Nanoparticle Mediated Drug Delivery Systems for Cancer Management

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Cancer is one of the main causes of death and low life expectancy worldwide. Although numerous approaches have been developed to lower mortality, ease chronic pain, and enhance quality of life, there is still a discrepancy in the effectiveness of cancer therapies. For the best possible cancer treatment, early cancer cell detection and high-specificity drug administration to reduce toxicities are crucial. Conventional cancer diagnosis has been expedited and made simpler by the use of nanoparticles (NPs). More surface area, a bigger volume proportion, and improved targeting abilities are among the notable traits of NPs. They can also functionally permeate the fenestration and have a better bioavailability and t-half due to their low toxicity to healthy cells. These particles are the most promising materials for many biomedical applications, particularly in the diagnosis and treatment of different illnesses, since they have drawn interest from a wide range of fields. Furthermore, nanoparticles enable the regulated release of medications with increased effectiveness and less side effects. Nanomaterials such as microbubbles are used as molecular imaging agents in ultrasonography. This overview covers the many types of nanoparticles that are commonly used in cancer diagnosis and treatment.

Keywords: cancer screening, imaging, diagnosis, nanoparticles, and nano-enabled formulations.

1. Introduction

Nanoparticles are able to deliver medications to specific sites by keeping a safe distance from the reticular endothelium and by increasing their penetration capacity into tumors to levels that allow for effective drug administration. The arrangement of these transporters allows them to freely and precisely reach the medicinal location. For the purpose of drug delivery, it is crucial to take into account the molecular weight, particle size, ionic strength concentration of monomers, pH, surface charge, and nanoparticle design. Multidrug resistance is the primary issue with chemotherapy, however it can be resolved with drug delivery strategies mediated by these nanoparticles. Reducing dose-associated toxicity to healthy tissues and maximizing in-vivo pharmacological potential are the two main difficulties in modern drug therapy. [1] A cancerous cell divides so fast when it is surrounded by other tissues that it keeps the therapeutic tissues from fighting with the diseased cells for the few nutrients that are available. High interstitial pressure, which occurs when there is no functioning lymphatic system, causes

surface-induced convective fluid movement in tumor interiors [6]. The delivery of an anticancer drug in the tumor's interstitial space will be regulated by numerous physiological factors, including low intravascular pressure, poorly vascularized tumor areas, high interstitial pressure, an acidic tumor environment, and the drug's physicochemical properties (such as molecular size, charge, composition, and structural organization). Anticancer drugs complexed with colloidal nanoparticles may be able to overcome drug transport resistance, improving the medication's selectivity towards the target and reducing its harmful effects on healthy cells [5]. Variables like the form of the nanoparticles, the kind and composition of the polymer utilized, the process of conjugating the drug with the carrier, and the manner of administration can all be modified to ensure regulated release of the medication. Following intravenous administration, NPs (Nanoparticles) show a surprising propensity to settle in a variety of malignancies. It has been demonstrated that a small number of cancers have increased vascular permeability, which may allow NPs to enter the extravascular cells of the tumor. When several anticancer drugs, such as doxorubicin, methotrexate, 5-fluorouracil, and dactinomycin, are conjugated to albumin nanoparticles, they become more effective against test cancers than when the medicines are not attached. The elimination of hepatic metastases is one of the most intriguing applications for NPs laden with the anticancer medication.[2] Intravenous injection of nanoparticles serves primarily as a drug reservoir and offers an alternate method of achieving tumor-directed targeting. The nanoparticles are created by coating them with monoclonal antibodies. These preparations pinpoint particular characteristics particular to malignant cells. Drug distribution to tumors is impacted by a multitude of biological variables linked to tumors.

