Research Article

Role of Nano Biotechnology and Impact of Magnetic Nanoparticles in Drug Delivery

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ABSTRACT

Nanotechnology is expected to have an impact on all industries including semiconductors, manufacturing and bio technology. Nano biotechnologies have been applied to improve drug delivery at nano meter scale. This review will focus on the development of nano scale drug delivery mechanisms. Nano structured drug carriers allow for the delivery of not only small-molecule drugs but also the delivery of nucleic acids and proteins. Delivery of these molecules to specific areas within the body can be achieved, which will reduce systemic side effects and allow for more efficient use of the drug. Many times, the success of a drug is dependent on the delivery method. Magnetic nano particles (MNPs) possess unique magnetic properties and the ability to function at the cellular and molecular level of biological interactions making them an attractive platform as contrast agents for magnetic resonance imaging (MRI) and as carriers for drug delivery.Nano particles are now being developed for applications in the detection, diagnosis, and treatment of malignant tumors, cardiovascular disease, and neurological disease.

Keywords: Nanotechnology, Drug delivery, Nano particles, NPs, Magnetic nano particle.

INTRODUCTION

Drug delivery is an interdisciplinary and independent field of research and is gaining the attention of pharmaceutical researchers, medical doctors and industry. A safe and targeted drug delivery could improve the performance of some classic medicines and moreover, will have implications for the development and success of new therapeutic strategies such as anticancer drug delivery, peptide and protein delivery and gene therapy. Nano particles (NPs) have been developed as an important strategy to deliver conventional drugs, recombinant proteins, vaccines and more recently, nucleotides. RNA nano particles containing siRNA (single strand ribo nucleic acid) would bind to the membranes and bring the siRNA into the cells, these RNA combine with the drug before it reaches in to the cell. Nanotechnology pertains to synthetic, engineerable objects which are nano scale in dimensions or have critical functioning nano scale components, leading to novel, unique properties [1, 2]. New biologic drugs such as proteins and nucleic acids require novel delivery technologies that will minimize side effects and lead to better patient compliance [3, 4]. New drug delivery methods may able to reformulating old drugs can reduce side effects and increase patient compliance,Thus saving money on health care delivery. Many times, the success of a drug is dependent on the delivery method. The mechanisms used to achieve alternative drug delivery typically incorporate one or more of the following materials: biologics, polymers, silicon-based materials, carbon-based materials, or metals. These materials are structured in nano scale formats[5]. Nano-vehicles, Which are pH sensitive, are usually designed to destabilize vehicles and release drugs in endosomal and/or lysosomal compartments, which have pH values typically as low as 5.5 and 4.5[6].Targeted drug-delivery systems can convey drugs more effectively and conveniently than those of the past, increase patient compliance, extend the product life cycle, provide product differentiation and reduce healthcare costs [7]. In addition, novel drug-delivery systems would offer protection and improve the pharmacokinetics of easily degradable peptides and proteins that often have short half-lives in vivo [8, 9]. Therefore, the development of techniques that could

selectively deliver drugs to the pathological sites is currently one of the most important areas of drug research. Nano particles (NPs) are at the leading edge, with many potential applications in clinical medicine and research [10]. Magnetic nano particles (MNPs) possess unique magnetic properties and the ability to function at the cellular and molecular level of biological interactions making them an attractive platform as contrast agents for magnetic resonance imaging (MRI) and as carriers for drug delivery MNPs are being actively investigated as the next generation of
Magnetic resonance imaging (MRI) contrast agents [11] and as carriers for targeted drug delivery [12, 13].

