

Nanoparticles – A Booming Drug Delivery System in Chemotherapy

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The current study proposed the “Nanoparticles -A Booming Drug Delivery System in Chemotherapy” is a Novel targeted approach which enhances the efficacy of chemotherapeutic agents by reducing the dose-related side effect as well as mortality rate in a patients due to its non-immunogenic, nontoxic nature. Drug bioavailability, drug solubility, drug biodistribution, drug resistance brought on by treatment, and nonspecific toxicity can all be improved with the development of nanoparticle chemotherapeutic drug delivery applications based on nanotechnology. It possesses active as well as passive targeting of tumour cells. Due to this reason, a wide range of chemotherapeutic agents like cisplatin, taxol, doxorubicin, and carboplatin are extensively utilized for treating cancer. Deep tissue penetration of nanoparticles is found to increase the enhanced permeability and retention (EPR) effect. There are some limitations with conventional drug delivery system which is minimized by utilizing nanoparticles as a drug delivery system. The current review has focused on targeted strategies and novel approaches in cancer treatment with nanoparticles.

Keywords: Bioavailability; Chemotherapy; Nanoparticles; Solubility; Targeted Therapy; Tumour.

Advanced drug delivery methods for targeted sites in chemotherapy are based on nanotechnology. Nanoparticles act as drug carriers for a wide variety of drugs irrespective of their solubility and permeability. Researchers are using techniques in the treatment of cancers by encapsulating the potent drug in the form of nanoparticles which act as an efficient tool in chemotherapy with minimum side effects¹. Significant toxic and adverse effects of conventional

chemotherapy are caused by the toxic effect of chemotherapeutic agents on healthy cells. The use of nanotechnology in tumour chemotherapy can improve the targeting of anticancer drugs, boost tumour killing, and lessen harmful and side effects. One of the biggest benefits of nanomaterial-based cancer therapy over free drugs is targeted delivery.

Chemotherapy is the process of treating malignant cells or tumour cells with medicines or drugs. Chemotherapy is given by IV, IM and orally

in a systematic order for a specific period. There are various side effects of chemotherapy depending upon the drug dose and its route. To overcome such problems nanoparticles are incorporated as a special tool².

Cancer

Uncontrolled cell proliferation and cell division are characteristics of cancer. It might be benign or malignant. Several approaches of novel drug delivery systems are being utilized to treat cancer³. Around the world mortality rate is very high due to late detection and insufficient treatment for cancer. A wide variety of treatments are available including radiation, surgery, immune therapy, targeted therapy, hormone therapy etc. depending upon the stage and tolerance and response of patients. The development of anti-cancer agents is a complex procedure because of the selection of suitable chemical moiety for drug entrapment⁴. Nanoparticles can increase the intracellular amount of medications in cancer cells while reducing their toxic effect in normal cells by employing both passive and active targeting tactics. Because of the improved permeability and retention (EPR) capabilities of nanocarriers, passive targeting takes use of the biological characteristics of tumours.⁵ Active strategies accomplish this by coupling molecules that attach to promote the target cells⁷ overexpression of antigens or receptors to nanocarriers that contain chemotherapeutics.

Nanoparticles

Drug half-life can be extended by nanocarriers, which can also lead to their accumulation in tumour tissues because of the size, surface, and retention-enhancing properties of NPs.⁶ The choice of a targeted drug delivery system is a need in cancer treatment. Thus, nanotechnology act as a boon in the field of nanomedicine. The major challenge is to discriminate the malignant cells from the healthy cells of the body. Current chemotherapy has issues with cytotoxicity, lack of selectivity, low solubility, short half-lives, the incidence of multi-drug resistance, and the development of stem-like cells. Nanomaterial-based chemotherapy, molecular therapy targeted therapy, photodynamic therapy, sono-dynamic therapy, and photothermal therapy are all used to treat cancer to get around these limitations. Nanoparticles are the new drug delivery system utilized in targeted therapy⁷. They are having a size range of less than 100 nm and can

