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Review Article

Recent Trends in Nano-Drug Delivery Systems for Breast, Prostate, Brain, and Other Cancers

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Abstract

Nano delivery system as well as Nano medicine is new initiative; however, it develops pharmaceutical science increasingly. Nanotechnology has several benefits to treat many chronic health issues, especially, cancer by target-oriented delivery of appropriate medicines. This assignment was about reviewing the existing literature on the Nano medicine and Nano drug delivery system, in context of different toes of cancer. It has discussed various nano particles that are considered for cancer treatment such as polymers, liposome, dendrimers, protein nano particles, and cellulose. It has provided information about both organic and inorganic nano particles.

The findings have shown that in case of nano-drug delivery of cancer, lipid, dendrimers, polymers, and liposome highlighted promising results. This review presents update summary of recent trends within NDDS and nanomedicine by comprehensive scrutiny of application and delivery of nanoparticles by improving efficacy of old and novel drugs. Lastly, it has provided short information on future of NDDS and nanomedicine based on the collected information. That information indicates that since nanotechnology is increasing day-by-day, it has an emerging future. Additionally, researchers have the chance to develop effective treatment solution with help of nanomedicine. This is a literature review which covers various aspects of recent trends in nano drug delivery systems with focus on selected cancers.

Keywords: Nano Drug Delivery Systems; Breast Cancer; Prostate Cancer; Cancer Treatment; Nanomaterials in Cancer Therapy

Introduction

Background

Nanomedicine refers to the medicinal application of nanotechnologies. It ranges from biological nanomaterial's medical applications to Nano-electronic biosensors. Nano delivery systems and nanomedicine are new approaches; however, it is a developing science where materials within nanoscale ranges are employed for serving as diagnostics tools and delivering therapeutic agents towards a particular targeted site [17,50]. Nanotechnology holds a huge potential regarding healthcare. It has several advantages, for example, it effectively delivers drugs, diagnoses diseases more quickly and sensitively, and lastly, it delivers vaccines through patches and aerosols. It offers several benefits for treating chronic healthcare issues by target-oriented, followed by site-specific delivery of medicines.

Evidence has suggested that a modern drug is obtained from herbs based upon traditional practices and knowledge. Approximately 25% of important pharmaceutical compounds, as

well as their derivatives, are acquired through natural resources [34]. Pharmaceutical nanotechnologies cover implementation of nanotechnology towards pharmacy, including nanomaterials and devices such as drug delivery imaging, biosensors, and diagnostics [37]. It has provided fine-tune diagnosis as well as paid attention to disease treatment at molecular levels. It offers numerous opportunities for fighting against several diseases including cancer. A research study elaborated that the application of nanotechnology in the pharmaceutical sector that provides smart and intelligent DDS are considered the most powerful and effective tools for forming conventional dosage [33,44].

Figure 1: Nanoformulations [34].

A review on recent trends in nano drug delivery systems

Methodology

This is a literature review which covers various aspects of recent trends in nano drug delivery systems with focus on selected cancers. We focussed on literature survey and information available on electronic media. We focussed mostly on research papers and review articles published in literature from 2015 onwards. The focus was limited to Breast, Prostate, Brain, and Other Cancers which are considered to be top killers in United States as well as worldwide.

Nanotechnology and nano carriers

Chemical and physical properties of nanoparticles influence their efficacy. Nanoscale compounds have been produced from lipids, synthetic polymers, inorganic particles, and prepositions [18]. It promotes stability, solubility, and drug protection by enhancing the delivery of drugs. The culmination of all these benefits decreased the toxic side effects as well as improved pharmacokinetics that changes as per surface physicochemical size of properties. Within organic nanocarriers, a liposome is a lipid vesicle with a spherical shape; that consists of a self-making phospholipid bilayer, which is nearby the aqueous internal cavity. Some major nanocarriers are dendrimers, carbon-based nanomaterials, and inorganic nanoparticles.

In addition to this, nano-based modalities give improved transport throughout biological barriers, enable particular targeting of cancer or malignant cells, and then offer different strategies regarding sustained drug release [33].