NANOTECHNOLOGY AS A SOLUTION FOR DRUG DELIVERY

Nanotechnology is the creation and utilization of materials, devices and systems through the control of matter on the nano meter-length scale, i.e., at the level of atoms, molecules and Supra molecular structures.[14,15] Nanotechnology focuses on formulating therapeutic agents in biocompatible nano carriers, such as NPs, nano capsules, micellar systems and dendrimers (Figure 1). Polymeric NPs are small polymeric colloidal particles with a therapeutic agent either dispersed in the polymer matrix (nano sphere) or encapsulated in polymer (nano capsule). MNPs are nano meter-sized ferrite-or magnetite (Fe3O4)-based spherical particles. These particles can be coated with various hydrophilic polymers for stability and can be loaded with therapeutic agents. Solid lipid NPs are made from solid lipids (i.e., lipids that are solid at room temperature and at body temperature) and stabilized by surfactants. The drug can be encapsulated either in the shell or in the core of the NP. Dendrimers are mono dispersed symmetric macromolecules built around a small molecule with an internal Cavity surrounded by a large number of reactive end groups. Polymeric micelles are formed of block copolymers, which assemble in aqueous solution as outer hydrophilic layer and inner hydrophobic core. To the hydrophobic core of the micelles, water-insoluble therapeutic agents can be loaded. They can also be conjugated with different ligands and antibodies to achieve site-specific targeting.
Moreover, one of the major advantages that nanotechnology offers is targeted drug delivery to the site of disease. This can be achieved either through passive targeting of drugs to the site of action or by active targeting of the drug (Figure 2)[16].

PASSIVE TARGETING

Enhanced permeability and retention effect

Passive targeting exploits the anatomical differences between normal and diseased tissues to deliver the drugs to the required site because the physiology of diseased tissues may be altered in a variety of physiological conditions through the enhanced permeability and retention (EPR) effect [17, 18]. The development of long-circulating nano particles has allowed for many MNP platforms to exploit structural abnormalities in the vasculature of particular pathologies, such as tumors, inflammatory, and infectious sites. This phenomenon, known as the enhance permeability and retention (EPR) effect [19, 20], passive targeting, has been demonstrated with nano particles ranging from 10 to 500 nm in diameter [20]. This occurs because tumor vasculature is leaky; hence circulating NPs can accumulate more in the tumor tissues than in normal tissues. At the site of infection or inflammation where excess bradykinin is generated also exhibits the EPR-effect. The only difference between infection-induced EPR effect and that of cancer is duration of retention period; the retention in normal tissue where undergo inflammation is less than the cancer tissue. Besides exploiting the structural framework of cancerous tissues, the EPR effect is also observed at the site of inflammation. A number of passively targeting nano carriers were developed in the 1980s and 1990s. One of the examples is Doxil (or Caelyx), a sterically stabilized PEGylated liposome that encapsulates doxorubicin. Doxil has shown good drug retention in the liposomal formulation with enhanced

circulation time and is up to 6 times more effective in comparison with free doxorubicin [21]. It was approved for the treatment of advanced ovarian cancer, metastatic breast cancer and AIDS-related Kaposi's sarcoma. Both in animal models and in patients, such systems have been shown to result in significant improvements in reduction of tumor size, working through the EPR mechanism [22]. Passive targeting can also occur through the inherent clearance by the RES. Comprised of bone marrow progenitors, blood monocytes, and tissue macrophages; the uptake of MNPs by these phagocytic cells provides a means of delivering contrast agents and drug carriers to related organs [23].

Localized delivery

Another approach is the direct intra tumor delivery of anticancer agents using NPs, which can be used in the treatment of local cancers such as prostate, head and neck cancers. Transferrin (Tf) conjugated paclitaxel (Tx) -loaded biodegradable NPs are more effective in demonstrating the anti proliferative effect of the drug than its solution or with unconjugated Tx-loaded NPs. The better efficacy of conjugated NPs was due to their greater cellular uptake and sustained intracellular retention than unconjugated NPs or the drug in solution.This characteristic of conjugated NPs maintains higher intracellular drug levels than in cells treated with drug in solution or with unconjugated NPs [24].

