Nanoparticles and their Different Drug Delivery Applications in Cancer Therapy-A Concise Review

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***Abstract*: In recent times the major challenge in the medical industry is cancer. Nevertheless, there are a number of drugs are on hand for the treatment of cancer. But imprecise distribution and disorderly release of such drugs in such conventional drug delivery applications have led to the advance of a smart nanoparticle-based drug delivery system in cancer therapy. These conventional treatments are able to cure cancer but they also have collateral toxicity to other healthy cells and tissues. Thus, to get better treatment and rise above these problems the nanoparticle-loaded drug delivery system is one of the solutions. This review highlights different type of nanocarriers such as liposomes, micelles, dendrimers, viral nanoparticles, protein-drug conjugated nanoparticles, polymeric nanoparticles, and carbon nanotubes, in drug delivery applications, their targeting methods, their advantages over chemotherapy. This article also delivers a significant overview on the future standpoint of these nanoparticles in such drug delivery systems.**

***Keywords*: Applications, Bio-compatibility, Cancer therapy, Drug delivery, Nanoparticles, Target methods, Toxicity.**

1. Introduction

In the current international data base of cancer evidently state that this disease is one of the major causes of deaths of 60092 people and 168870 are new cases of cancer is reported in the year of 2017. Moreover, these data also gave an information about the 70% increase the patient of cancer in next 20 years [1]. There are several conventional treatments such as surgery, radiation and chemotherapy in the treatment of cancer. Such treatments are not most efficient because of its collateral side effects on other cells. Weinberg et.al. Suggested the six diverse type of features that differentiate the tumor tissue from normal tissue of the body. These six different features are angiogenesis, metastasis, and invasion, defend against cell death, signaling, enabling immortality and growth suppressing effects [2]. Due to these exclusive features of cancer cells new investigation have been extensively developed to establish a new practice for the treatment of the disease .These new practice is known as nano medicine. Nanoparticles with characters such as size ranging from 1nm to100nm, constructive drug release Outline, high surface-to-volume ratios, and some modification on surface makes it more acceptable as modern treatment of cancer over our conventional treatment remedies [3, 4] .The exceptionally high ratio of surface to volume ratio that is distinctive features of nanoparticles, enable them to interact competently with their environment. Therefore serve as potential carriers for the drug delivery agents in cancer therapy. Different nanocarriers such as gold and magnetic nanoparticles, liposomes, micelles, mesoporous silica, polymeric nano materials, have better biomedical roles that comprising drug and gene delivery systems. Besides this, suitable modification on the surface of the nanoparticle can increase their target specificity by ligand-recognition as well as enable the monitoring of drug delivery by attached reporters. Furthermore, nanoparticle drug delivery vehicles considerably reduce the side-effects of the drugs by making them more water soluble as a result lessening the required overall dose [5].

2. Types of Nanoparticles

A. Protein-drug conjugated nanoparticles

The protein part is directly conjugated with the drug which is categorized as Protein-drug conjugated nanoparticles. After coming in the cell, the connection develop into a characteristically biodegradable which is developed between the protein and the drug. As connection can be destroyed readily by proteases and redox-altering agents which are formed in blood which results into premature release of the drug. Such protein-drug conjugated system with their linker assists to keep on the place until the nanoparticles reach the target site. This system helps to decreases the toxic effect of drug molecules that permits more precise and handy drug delivery system [6].Typically Protein-drug conjugated nanoparticles have a long half-life because of there are small size (10nm) in vivo condition. Most recently, this type of conjugated nanoparticles included antibody proteins to enhancing their targeting capability [7]. However some drugs show structural sensitivity which makes them difficult to attach to a protein part which is a basic issue with protein-based nanoparticles [8, 9].

B. Liposomal nanoparticles

Liposomes are phospholipid-based amphipathic nanoparticles. Phospholipids is the most important constituent of the cell membrane, consist of a hydrophobic nonpolar fatty acid tail and a hydrophilic polar head. On the basis of the size and the number of bilayer the liposome are of two types: multi-lamellar vesicles and unilamellar vesicles. Unilamellar vesicles again can be grouped into two types, that is, large unilamellar vesicles (LUV) and small unilamellar vesicles (SUV) [10]. Liposomes can be formed with different conventional methods such as various methods [11, 12], solvent injection technique [14], reverse phase evaporation [15], and detergent dialysis [16]. These methods may have some obstacles. To remove those boundaries some novel methods have been evolved such as supercritical anti-solvent method [17], supercritical fluid technology, and supercritical reverse phase evaporation [18].Conservative liposomes have many difficulties which includes unsteadiness, inadequate drug loading, quicker drug release and less circulation time in the blood this problem can be overcome by using PEGylated liposomes which help them to run off the reticuloendothelial system. Radiolabeled liposomes are used to determine the distribution of the liposomes throughout the body and also for the tumor diagnosis [19].