Nano-materials in cancer

In the context of nanotechnology, it is been explained that nanotechnology applies curative agents at a nanoscale level for developing nanomedicines. Nanotechnology is vastly used regarding treatment and diagnosis of several diseases and cancer is one of them. According to them, nanoparticles have considerably enhanced therapeutic and diagnostic of numerous cancers because of their small size, improved drug loading, enhanced retention within target tissue, and smooth fictionalisation [27,34].

Figure 2: Nanomaterials in cancer therapy [33].

Figure 3: Metallic, lipid-based, and polymeric nanomaterials regarding cancer theranostics [27].

According to an article [27], metallic, polymeric, micelles, protein, and liposomes are the nanomaterials that are used in cancer therapy and these nanomaterials are used in two procedures such theory and imaging. In case of therapies, these materials are used as nucleic acids, proteins or peptides, antibodies, and chemotherapeutic drugs. Additionally, in imaging, these are used as quantum dots, fluorescent probes, and contrast agents. Some researchers discussed that advancement of nanotechnologies has made nanoparticles likely looking candidates regarding controlled DDS (drug delivery system) [10]. Nanomaterials mention particles with 10 to 1000 nm diameters. In case of DDS, nanomaterials have improved efficiency of a drug by increasing the half-life of the drug, solubility regarding hydrophobic drugs, and releasing drugs within a sustained fashion. Research has suggested that protein-based nanomaterials set high hopes within scientific minds regarding natural availability.

Nanoparticles can contain anticancer drugs, and then deliver them towards target cancer or malignant cells by sparing the normal cells [4,50]. Additionally, opportunities regarding drug delivery towards targeted cells with help of peptide and PEGylation can provide mechanisms for producing an appropriate concentration of drugs.

Nano-based drug delivery system

In recent times, a huge development has been noticed in delivery systems for providing therapeutic agents towards target locations regarding treatment of different diseases, especially cancer [34]. Nanomedicine is a branch of medicine, which utilises nanotechnology science to cure different diseases by utilizing nanoscale materials, for example, biocompatible nanoparticles regarding different applications, such as sensory, diagnosis, and delivery. Drugs encounter several barriers within living organisms through administration time, where particular dosages form until the therapeutic molecule reaches the target tissue or cell. Technological advancement allows people for making structural changes, which create remarkable improvements within drug properties as well as overcoming limitations of decreased probable safety problems and drug efficacy [31]. Advancement in nanotechnology does extraordinary DDS through enhancing pharmaco-dynamic and pharmacokinetic properties, for example, exposure duration, solubility, and targeted delivery towards action site.

The above figure shows the different nanocarriers for drug delivery. Nanomaterials have differed in surface, shape, and size, which lead to considerable variability within pharmacologic effects and safety of various nanocarriers. Nanomaterials between 100 to 200 nm have been observed for being most proactive in up-taking by tumours, conversely, particles below 50 nm size highlighted short circulation time [13,39].

Nanostructures can deliver drugs such as self-delivery and passive in two different ways. In the past, drugs were incorporated within the inner cavity of structures through hydrophobic effects. However, in the case of nanotechnology, materials are targeted towards particular sites, and then desired amounts of drugs are released because of the low content of medicines that are enclosed within a hydrophobic environment [12]. Nano delivery systems use advanced pharmaceutical technologies for packaging drugs regarding precise delivery, and enhance stability, solubility, and bioavailability of drugs [13]. Moreover, a combination of advanced CAFs-targeted (cancer-associated fibroblasts) nano DDS with radiotherapy, chemotherapy, and immunotherapy showed huge potential within cancer treatment.

Figure 4: Nanocarrier classification regarding drug delivery [31].

Figure 5: Timeline of DDS.
(Source: Dang NS Guan, 2020).