ACTIVE TARGETING

Active targeting, on the other hand, requires the conjugation of receptor specific ligands that can promote site specific targeting [25, 26]. The active targeting can be achieved by molecular recognition of the diseased cells by various signature molecules over expressed at the diseased site either via the ligand-receptor, antigen-antibody interactions or by targeting through aptamers.The therapeutic agent can be actively targeted by conjugating the carrier with a cell or tissue-specific ligand, thereby allowing a preferential accumulation of the drug at the diseased site [27] .The various nano systems can be accumulated at higher concentrations than normal drugs, targeted NPs can provide greater intracellular delivery of therapeutic agents to the cancer cells within solid tumors than their non targeted analogs[28].In another studies cancer cells were actively targeted using PLGA NPs that were surface-modified with monoclonal antibody[28] Their results demonstrated the superior capability of active recognition of the surface- modified NPs, because these NPs showed enhanced binding to the targeted cells than non coated NPs. Aptamers are DNA or RNA oligo nucleotide sequences that selectively bind to their target with high affinity and specificity [29].Receptor–ligand or antigen–antibody interactions provide an effective strategy to improve the residence time in malignant tissues, such as tumors . Targeting ligands, such as proteins[23], peptides [30], aptamers [31-33] and small molecules [34], have been investigated to increase the site specific accumulation of MNPs [23].

NANO PARTICLES IN MEDICINE:

Therapeutics

NPs have widespread use in drug delivery as discussed with regard to the various types of NPs. Some recent applications of NP in therapeutics are discussed. Many chemotherapeutic drugs such as paclitaxel, doxorubicin and etoposide, etc., have been successfully loaded onto NPs and these nano particulate systems are very potent against various cancers. Many NPs are also useful as therapeutics due to their antimicrobial properties. Table 1 highlights some of the NPs that can be effectively used for therapeutics[35- 43].

MAGNETIC NPS

(MNPs) are increasingly being realized as one of the most important materials in the industrial sector, and they are being widely used for biotechnological and biomedical applications. Drug delivery may be immensely benefited by the use of MNPs because these Particles have the ability to target a specific site, such as a tumor, thereby reducing the systemic distribution of cytotoxic compounds in vivo and enhancing uptake at the target site, resulting in effective treatment at lower

doses [44]. In the preparation of colloidal MNPs, the stability of the colloid is of utmost importance. Magnetic iron oxide particles without any surface coatings have hydrophobic surfaces with a large surface area to volume ratio, this leads to particles' agglomeration and formation of large clusters, resulting in increased particle size. This inherent aggregation behavior of MNPs is a crucial limiting factor that reduces the intrinsic super paramagnetic properties and triggers the opsonization process[45]. Therefore, to minimize the aggregation, it is necessary to engineer the surface of the MNPs.

Synthetic and natural polymers (dextran, polyethyleneglycol (PEG), and poly Vinylpyrrolidone (PVP), streptavidin, poly-Llysine (PLL), polyethylene imide (PEI), etc., have been employed to modify the surface of the MNPs46. the superparamagnetic MNPs by surface modified with PEG to resist the protein adsorption and thus avoid the process of opsonization and also to facilitate the intracellular uptake by specific cancer cells for cancer therapy and diagnosis Magnetic-based delivery strategies are based on binding drugs with magnetic fluids that concentrate the drug in the site of interest. In magnetic drug targeting, magnetic carrier particles with surface-bound drugs are injected into the vascular systems that are then captured at the tumor via a locally applied magnetic field.

Advantages of Nano biotechnology in drug delivery

Nanotechnology (nano materials and nano scale devices) applied for diagnosis, treatment and monitoring diseases [61] as well as controll and understand of biological systems [62].