C. Polymeric nanoparticles

Polymeric nanoparticles are composed of synthetic polymers. Use of such synthetic polymers allow different types of customization of properties of nanoparticles, for instance, as biodegradability, molecular weight and hydrophobicity. These nanoparticles permit the drug to release easily to in contrast to other nanoparticle drug delivery system [20]. There is a difficulty while using these polymeric nanoparticles which includes the narrow shape and broad size distribution. Nanoparticles size may be dissimilar that may be produced during synthesis; typically it is spherical in shape. The most recent approach is in which particles are produced with templates. This approach permit the creation of uniform polymeric nanoparticles with proper manipulation of shape and size. A lots of polymers are applied for the synthesis of such polymeric nanoparticles that is poly lactic acid, poly lactic-co-glycolic, and polyethylene glycolic reported my many researchers. Sometime natural polymers such as chitosan, albumin, and heparin that occur naturally and have been a matter of choice for the delivery of DNA, oligonucleotides, and protein, as well as drugs. These molecules are prepared with simple monomers which are present naturally in our body and as a result easily excreted without showing any major toxicity in our body [21].

D. Polymeric micelles

Micelles are Amphiphilic molecules, with both hydrophilic and hydrophobic
Segments, demonstrate an exclusive features of self-assembly when exposed to a solvent. When the solvent is hydrophilic in nature its concentration in the solution goes beyond the critical micelle concentration (CMC).The polar portion of the co-polymer are assembles toward the solvent, at the same time as hydrophobic portion orients away from the solvent. In this manner, the hydrophobic segment form a core, while hydrophilic segment forma corona in a reverse micelles. This type of arrangement is known as direct or regular polymeric micelle [22]. The hydrophobic core supplies a pool for hydrophobic drugs, whereas the hydrophilic outer region stabilizes the core and gives the polymers water-soluble properties making the particle suitable for administration[23].In contrast, when these amphiphilic substances are exposed to a hydrophobic solvent produce a reverse arrangement known as a reverse micelle. Diverse types of ligands are used to decorate the micelle surface, such as peptides, folic acid, antibodies, carbohydrates, aptamers, etc.ro dynamically target the cancer cells.(Sutton et al., 2007). The core or the corona of the micelles are able to be functionalized to discharge the anti-cancer drug at the accurate concentration. The stimuli applied in micelle based drug delivery system are different pH gradients, temperature adjustment, enzymes, ultrasound [24] and oxidation [25].

E. Viral nanoparticles

A wide number of viruses consist of cow pea chlorotic mottle virus, cowpea mosaic virus, canine parvovirus, and bacteriophages have been evolved for nano technological and biomedical applications which comprise tissue targeting drug delivery. A number of peptides and targeting molecules are exhibited in a biologically efficient form on the surface of their capsid using different chemical or genetic ways. For that reason a number of antibodies and ligands consist of folic acid, transferrin, and single-chain antibodies have been attached to viruses for precise tumor targeting in vivo condition [26]. In addition to this this artificial method a group of viruses for example canine parvovirus have usual affinity for receptors like transferrin which is subjected to up-regulation on different tumor cells [27].

F. Carbon nanotubes

Carbon nanotubes are cylinderic structure consists of benzene rings that are applied in biological science as analytic devices for the inequity of different proteins from serum samples and for detecting DNA and protein. Such carbon nano cylinder also used as a carrier to transport protein or vaccine [28]. Carbon nanotubes totally remain in insoluble form in almost all solvents, producing some health problem specially related with toxicity. Nevertheless, some chemical modification have been introduced in the carbon nanotubes that can give them water-soluble prosperity. They also get functionalized by attaching a different groups of active molecules such as nucleic acids, proteins, peptides, and wide range of therapeutic agents [29]. According to some authors anticancer drugs (methotrexate) have been attached covalently to the carbon nanotubes with a fluorescent agent in an invitro condition.