Additionally, novel nano DDS based upon CAF's reprogramming distinct subunits can be the prospective strategies for improving antitumor response of the immune checkpoint blockade in future. NDDS (nano-drug delivery system) is functional drug-loaded nanocarriers that have 10-1000 nm diameters and consist of different synthetic and natural materials [51]. As compared to DDS at the mm scales such as microcapsules, micro-particles, and microspheres, NDDS has attracted wide scientific interests regarding anticancer treatment because of different characteristics such as ability to reduce size and surface modification capability [10]. This author has proposed the most effective NDDS regarding cancer treatment and that is LBL (layer-by-layer) assembly of films over nano-template nanoparticles. Compared to other methods to generate NDDS, for example, solvent evaporation, nano precipitation, and in-situ polymerisation, LBL has inherent advantages that make it more appropriate for application in fabrication of NDDS [51]. For instance, compared to a nano precipitation process that is mostly used for nanoparticles formation through water-insoluble polymer's precipitation diffused in a water-mixable organic solvent by water, LBL technique cannot only accomplish homogeneous nanoparticles formation; it also generates different heterogeneous NDDS along with other complicated structure and component, for example, multilayer.

Breast Cancer (BC) is the most common malignancy among females throughout the world [11,40]. Due to advancement of treatment approaches, drug development, drug target, pathogenesis research has been improved, which significantly influenced the mortality rate of breast cancer. There are several treatments regarding breast cancer; for example, surgery, and radiotherapy, and immune and chemotherapy. Delivery of the chemotherapeutic drugs towards tumour site by utilising NDDS can induce killing of tumour; therefore, it has become an effective strategy for therapy of breast cancer [42]. DDS has some major characteristics such as; increased drug solubility and improves bioavailability and absorption rate [22].

Additionally, it can pass by the blood-strain barrier and penetrate through interstitial space. Moreover, it can be administered to observe within real-time through several imaging technologies that allow applying visual operation of NDDS. Diameter of NDDS is lower than 200 nm and it can smoothly pass through the tissues. Lastly, it reduces thrombosis risk while drug-packed nanoparticles are injected into blood vessels.

Drug designing and delivery process

Since nanomedicine has progressed and because of advancement of drug design and DDS, several therapeutic procedures have been presented. Moreover, traditional diagnostic methods have been studied for increasing diagnostic accuracy and drug specificity. For example, new drug administration routes have been explored that targeted action occurs in particular regions so that it can reduce toxicity as well as increase bioavailability in organisms. Drug designing is an appropriate feature that defines discovery of novel drugs based upon knowledge of biological targets. Advancement within computer science as well as progressing experimental procedures regarding purification and categorisation of biological targets, peptides, and proteins are crucial for growth of the nanotechnology sector [34].

DDS has gained importance within the past few years and this type of system can be evolved and these can promote modified release of active ingredients within the body [6]. For instance, utilisation of nanocarriers regarding sensory and imaging applications is an example of DDS. All these DDS have their own physical, morphological, and chemical characteristics and it has affinity regarding various drug polarities by different chemical reactions such as hydrogen bonds and covalent bonds, and physical interactions. For example, the chemical reaction of neem bark that is extract-grafted biogenic silica nanoparticles is lower than the neem bark that is extract-loaded biogenic silica nanoparticles [29]. However, the drug delivery process for cancer therapy and its mechanism pathway are briefly elaborated [41].

Before explaining the drug delivery process, the authors explained different strategies and materials that are utilised within cancer therapy. For example, in cancer, supramolecules are used as delivery vehicles; they provide vehicles regarding targeted delivery and encapsulation of bioactive materials. Traditional anti-cancer drugs, for example, doxorubicin could be repressed by utilising amphiphilic dendrimers, which generates supramolecular micelles regarding cancer therapy [41].

According to this scholar [41], the therapeutic agent's target-specific delivery is based upon stimuli-responsive factors that are induced by exogenous (light, temperature) or endogenous (enzyme, pH) stimuli. Additionally, an antimetastatic mechanism about glutathione disulfide based upon the liposome entirely

prevents cell migration and detachment as well as inhibits invasion of cancer cells. Thus, this treatment approach has been considered as a potential treatment regarding cancer metastasis.

Figure 6: Targeted and untargeted drug delivery [9].

Drug delivery process in cancer therapy starts with targeting and it has two different types as active and passive. In the active targeting process, nanoparticles contain chemotherapeutic agents, which are made in a particular way and help them to work directly with defective tissue or cells. This process is based on molecular recognition [46,49].

Figure 7: Active and passive targeting by nanoparticles in cancerous cells [46].