- Nanotechnology in Drug Delivery

Drug delivery vehicles based on polymers or lipids can improve the therapeutic and pharmacological properties of medications. Drug delivery systems are powerful because they can alter the pharmacokinetics and biodistribution of medications. Nanoparticles have special properties that can improve the way medications are delivered. These nanoparticles' small size allows them to be absorbed by cells in places where the body would have discarded larger particles. Among the advanced medication delivery techniques being investigated are substances that may cross cell membranes and reach the cytoplasm of cells. Efficiency is important since many diseases are caused by processes that take place inside of cells and can only be stopped by drugs that penetrate cells.Triggered reaction is one way to better utilize pharmacological substances. Injected into the body, medication is only activated in response to a certain signal. For example, a drug delivery system with surroundings that are both hydrophilic and hydrophobic will replace a pharmaceutical with low solubility, boosting the solubility [12]. Furthermore, a medication may cause tissue damage; however, this problem with drug delivery can be resolved with controlled drug release. If a medication leaves the body too rapidly, a patient might have to take higher dosages of it; however, drug delivery devices can reduce drug clearance by altering the pharmacokinetics of the medication.Drug delivery system particles reduce the amount of distribution and their impact on non-target tissue, so mitigating the issue of poor biodistribution, which can cause damage to normal tissues due to widespread distribution. One of the primary benefits of nanotechnology and nanoscience will be to drive the creation of completely new drugs with more advantageous properties and fewer side effects. The mechanisms by which prospective nanodrugs work are

incredibly precise and well-understood.

- Significance of Nanoparticles in Cancer Diagnosis

Numerous types of nanoparticles, including metallic, magnetic, polymeric, metal oxide, quantum dots, graphene, fullerene, liposomes, carbon nanotubes, and dendrimers, are used in the diagnosis of breast, colon, and cervical malignancies. They are also required for many jobs involving imaging. It has been found that before entering target cells, where they interact with biological systems and get beyond a range of biological barriers, including cell membranes, nanoparticles remain in the bloodstream for a considerable amount of time (figure 1). Additionally, conjugating nanoparticles with cancer-specific antibodies can improve cancer binding and detection. Recent research has shown the great promise that sensors and nanoparticles hold for enhancing the sensitivity of cancer diagnosis and tumor detection [9]. It has been documented that methylation patterns and mutations can be recognized and used as cancer diagnostic markers. Further research may be necessary before cell-free RNA, circulating tumor cells, and extracellular vesicles are used in clinical diagnosis. Researchers have used superparamagnetic (Fe3O4/GNCs) trimethoxysilane (γ-Mercaptopropyl) or fluorescent gold nanoclusters (GNCs) as a stabilizing agent. Fe3O4/GNCs nanoprobes were created by conjugating the generated GNCs@MPS on the surface of "Fe3O4@SiO2 nanoparticles" and then adding "poly ethylene glycol dimethacrylate (PGD)."[4]

