. Polymer-based drug delivery system is developed by the use of various synthetic polymers like poly(ethylene glycol) PEG, poly(l-lysine) PLL, poly(dl-lactide co-glycolide) PLGA, polymeric micelles and naturally occurring polymer like chitosan. Polymeric based nanoparticles have a major role in the delivery of anti-cancer drugs because of their unique advantages like protection of drugs against degradation, site-specific drug delivery, control release of the drug. Along with such advantages the polymeric NPs have, the framework of the conjugate system could be tuned with functional groups to have better efficacy. In the study conducted by showed that Doxorubicin (DOX) was used in combination with Thiordinazine (THZ), along with formation of mixed polymeric micelles of acid-functionalized poly(carbonate) and poly(ethylene glycol) diblock copolymer (PEG-PAC) and urea functionalized poly(polycarbonate) (PUC) and PEG diblock copolymer (PEG-PUC) were used to test anti-cancer activity on BT-474 xenograft in nude mice. Another study showed that active tumor-targeted co-delivery micelles (DOX + Cur)-PMs, with two synergistic drugs of a therapeutic drug of doxorubicin (DOX) and a chemosensitizer of curcumin (Cur) co-encapsulated into hyaluronic acid-vitamin E succinate (HA-VES) graft copolymer, were prepared and delivered simultaneously into tumor cells for improving therapeutic effects of DOX.

3.6 Miscellaneous

Reported that drug-loaded (paclitaxel) magnetic Janus particles (DMJPs) showed higher toxicity only to human breast cancer cells (MDA-MB-231) but not to mouse embryonic fibroblasts (NIH-3T3). Constructed Photothermal therapy (PTT) agent by coating carbon nanosphere by patchy gold and tested its activity in MCF-7 cells in vitro and in vivo in mice. Prepared Janus nano-prodrug of camptothecin and gemcitabine, with redox-sensitive disulfide bond linking them together. The anti-tumor activity testing was done on A549, NCI-H460, HCT116, HT-29, and MCF-7/ADR cell lines and the inhibition of cancer cell proliferation inhibition exceeded 50%.
4. Drawbacks and Challenges

Besides distinctive features of Nanotechnology in oncological applications such as improvement of drug therapeutic index by enhancing drug efficacy or reducing toxicity, targeted delivery of drug in a specific manner, enhancement of pharmaceutical properties (stability, solubility, circulating half-life, sustained or controlled release), co-delivery of multiple drugs to improve therapeutic efficacy and overcome drug resistance, Nanotechnological application in cancer nanomedicine development has many drawbacks.  

4.1 Physiochemical properties change concern

Variability within physiochemical properties structure, composition, size, surface properties, porosity, charge, etc. makes it difficult to characterize nanomedicine products before and after administration. Nanomedicine products should be characterized on batch to the batch basis, using multiple methods. The final product form of nanomedicine should be characterized under clinically relevant conditions as nanocarriers when present in a biological fluid may interact with it causing agglomeration of particles. Storage and stability of nanomedicine are also challenging aspects because polymer-based NPs degrade in body fluids and alter their physicochemical properties such as size, drug loading, and release profile. This would eventually have an impact on the performance of nanomedicine in vivo.

4.2 Scalable Manufacturing Issues

Manufacturing of nanomedicine drug products for commercial use in the market is technically difficult and challenging due to the fact that during the scale-up production of it, batch to batch variation in physical and chemical properties may occur due to polydispersity of the nanomaterial. Good Manufacturing Practice (GMP) compliant production is a major hurdle along with manageable scale-up production of nanomedicine. Due to this reason, the precision production of nanomedicine at the industry level fails. An example of this is, the production of Doxil had to be suspended in November 2011 due to sterility and manufacturing issues until 2014 which lead to increased medication costs. The cost for the production of commercially available nano-sized drugs is tremendously high as compared to it’s conventional counterparts. An example of this Abraxane and Doxil, also their clinical benefit is not high enough to offset the development and production cost.