Conversely, passive targeting eases Nano vectors deposition within the tumour environment, owing to different characteristics inherent to the tumour milieu, which is generally not present within healthy tissues [5]. Additionally, in case of, stimuli-responsive Nanocarriers, Nanoparticles that are super paramagnetic iron oxide are associated with lipids or polymeric Nanocarriers for initially stimulating controlled-release system by applying an external magnetic field [2].

Nano-particles within drug delivery system

Bio polymeric nanoparticles

In the nanotechnology field, several polymeric materials are present that are being utilised within DDS. Some of these materials are discussed below.

Chitosan

Chitosan has muco-adhesive properties and is used for acting tight epithelial junctions. Therefore, this type of nanomaterial is highly utilised for continued drug releasing systems regarding different kinds of epithelia, such as nasal, buccal, eye, pulmonary, and intestinal [34] chitosan is also the potential nanoparticles regarding drug administration into oral cavity [35].

Alginate

Alginate represents final -COOH (carboxyl) groups and it is classified as an anionic mucoadhesive polymer and represents huge mucoadhesive strength while comparing it with neutral and cationic polymers. Alginate microcapsules contain epidermal growth factors bound on the exterior part for targeting non-small cancerous cells of the lung [38]. Cisplatin is a carcinogen drug that contains alginate nanoparticles. Particles that are chitosan-coated alginate can enhance daptomycin permeation within ocular epithelium targeting for antibacterial effect [7].

Figure 8: Different types of Nanocarriers [18].

anthan gum

A non-irritating and non-toxic gum is highly utilised as the pharmaceutical excipient. Research has found that injectable hydrogels consisting of carboxymethyl-modified chitosan and aldehyde-modified xanthan have angiogenic factors that can enhance reconstruction of abdominal wall [15].

Cellulose

Cellulose is extensively utilised in DDS regarding solubility modification and drug gelation, which resulted in control of release profile [45]. Cellulose nanoparticles, as well as chitosan nanoparticles, are used for repaglinide oral release [1].

Figure 9: Nano materials as Drug carriers regarding cancer [24].

Liposome

Liposome contains an aqueous core that is surrounded by many layers of cholesterol and phospholipids, which form lipid bilayers. Due to the unique structure, this nanoparticle can hold and load hydrophilic agents within aqueous department as well as hydrophobic agents within lipid space. Due to their similar composition to cell membrane, they have more biodegradable characteristics as compared to synthetic materials [24]. Besides increasing drug's intracellular update, liposome is also used for modifying anti-cancer cells, DNA, and antibiotics [9,24].

Polymers

These nanoparticles are made up of amphiphilic block copolymers, which collect by it for forming shell structures within an aqueous solution. Polymers are categorised as synthetic, microbial fermentation, and natural polymers [47]. Polymer nanoparticles such as nanosponges, micelles, and nanogels are extensively used for wound healing. Albumin is a natural polymer, which incorporates paclitaxel and it has enhanced the drug's water solubility as well as reduced dose-limiting toxicity through modifying the pharmacokinetic formulation.

Dendrimers

Dendrimers are polymeric macromolecules and it is characterised by a central core, branches, repeat units, and several groups of terminal functions. Dendrimers have several benefits about being biocompatible and they can be easily separated from body. These nanoparticles are washed out from the body by the kidney with similar metabolic pathways taken through peptides, antibodies, growth factors, and folate [24]. However, in this regard, several scholars have argued that dendrimers can be cytotoxic towards normal cells as well as the ends groups situated on peripheries, for example, PLL, PPI, and PAPAM are cationic groups that have physiological stability [1,15,35,45].

Inorganic nanoparticles

Several inorganic nanoparticles are present that help the drug delivery system such as Nanocrystals, quantum dots, metallic nanoparticles, and polysaccharide nanoparticles.

Nanocrystals

These are solid drug molecules with a 1000 nm range and these drugs do not require any carrier molecule. Additionally, it can be stabilised by utilizing polymeric-steric surfactants or stabilisers. Nanocrystal suspensions within a medium of marginal liquid are alleviated by adding a surfactant agent that is called Nano-suspension [19]. These nanoparticles have particular characters, which permit them for overcoming difficulties such as induced saturation stability, induced glueyness towards cell membrane or surface, and increased dissolution velocity.