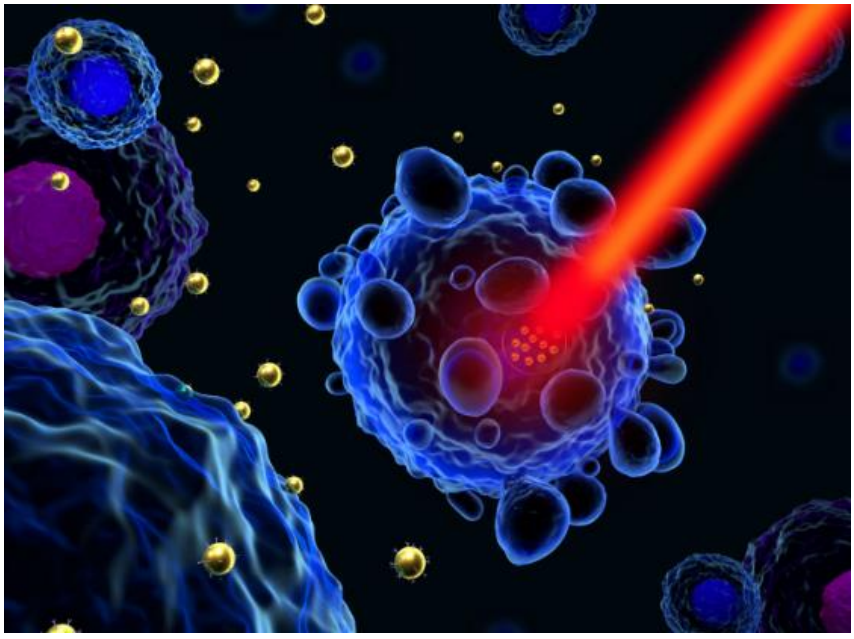

Figure 1: Entry and movement of nano-enabled anticancer drugs in a cancer cell.

2. Literature Review

The amine-capped Au nanocrystals with a diameter of 0.25–0.70 nm have been studied by Leff et al. [13]. The charge-neutral amino/Au surface contact is defined by a weak covalent

bond in all physical characterizations that have been done. The acquired data show that the Au NCs that were generated were stable and appeared to have kinetic rather than thermodynamic properties.

Lauren et al.'s [7] reduction of HAuCl4 with sodium citrate produced stable and remarkably pure Au NPs. The effect on embryonic development was then assessed by moving cleavage-stage zebrafish embryos using these NPs as a probe. According to Yuan et al. [8], biocompatible block copolymers (poly(2-methacryloyloxy) ethyl phosphorylcholine) PMPC block and a poly(2- (dimethylamino) ethyl methacrylate) PDMA) were used to create statically stable Au nanospheres in an aqueous solution. This research investigation enhanced the adsorption of the PDMA block on the surface of Au NPs, and the stabilizing block function of PMPC created highly biocompatible Au in an aqueous solution without requiring an extra reducing agent.

Win et al. observed in a prospective review of 110 patients undergoing potentially curative lung cancer surgery that the patients had high functioning levels and little symptoms after the procedure. One month following surgery, there was a substantial decline in overall quality of life ($p = 0.001$), but after three months, it had restored to preoperative levels ($p = 0.93$). Additionally, six months later, symptoms had returned to baseline [15].

According to Myrdal et al., patients with lung cancer undergoing open conventional surgical resection have a life quality that is similar to that of patients undergoing coronary bypass surgery [3]. Due to decreased pulmonary function, lung cancer patients have worse physical outcomes but do not exhibit elevated levels of worry or sadness. Individuals with compromised mental health were those who kept smoking after surgery [10].

Handy et al. studied patients from three hospitals who had lung cancer surgery and discovered a significant impairment in preoperative functional health status in patients after the procedure [14]. Prior to and six months following surgery, patients completed the Short-Form 36 Health Survey (SF-36) and the Ferrans and Powers quality-of-life index (QLI). Approximately half of the patients died within six months after surgery. After lung cancer is removed, pain and a decreased level of functional health status last for six months. [11].

3. Materials and Methods

The drug of choice for this investigation, docetaxel (DTX), was given to us as a gift sample by Mumbai, India-based Neon Laboratories Ltd. An unpaid sample of D-alpha-tocopheryl polyethylene glycol 1000 succinate (TPGS) was sent to us by Antares Health Products located in St. Charles, United States of America. The dialysis membrane (Spectra/Por7®) with a molecular weight cut-off of 1 KDa was obtained from Spectrum Laboratories Inc., which is based in Rancho Dominguez, CA, in the US. DocelTM was supplied by RPG Life Sciences Limited, an Indian company located in Mumbai. The dialysis bag was bought from Sigma-Aldrich Chemicals in France, and it had a cutoff of 12 KDa molecular weight. The other substances were all analytically graded.

3.1 Characterization of TPGS-COOH

- FTIR spectroscopy

Activated TPGS (TPGSCOOH) and Tf conjugated TPGS (TPGS-Tf) were investigated molecularly using an FTIR spectrophotometer (Perkin Elmer Spectrum Two, Waltham, Massachusetts, U.S.A.). The resolution used was 2 cm-1, and the scanning range was 400–4000 cm-1, according to Ha et al. (2010) and Raju et al. (2013).