encapsulate a wide variety of drugs which enhances their solubility and permeability. Solubility is a major problem in chemotherapeutic agents. Nanoparticles can administer chemotherapeutic treatments with various benefits compared to using free medications directly. Some of them have to do with the fact that chemotherapeutic drugs can become more stable and solubilize better when delivered by nanoparticles, while intravenous administration of nanoparticle-delivered drugs can enhance biodistribution, prolong circulation time, and lessen the side effects of chemotherapy reactions. A wide range of prodrugs can be encapsulated in nanoparticles for target drug delivery. These drugs are target specific and only show their response after activation at the actual diseased cell in case of a tumour⁸. Example: cisplatin. The brain-blood barrier (BBB) is a unique defence mechanism designed to shield the central nervous system (CNS) from poisonous and damaging substances. The “brain capillary endothelial cells” are organized to form a wall that feeds the brain with vital nutrients. Since the BBB’s main purpose is to prevent hazardous substances from entering the brain, the only effective chemotherapeutic treatments for brain cancer at the moment are intracerebral infusions or intraventricular.⁸ But NPs have been known to cross the BBB. Currently, Nanoparticles are delivered by a variety of methods, including transcytosis, the EPR effect, targeted ultrasound, and peptide-modified endocytosis. Methotrexate absorption in rats was improved by glutathione PEGylated liposomes that were encapsulated with the drug.⁹ Due to their ability to carry medications that cause apoptosis, AuNPs are frequently employed.

Mechanism of Tumor targeting

Active Targeting

Through active interaction between receptors and ligands, active targeting precisely targets cancer cells. Targeted cells are distinguished from normal cells by the ligands on the surface of NPs, which are selected to focus on the target molecules that are abundantly expressed on the cancer cell’s surface. When ligands on Nanoparticles interact with receptors on the surface of cancer cells, a process known as receptor-mediated endocytosis occurs, successfully releasing therapeutic drugs from internalized Nanoparticles.¹¹ Active targeting is ideally suited for the delivery

of macromolecular medicines like proteins and siRNAs due to their nature. Monoclonal antibodies, amino acids, peptides, carbohydrates and vitamins are examples of targeting moieties.^[12] The folate receptor, transferrin receptor, epidermal growth factor receptor, and glycoproteins, are among the receptors that are extensively investigated. These ligands precisely attach to cell-specific receptors (EGFR). Examples: EGFR, a tyrosine kinase (TK) receptor from the ErbB family, is overexpressed in several cancer forms, particularly those with squamous cell histology. Human SCC can be targeted using gold nanoparticles using anti-IgG-PEG-AuNPs and anti-EGFR-PEG-AuNPs. Human EGF receptor-2 (HER2), which is overexpressed on the surfaces of breast cancer cells, is inhibited by the drug Herceptin®. HER2-targeted PEGylated liposomal doxorubicin was developed to decrease cardiotoxicity, a common side effect of anthracyclines.

Passive Targeting

Passive targeting's goal is to focus on the variations between tumours and healthy tissue. By using passive targeting, drugs are successfully delivered to the target spot where they can carry out a therapeutic action. Neovascularization is a result of high cancer cell proliferation, and large holes in the vascular wall increase the perm selectivity of tumour arteries in comparison to healthy vessels.¹³ Due to the rapid and inadequate angiogenesis, macromolecules, such as Nanoparticles, may leak from blood vessels supporting the tumour and concentrate within tumour tissue. Due to insufficient lymphatic drainage, which allows the nano-carriers to transport their contents to tumour cells, the retention of Nanoparticles is enhanced in cancer. The EPR effect, one of the forces underlying passive targeting, is produced by these processes.¹⁴ Numerous studies have demonstrated that the size of Nanoparticles has an impact on the EPR effect because smaller Nanoparticles have higher penetrability but do not leak into healthy vasculature.¹⁵ However, larger particles have a higher chance of being eliminated by the immune system. Example: Abraxane® (albumin-bound paclitaxel, Abraxis Bio-Sciences), used to treat advanced or metastatic breast cancer, was given US FDA approval in 2005. (MBC). A cancer treatment called DaunoXome® (liposomal daunorubicin; Gilead Science/Diatos) slows the proliferation