1. Nano technology may help in increasing the solubility & bioavailability of drugs as well as nano particles with diameter less than 200nm are not screened out of circulation by liver and spleen .so, we can achieve the drug administered to the desired sites [61]
2. Normally, drugs work through the entire body before they reach the disease affected area. Using nanotechnology, the drug can be targeted to a precise location which would make the drug much more effective and reduce the chances of possible side-effects [63].
3. The pharmacokinetics and antibacterial effect of the nano particle-bound anti-TB drugs administered via respiratory route was investigated in guinea pigs The potential advantages of direct delivery of the TB drug to the lungs include the possibility of reduced systemic toxicity [64].
4. Micro particles with a diameter of more than 1µm that cannot be administered via intravascular routes, nano particles are small enough to allow intra capillary passage followed by an efficient cellular uptake [64]. Intravenous administration of the nano particles has the further advantage of passive drug delivery to inflammatory sites where the endothelium becomes permeable due to pathologic processes [64].
5. Nano scale powders of antiasthma and analgesic drugs are quickly absorbed in the human body in comparison to the traditional drug delivery systems [61].
6. Nanotechnology based drug delivery is less toxic as well as in expensive [61].
7. Nano technology is suited for better drugs delivery to small regions within the human body as such drugs can easily cross biological membranes [61].
8. MNPs can be successfully used for a wide range of drug-delivery applications to improve management and general health by an advancement of early diagnosis of many killer diseases.
9. AuNPs are carriers for efficient transmucosal insulin delivery. Their results showed that there was a significant reduction of blood glucose levels.

CONCLUSION

Nano biotechnologies have been applied to improve drug delivery at nano meter scale leading to novel, unique properties. Nano-components, each designed to achieve a specific task with the common goal of site directed delivery of therapeutics to a target lesion. MNPs of various formulations have been developed to diagnose and treat diseases for which conventional therapy has shown limited efficacy. In particular, the use of MNPs as MRI contrast agents and drug carriers has drawn enormous attention, as it holds great potential of providing new

opportunities for early cancer detection and targeted therapies. This technology will not only minimize invasive procedures, but also reduce side effects to healthy tissues, which are two primary concerns in conventional cancer therapies. Improving imaging contrast, biocompatibility, and specific targeting capability of the drug. Advantages of nano particle-based carriers include improved delivery of water insoluble drugs, prolonged circulation half life, and reduced immunogenicity.

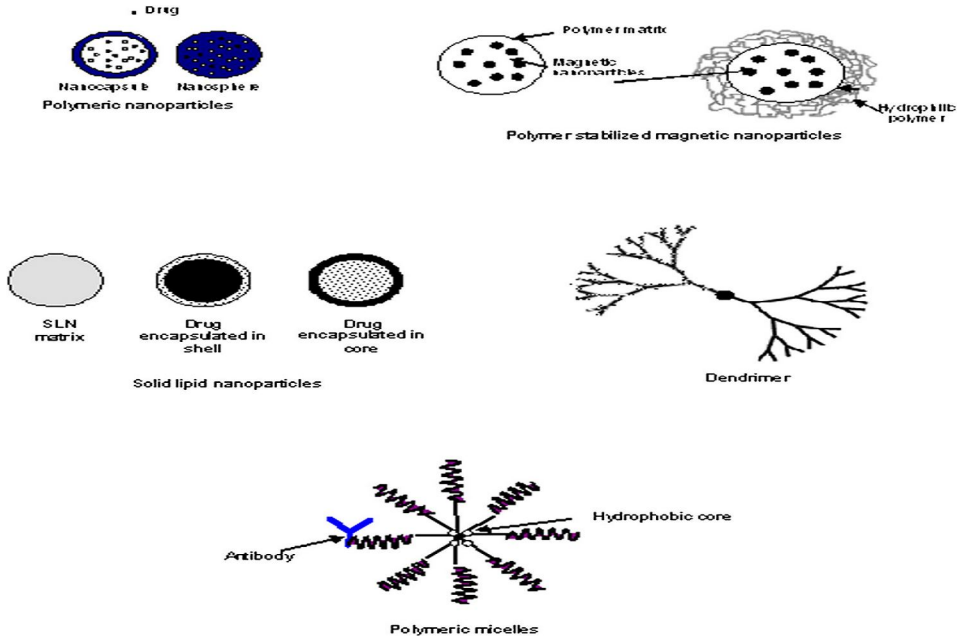

Fig. 1: Schematic representation of different nanotechnology-based drug-delivery systems