- Synthesis of TPGS-COOH (activation of TPGS) and its conjugates

Prior to conjugating transferrin to TPGS, TPGS (i.e., TPGSCOOH) was first activated by succinic anhydride via ring-opening reaction in the presence of DMAP (Figure 3.1 A). (Raju et al., 2013; Muthu et al., 2015). In conclusion, 0.77 g of TPGS, 0.5 mM, 0.10 g of succinic anhydride, and 0.12 g of DMAP were mixed together and heated in a nitrogen environment at 100 0C for 24 hours. Following room temperature dissolution, the mixture was filtered to remove surplus succinic anhydride, dissolved in 5 milliliters of cold dichloromethane, and allowed to precipitate overnight at -10 degrees Celsius in 100 milliliters of diethyl ether. The white precipitate of TPGS-COOH was filtered, and then vacuum-dried. The Tf was bonded to the TPGS-COOH carboxyl group by carbodiimide chemistry using EDC and NHS in phosphate buffer saline (PBS) (pH 5.5) (Figure 2 A). (Muthu et al., 2015). Overall, to conjugate Tf to TPGS-COOH, catalysts 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) and N-hydroxysuccinimide (NHS) were added in a molar ratio of 1:5 (TPGS-COOH: EDC or NHS) in PBS (pH 5.5). After being blended in 2 ml of pH 5.5 PBS at 25 0C for five hours, TPGS-COOH (200 mg), EDC (96 mg), and NHS (74 mg) were chilled at 4 0C for twenty-four hours. The mixture was then mixed with 1 milliliter of 0.2% (w/v) Tf and left to stir at 4 0C for eight hours. To get rid of extra TPGS-COOH, NHS, and EDC, the final product was dialyzed against PBS (pH 5.5) for 48 hours using a dialyzing membrane (MWCO: 12 kDa). The dialyzed product (TPGS-Tf) was freeze dried in order to produce micelles.

4. Results and Discussions

Infrared Spectroscopy using Fourier Transform (FTIR) Fourier transformed infrared spectroscopy (FTIR) was used to obtain the infrared spectra of genistein alone (GEN), PLA-NPs, and GEN-PLA-NPs (Thermo Electron Corporation, Nicolet IR 200, FTIR). Using the KBr pellet disk technique, FTIR spectra were obtained at ambient temperature in the wavelength range of 4(XX) to 4(X) cm^*; materials were pelletized at 10.3X10^* Pa. Using DLATGS detectors at room temperature and a high energy ceramic source, all samples were scanned in the infrared region from 4(XX) to 400 cm"*.

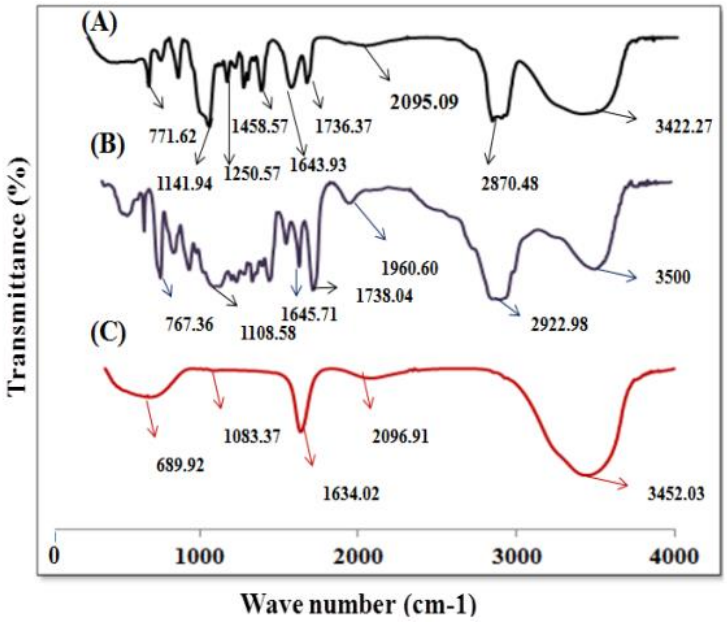

Figure 2. FTIR spectra of (A) TPGS (B) TPGS-COOH and (C) TPGS-Tf.