Drugs linked to the carbon nanotubes were more efficiently internalized into cells as attachments on the sidewall as well as on the tips of carbon nanotubes makes them able to carry several molecules at one time and this practice offers a essential advantage in the cancer treatment.

G. Dendrimers

Dendrimers are the Polymers with numerous branches. It has three major parts branching dendron's, a core different surface-active groups [30]. The functional groups on the dendrimer surface decide the physical as well as chemical properties of the dendrimer. They can be divided based on the surface groups-hydrophobic or hydrophilic. Because of its mono disperse nature, nanoscale size, high water solubility, less toxicity and bio-compatibility, it is of high interest of researchers. Its Nano scale size makes them a good candidate for drug carrier [31]

3. Cancer Cell Targeting Mechanisms

If the anti-cancer drug linked with a nanocarrier shows to type of drug delivery systems: passive targeting and active targeting [32]. Passive targeting utilizes the enhanced permeability and retention (EPR) effect [33] to find cancerous cells. On the other side active targeting exploits the ligand-receptor machinery to find the final target.

A. Passive targeting

Due to the leaky endothelium of the tumor tissue accumulation rate of drug-loaded nanoparticles into a tumor is much elevated than in normal tissue. This observable fact is known as the enhanced permeability effect. The lymphatic system in our body is the main drainage system. A lack of the lymphatic system in tumor tissue leads to retention of the nanoparticles loaded with drug in the tumor. This phenomenon is known as the enhanced retention effect. Both the effects in together known as the EPR effect [34].The concentration of anti-cancer drugs in the tumor tissue can be elevated many times by using this EPR effect as compared to the healthy tissue of our body. Nevertheless, efficient modifications on the different nanocarriers can be defeated many biological barriers such as Interstitial fluid pressure (IFP) and the (reticuloendothelial system) RES that doesn't allow the nano carriers to accumulate in right concentration within the tumor tissue [35].

B. Active targeting

Active targeting of the drug loaded nanocarriers is a mechanisms in which drug-carrying nanocarriers are guided to the cancer cells. Cancer and normal cells can be distinguished on the basis of antigen expression and cell surface receptor .Cell surface receptors are embedded trans-membrane proteins in the cell membrane responsible for communication. Cancer cells typically shows the over expression of this cell membrane receptors such as folic acid and cell surface antigen. In this mechanism drug-loaded nanocarriers are linked with different targeting ligands. These ligands can recognize their matching receptors on the surface of the cancer cell. Antibodies, peptides, transferrin, folate and aptamers are some of the explored ligands.

4. Conclusion and Future Standpoint

Nanoparticles area wonder of current science which serves a essential roles in modern biomedical applications, particularly in anti-cancer drug delivery systems. To overcome the boundaries linked with conventional chemotherapy, in cancer nanoparticles based drug delivery systems, have been launched. On the other hand, there are many limitations associated with effective nanocarrier based drug delivery system that applied as a suitable and promising alternative in cancer therapy. Consequently, the machinery behind this smart drug delivery system is a continuous research topic. The toxicity of different nanocarriers is a chief obstacle in the way of a successful drug delivery system. Researches have been performed to optimize the toxicity of different types of active nanocarriers and also developed some other new nanoparticles with lesser toxicity. Six nanoparticles as mentioned in this article show some degree of toxicity in human body. It propose that more research is needed for this smart drug. The future research scope and connected disputes may support the enduring perceptions and improvement of this nanoparticles –based drug delivery systems for cancer therapy. Simultaneously with the development of this nano scale drug delivery systems, progress in nano scale propose the possibility for the advancement of multifunctional nanoparticles that may make easy the understanding of individualized cancer therapy. Approximately all the seven types of nanoparticle which includes polymeric nanoparticles, polymeric micelles, dendrimers ,viral nanoparticles, carbon nanotubes, liposomal nanoparticles, protein drug conjugated nanoparticles have been reported for their multifunctional roles in the treatment of cancer. These multifunctional uses includes detection of malignant cells, visualization of their position in the body, killing the cancerous cells with minimal sides effects on the rest of the normal tissue of our body and monitoring the treatment effects in time to time.

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