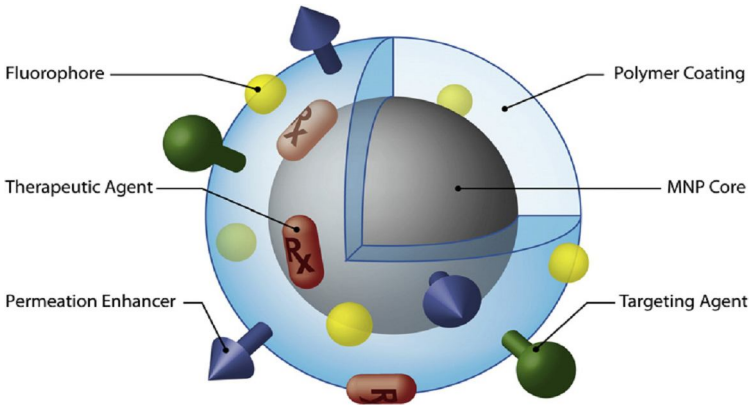

Fig. 2: MNP possessing various ligands to enable multi functionality from a single nano particle platform.

Fig. 3: Schematic representation of different Drug-targeting approaches

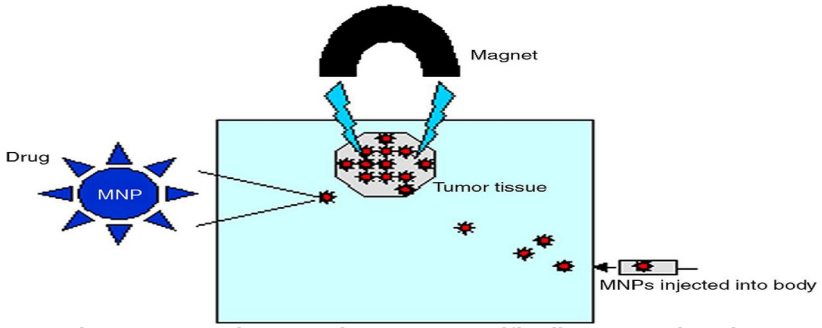

Fig. 4: External magnetic MNPs specifically targeted to the tumor tissue with the help field

Table 1: NP's As Therapeutic Agents

Type of Nano material	Encapsulant	Indicator	Therapeutic improvement
Polyisohexylcyanoacrylate NPs	DOX	Hepatocellular Carcinoma	Higher antitumor efficacy than native doxorubicin and can overcome multiple drug resistance phenotype
PLGA NPs	Paclitaxel	Various cancers	Effective in chemotherapeutic and photothermal destruction of cancer cells
Gold NPs (AuNPs) -		Various cancers	Effective as radiation sensitizers for cancer therapy
Chitosan NP (CNP)	siRNA	Ovarian cancer	Increased selective Intra tumoral delivery and significant inhibition of tumor growth compared to controls
Cetyl alcohol/polysorbate NPs	Paclitaxel	Brain tumor	Higher brain and tumor cell uptake, thus leading to greater cyto toxicity; also effective towards
Lipid nano capsules	Etoposide	Glioma	Greater cyto toxicity. Can overcome p-glycoprotein dependent multidrug resistance.
Multifunctional super paramagnetic iron oxide NPs	DOX	Liver cancer	Promising candidate for treating liver cancer as well as monitoring the cancer using MRI

ABBREVIATIONS

MNPs: Magnetic nano particles
MRI: Magnetic resonance imaging
EPR: Enhance permeability and retention effect
NPs: Nano particles
RES: Reticulo endothelial system

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