Transmission electron microscopy The micelles were spherical in shape, according to the TEM of the non-targeted and targeted DTX-loaded micelles shown in Figure 3.6 (A), (B), (C), and (D). It was also discovered that the DTX-laden non-targeted and targeted micelles in Chapter 3 74 DTX loaded in 50 nm scale and 100 nm scale were Tf targeted. A relationship exists between the micelle size measured by PCS and the size observed by TEM. Furthermore, Tf coating on the micelle surface was verified by TEM images (Figure 3).

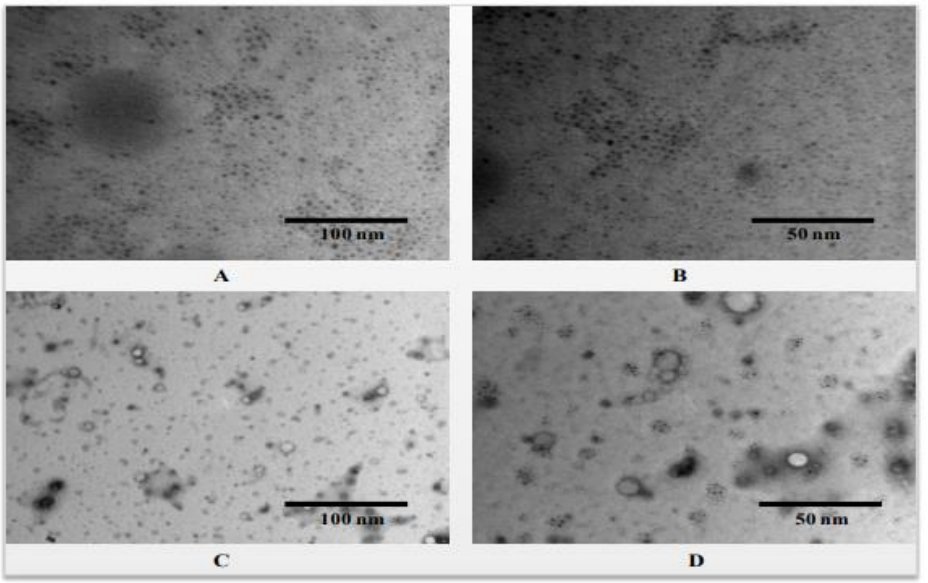

Figure 3: Transmission electron microscope (TEM) image

5. Conclusion

The development of cancer nanotherapeutics has been steadily advancing since the early 2000s. The road to oncology-based medication commercialization is arduous and fraught with danger. The majority of traditional anticancer medications have low bioavailability, cause multidrug resistance, and are dispersed throughout the body in an unspecific manner, which can result in systemic toxicity and inadequate therapy. Colloidal nanoscale systems known as nanocarriers are used in an indirect approach to targeted therapy to transport anticancer medicines, such as macromolecules like proteins or genes or small molecular weight medications. Compared to free medications, the anticancer agents can achieve a lethal concentration many times greater in tumors with less toxicity for the rest of the body since they can concentrate in tumors rather than building up in normal tissues. Considering the limitations of nanotechnology, further research and development is needed to enhance medicine delivery, optimize its effectiveness, and minimize its drawbacks. Improvements in the physicochemical properties of the employed nanomaterials may result in the creation of safer and more efficient derivatives for the diagnosis and treatment of cancer.

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