of malignant cells. Daunorubicin is an active chemical. The treatment for Kaposi's sarcoma, a type of cancer that affects the lungs, intestines, and skin, uses a special formulation of daunorubicin (in liposome form). In 1996, US FDA gave its approval.¹⁶

Retention effect and enhanced permeability

The vasculatures of tumours are typically abnormal, with misaligned branching and porous walls¹⁷. The rapid proliferation of endothelial cells and the decreased number of pericytes are the causes of this leakiness. Due to these features, tumour vasculatures have large pores with diameters between 100 nm and several hundred nm as opposed to the 5–10 nm of normal vessel junctions. Because of the larger pores, tumours have higher levels of vascular permeability and hydraulic conductivity, which makes it possible for macromolecules like nanoparticles to enter tumours¹⁸. The lymphatic system removes macromolecules from healthy tissue. However, weakened lymphatics are typically present in solid tumours¹⁹. Lymphatic vessels are compressed by expanding tumour cells, which also cause the majority of the vessels to collapse, particularly in the tumour's centre. The EPR effect is caused by the compromised lymphatic system and enhanced permeability of the tumour vasculature. Similar to other macromolecules, nanoparticles have longer retention durations in tumours, causing their concentrations to be higher than in plasma or other tissues. As a result, nanoparticles can passively target tumours via the EPR effect.

Nanoparticle Targeted Delivery

Anticancer drugs should ideally be able to pass through physiological barriers after administration and reach the targeted tumour tissues with low volume loss or blood circulation activity to be successful in the treatment of cancer. Second, once the drugs have reached the desired location, they ought to be very selective in their ability to kill cancer cells while sparing healthy cells. These two primary strategies are also linked to improvements in patient longevity and quality of life by increasing the intracellular concentration of drugs while reducing toxicities related to dose-limiting dosages. A growing body of research indicates that nanoparticles might be able to satisfy both of these requirements for effective medication delivery systems.²⁰

Advantages²¹

1. Enhance the stability of drugs.
2. Increases encapsulation efficiency.
3. Reduces dose frequency.
4. They have higher carrier capacity.
5. It can also be utilized as controlled drug delivery.
6. It possesses active as well as passive targeting of tumour cells.
7. It enhanced solubility and bioavailability due to the presence of organic moieties.
8. Modification of the surface can be easily done.
9. It enhanced therapeutic activity.
10. Site-specific targeting.
11. Reduce toxicity.
12. Oral, nasal, and parenteral routes can be used for administration.
13. Hydrophilic, and hydrophobic drugs can be used.

Types of Nanoparticles^{21,22}

Wide varieties of polymers are utilized in the preparation of nanoparticles like PEG, and Chitosan, for delivering anti-cancer agents.

1. Polymeric nanoparticles: e.g.: Nanocapsules, Nanospheres, micelles, Nano gels, dendrimers.
2. Lipid-based nanoparticles: e.g.: SLN, phospholipid micelles, liposomes.
3. Inorganic nanoparticles: e.g.: gold nanoparticles, silver nanoparticles, mesoporous silica nanoparticles.

Polymers used

1. Natural polymers: proteins, gelatin, albumin, dextran, chitosan
2. Synthetic polymers: polystyrene, polyacrylate.
3. Semi-synthetic polymers: cellulose derivatives

Techniques of preparation of nanoparticles²³

Different physical and chemical, biochemical, and biological methods are utilized for producing nanoparticles. Approaches like emulsification, precipitation, spray drying, salting out and nano-emulsification are used in preparation.