Quantum dots

These are also called semiconductor nanocrystals, their optimal features are photoluminescence, and absorbance is based on size. In context of cancer therapy, Oxide quantum dot with multifunctional biocompatible graphene and nanoplatforms that is luminescent magnetic; can help in diagnosing or recognizing a particular tumour cell in liver cancer [43].

Metallic nanoparticles

Metallic nanoparticles are also inorganic nanoparticles that are currently used in the medical sector. Some medical applications that use metallic nanoparticles are biosensors, target drug delivery, photoablation therapy, and bioimaging applications. Fictionalisation and modification of metallic nanoparticles along with particular functional groups can allow them for binding with antibodies and drugs and make the DDS system more promising in case of biomedical application [20,30].

Polysaccharides nanoparticles and protein

Proteins and polysaccharides are natural biopolymers and these are extracted by different biological sources. Protein-based nanoparticles can be chemically altered for combining them with the target ligands, which identify actual tissues and cells for promoting and augmenting targeting mechanisms [26]. According to this scholar, different drug delivery carriers are used for improving efficacy and reducing cancer therapy side effects. However, biocompatible and biodegradable nanoparticles have gotten the most attention. The below figure shows the different sources of natural biopolymers.

Figure 10: Source of natural biopolymers [34].

Albumin has been signified as a flexible delivery platform regarding low water-soluble medicines such as rapamycin. This protein-based medicine will be used for non-hematologic malignancies, as well as clinical tests are still ongoing. In the context of cancer therapy.

Different Nano-drug delivery systems against cancer

In spite of advanced treatment options regarding cancer, no specific methods are present currently for curing cancer completely. That is why; scientists are continuing their research related to anticancer drugs as well as an effective manner of administration. Many studies have been done on different types of cancer and cancer-specific nano-drug delivery systems. A detailed illustration of different types of cancer is provided below.

Lung cancer

Lung cancer is also called pulmonary carcinoma that is characterised by the uncontrolled growth of cells within lungs. Polyphenol, honokiol has been found for having a therapeutic impact upon lung cancer [44]. It is packed to micelles based upon poly-caprolactone-ethylene glycol copolymer (PCEC). In the case of lung cancer, lipid-based nanoparticles represent significant drug delivery regarding treatment of cancer. Cisplatin has been successfully used for lung cancer as well as carboplatin; cisplatin and oxaliplatin have also significantly been used within clinics [16]. In contrary, it is explained that inhaled chemotherapy has been proven promising against lung cancer [28]. In addition to this, authors have explained that nanocarriers can be used regarding inhaled drug delivery. Nanoparticles' pulmonary administration can decrease systemic toxicity of the chemotherapeutic compounds and compare to the free drugs. Research has found inhaled doxorubicin exhibits lesser cardiac toxicity as compared to the exact free doxorubicin dose after intratracheal administration.

Breast cancer

Breast cancer (BC) is a malignant tumour, which starts in breast cells and this health issue mainly affects women. Metastasis of BC is frequently found for causing lung cancer. Diarylheptanoid compound delivered by utilising biologically obtained nanoparticles to BC cell lines and recorded its therapeutic effects [44]. This nanoparticle was produced from the covalently blended SFCS (silk fibroin and chitosan) polymer alone with help of the capillary-microdot technique. Polymer-based nanoparticles have been used in treatment of breast cancer [25]. NDDS provides powerful means regarding drug targeting to BC and enhancing bioavailability as well as reducing anticancer drugs' adverse effects [3,52].

Colorectal cancer

Colorectal cancer occurs in rectum or colon. Research has found that Triptolide is diterpenoid tri-epoxide, that is purified from a Chinese herb named *Tripterygium wilfordii* and it has anti-cancer properties; however, it also exhibits few side effects. Additionally,

TP-PM (triptolide loaded polymeric micelles) was synthesised by utilizing MePEG-PLA (methoxypoly (ethylene glycol)-polylactic acid) copolymer with help of solvent evaporation process. In case of colorectal cancer, curcumin nanoparticles have been used and it has been prepared by re-precipitation method. NDDS generates promising applications regarding oral drug delivery as it offers a large surface area regarding interactions with gastrointestinal tract [32,36]. It can be modified in different ways for tackling hurdles connected to oral delivery.