4.3 Evaluation and Screening

In vitro and in vivo evaluation and screening plays an important role as new NPs with the emergence of novel biomaterials are rapidly developed. In vitro cell assays could improve the understanding of NP-cell interaction but the disadvantage is that the NP interacts in biological tissue and physiological system in a complex manner. Lately, efforts are being made to develop organ/tissue-to-chip models to mimic the tissue system and test the activity of NPs. It has the potential to show the preview of the actual behavior of NP in a biological system, than just making a transition to test it in a clinical or pre-clinical scenario. In the case of in vivo testing, there have been discrepancies in results between pre-clinical and clinical studies. Although some studies have shown differences in vivo models like Patient-derived xenograft (PDX) and Genetically engineered mouse models (GEMMs) but still, no animal model can complete the scenario of human malignancy.
4.4 Safety concerns and Regulatory issues

The majority of nanomedical products have been approved by FDA and EMA as they fulfill the current safety requirements put forth by the organization but specific guidelines for safety and other concerns for products containing nanomaterials have not yet been implemented by the regulatory organizations. Another issue with the regulation of nanomedicine is that the approval for the product itself is a very time-consuming process due to the fact that NPs involve various criteria for their actual behavior in a biological system. As more and more new complex nanomedicines are developed rapidly, the regulation of nanomedicine will require a high level of expertise in innovative technologies and it will also become a more time-consuming process. As a part of the Horizon 2020 project, the European Technology Platform on Nanomedicine (ETPN) intends to set up a European Nano-Characterisation Laboratory. Nanoparticles being a potential therapeutic option for the treatment of cancer has safety concerns as well. NPs have a dimension similar to that of intracellular organelles or biomolecules involved different cellular activities. Several studies have demonstrated that NPs have detrimental effects on the biological system which has led to the emergence of an independent research field, nanotoxicology. Nonetheless, the assessment of the toxicological effects of nanomedicine is still difficult as assays used for it are the same as those used for macro materials. Hence, the comparison of toxicity of nanomedicine with that of conventional products is questionable.

5. Conclusion and Future directions

Over the past decade, many scientific advances have occurred in the field of medicine including cancer therapeutics. Cancer nanomedicine has the potential to treat patients suffering from cancer but some aspects like scalable manufacturing targeted NP delivery, safety, and regulatory concerns, lack of pre-clinical and clinical evaluation studies, manufacturing cost, etc. has held back the transition of laboratory drug-conjugate system from pre-clinical stage to clinical stage. There is a substantial need to improve the quality assessment of nanomaterials by developing well-defined and reproducible standards. Moreover, in vitro and in vivo models accurately representing the clinical setting must be developed. A complete understanding of drug in nano dimension form is required along with its nano-bio interactions, heterogeneity of tumor, passive or active targeting of TME, which will lead to the progressive development of nanotherapeutics for cancer treatment. We expect that new novel NP systems are formed with the incorporation of siRNA, mRNA, kinase inhibitors rather than biodegradable polymers only. By overcoming all the challenges involved in the development of cancer nanomedicine, a significant impact will be made to millions of patients suffering from cancer worldwide.

This review has explored the potential of nanotechnology that it has on tumor biology and its drug development along with the challenges involved in the clinical translation of nanotherapeutics.

6. Acknowledgments

This Review has been benefited from all the available research data in search engines like Pubmed, Science direct in this field of medicine. We appreciate all fellow scientists and researchers for their contribution to this field.
7. Conflict of interest

The authors have no conflict of interest.

8. References


35. Chanakya Patil; Yashwardhan Ghanwatkar; Pushkaraj Wagh NP. Nanocarriers for Cancer Diagnosis and Targeted Cancer Therapy. *International Journal of Emerging Technologies and Innovative Research (www.jetir.org)*, ISSN:2349-5162. August 2018;Vol.5(Issue 8,):page no.538-540,


---

**Fig. 1** Schematic illustration of established nanotherapeutic platforms. Different nanomedicine products such as drug conjugates, lipid-based nanocarriers, polymer-based nanocarriers, inorganic nanoparticles, and viral nanoparticles are used in clinical cancer care. ▪