Emulsion-Solvent evaporation Method

It is a common method of preparation of nanoparticles involving two steps, in the first step polymer emulsification solution in the aqueous phase is followed by evaporation of the polymer to form Nanospheres by precipitation reaction. Ultracentrifugation is done for the collection of drug-loaded nanoparticles.

Double Emulsion & Evaporation Method

This technique is used for hydrophilic

drugs because of poor entrapment efficiency. W/o emulsion is prepared and to this emulsion, another aqueous phase is added with continuous stirring to obtain a w/o/w type of emulsion. In the next step, the solvent is evaporated and nanoparticles are obtained by centrifugation.

Salting-out Method

It is a modified emulsification/solvent diffusion method in which the drug and polymer are dissolved in a suitable vehicle and added to an aqueous gel consisting of electrolyte agents (salting-out agent) with colloidal stabilizers.

Polymerization Method

In this method, a polymerization reaction is induced in monomers in an aqueous environment as soon as polymerization is completed drug is entrapped onto the nanoparticles by the adsorption method.

Evaluation Parameters²⁴

1. Particle size: the particle size of the nanoparticle is determined by SEM scanning electron microscopy and TEM transition electron microscopy.
2. In vitro drug release study: It is done by using a USP Type II dissolution apparatus with 900 ml phosphate buffer at $37 \pm 0.2^\circ\text{C}$ temperature at a rotation speed of 50 rpm.
3. Stability of nanoparticle: prepared nanoparticles preparation is placed in a stability chamber for 90 days at a temperature range of $4^\circ\text{C} \pm 1^\circ\text{C}$ and $30^\circ\text{C} \pm 2^\circ\text{C}$.
4. Structure and crystallinity: The X-ray diffraction method is used to identify the structure and crystallinity of the formulation.
5. Yield of nanoparticles: % Yield = Amount of nanoparticle / Amount of drug + polymer $\times 100$
6. Surface charge: The surface charge of the nanoparticle is identified by Zeta-potential analysis.
7. Drug content: the drug content is identified by UV spectrophotometer analysis or by HPLC technique.

Application

1. In cancer therapy
2. Intracellular targeting
3. As a vaccine adjuvant
4. For DNA delivery
5. Ocular delivery
6. For skin and hair care therapy
7. It can also be effective to cross the blood-brain barrier
8. It can also be used for diagnostic purposes

CONCLUSION

A new era in cancer treatment has been brought in by the use of nanotechnology in cancer therapy. In comparison to conventional drugs, Nanoparticle drug delivery methods have better tumour targeting, pharmacokinetics, stability and biocompatibility. They also contribute significantly to lowering systemic toxicity and combating drug resistance. Due to these benefits, Nanoparticle medications are frequently used in targeted therapy, gene therapy, hyperthermia, chemotherapy and radiation. Nanoparticles are an efficient weapon in the treatment of cancer because of their improved, enhanced, efficient target drug delivery, and better bioavailability with minimum side effects. To enhance their biodistribution and lengthen their stay in the bloodstream, nanoparticles have been engineered for the best surface and size properties. Utilizing the EPR effect, passive targeting can enhance the exposure period of tumour cells to cytotoxic drugs, lengthen the duration that drugs remain in the body's bloodstream, and decrease the number of harmful side effects. To develop selective nanoparticle drug delivery systems that recognize certain targets, active targeting makes use of several compounds that are overexpressed in tumour cells. Chemotherapeutic agents like Doxil and Abraxane are the milestones in chemotherapy which shows improved efficacy as compared to conventional dosage forms. Drugs can be encapsulated in vast quantities without undergoing any chemical reactions. In comparison to analogous passive targeted drug delivery systems, active targeted drug delivery systems are anticipated to offer enormous advantages. There is no question that in the future, nanocarriers, particularly NP-based drug delivery systems, will be the primary form of treatment.

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Conflict of interest

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