Figure 11: Drug delivery in colorectal cancer [32].

NDDS has a huge role in drug targeting towards diseased colon and present NDDS regarding colon-specific disease pays attention to lipid-based, inorganic, polymeric as well as hybrid materials.

Skin cancer

Skin cancer is a common type of cancer and globally minimum of 40% of skin cancer cases are present. This cancer is most common in light skin people. In case of skin cancer, apigenin-loaded poly nanoparticles have been prepared by solvent displacement process. Additionally, another study discussed dihydrostilbenoid, combretastatin A-4 is co-encapsulate along with doxorubicin as well as tested regarding anticancer properties within both *in-vivo* and *in-vitro* conditions. To manage skin cancer, chitosan-PEO nanofibers have given promising results [21]. This nanoparticle formed a double barrier that showed continuous and sustained release of active material. According to this scholar, a combination of this approach has proven beneficial in regards to the improved effectiveness of active compounds regarding skin cancer treatment.

Figure 12: Type of Skin cancer [21].

Prostate cancer

Growth of malignant cells within the prostate gland develops prostate cancer. Ester derivative of gallic acid, EGCG (epigallocatechin 3-gallate) was delivered towards cells of prostate cancer through biodegradable nanoparticles [14]. EGCG was merged with polylactic acid-polyethene glycol polymeric and PSMA (prostate-specific membrane antigen) [44]. The result of this test showed that nanoparticles loaded with EGCG are target-specific and have high efficacy.

Brain cancer

In case of brain cancer, biodegradable nanoparticles are created by MePEG-Poly (caprolactone) (PCL), which resulted in smooth spherical shaped nanoparticles. Regarding this nanoparticle, the efficiency of drug loading was 19%; however, the efficiency of encapsulation was 91% [44]. This scholar had done this test on C6 glioma cells and in the case of glioma nanoparticles loaded with resveratrol had exhibited huge toxicity as compared to free resveratrol. Elemene liposome injection is used as an anticancer drug that has high anticancer active ingredients such as β-elemene [23].

Conclusion

This assignment aimed to review the recent trends within nano-drug delivery systems regarding different types of cancer, since, prostate breast, brain, colorectal, lung, and skin. It has provided information about nanotechnology and the different nanoparticles

that are used in drug delivery. Additionally, it has discussed nanomaterials that are especially used in cancer. From this nature discussion, it can be concluded that nanotechnology utilisation has primarily been based upon enhancing solubility, bioavailability, controlled release, and absorption of drugs. Nowadays, enhancing the efficiency of natural bioactive materials by nanotechnology has become a common feature. Several examples have been provided in the above section; however, some important examples are nanotechnologies' therapeutic application regarding ellagic acid, resveratrol, and curcumin.

All these nanoparticles are responsible for the treatment of different cancers such as prostate, and lung cancer. Additionally, the efficacy of natural products has improved by utilizing nano carriers that are formulated with silver, cadmium, and gold. Additionally, one of great interest within nanomedicine development refers to the integration of diagnosis and therapy for cancer. Hence, the information of this review concludes that nanomedicine has significantly changed cancer treatment, and with help of nanoparticles; it has become possible to deliver high-quality treatment.

Future of DDS and Nanomedicine

Nanomedicine is currently the most fascinating area in the research field. Many studies have been conducted in this field. By utilising different types of nano carriers medical science can deliver an accurate amount of drugs towards affected cells such as tumours or cancer cells. Examples of nano medicines showed that gold-nanoparticles, which appear to be perfectly absorbed within soft tumour tissue and make the tumour susceptible to radiation. Since there is no particular cure for cancer; nanomedicine has a significant future as it can come with more proactive treatment approaches in the future. Since chemotherapeutic, nano particle inhalation assures an effective method for appropriate drug delivery towards lung cancer by comparing it with CIDD (conventional intravenous drug delivery). Therefore, it can be expected that in the future researchers will come up with an effective way in nanotechnology to reduce the disease impact on health.

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