

Article on latest trends in nanomedicine

Abstract

In this 21st century, various natural as well as synthetic drugs have been developed, and are still in process of development. But the most common problem faced by drug industry is their efficiency. Almost all the traditional drugs get released in the body in an uncontrolled way, creating side effects for the patient. Many drugs have adverse effect on digestive system, neurological system and other systems too. Some patients have a weak digestive system, and the drug gets excreted out of the body as it is. All these problems have now come to a conclusion, to create and tune and optimize the drug according to the need of patient. The answer to all this is, the use of nanotechnology in the field of drugs (medicine).

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Anjneya Verma

Amity Institute of Nanotechnology, Amity University, India

Correspondence: Anjneya Verma, Amity Institute of Nanotechnology, Amity University, Uttar Pradesh, India, 201303
Email anjneya-verma@yahoo.com

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Introduction

Many new techniques are now under development in labs and some of them are also now commercially available, especially in the field of cosmetics, cancer therapy, detection techniques, etc. Talking about the word “cancer”, which is the uncontrolled cell growth, every person in this world has cancerous cells, even right now also!!! But because of our body’s immune system they are eliminated.

The history about cancer says, that it is about 1500-3000 B.C. old and its cases in Egypt are known to us.

It is an old disease, but its permanent cure has not been made till now. Even cancer is so common that it is the second leading cause of death in United States, and millions all over the world. The use of Nanotechnology seems to be a promising technology in terms of detection of cancer in the early stages, as well as efficiently treatment of cancerous cells even at fatal stages as well.

In this article, we will discuss about drug delivery and how it can be used to treat cancerous cells.

- a. Drug Delivery
- b. Dendrimers
- c. Caged Nanoparticles
- d. Carbon nanotubes

Only the selected topics have been taken keeping cancerous and tumorous cells as a reference, a number of scientific groups are working on drug delivery, and dendrimers, caged nanoparticles as well carbon nanotubes may be used to achieve successful drug delivery process, depending on situation and condition of disease as well as condition of patient.¹

In Drug delivery, the drug or medicine is meant to reach and work at specific cells, this is possible with the use of nanoparticles, in treatment of tumors, cancerous cells, fat cells etc.² Some common routes of administration are non-invasive per oral or through mouth, skin or topical, trans-mucosal and inhalation routes. Depending on the reactivity of the drug, and its interaction with the body, they can be injected into the blood flow also.

Drugs released in the form of degradation, swelling, affinity based interactions (like Au nanoparticle does), and diffusion. The drug delivery, the drug is either taken orally or injected in the body.

There can be two kind or drug delivery methods possible:

- a. Active targeted drug delivery, such as antibody medications.
- b. Passive targeted drug delivery, such as enhanced permeable and retention effect.

Drug is released by simple degradation, affinity based techniques, diffusion, swelling (polymers).

Drugs can be delivered by the use of following:
Liquid crystals, core shell nanoparticles, vesicles, dendrimers.

The advantage of this technique is that, overall reduced consumption of drug. Toxicity will be low, as amount of consumption is fairly less. Depending on the type of nanoparticles, their rate of excretion can be tuned, that is, the time duration of the medicine in the human can be altered according to requirement, by functionalizing it or making shells around it.³⁻⁶

In drug delivery these points must be taken care of:

- i. Successful delivery of the drug to the targeted cell
- ii. Controlled release of drug their at cell
- iii. No or very low toxicity of the drug.

Why Dendrimers?

Dendrimers are hyper branched macromolecules, they consist of a core and 3-D tree like branched layers. They are globular structures of nano-dimensions that are tailored to carry molecules. The diameter of these dendrimers is approximately between 5-10nm.⁷ Although dendrimers are derived from polymers, but they have lower viscosity than polymers, due to their spherical shapes, also their size, and molecular mass can be well controlled, which was not possible with polymeric molecules. Dimensions such as shape, size and reactivity are a function of its shells or generation and chemistry of the core, branching and interior as well as terminal functionalities (Figure 1). Convergent and Divergent methods are the two ways of its synthesis.⁸

In divergent methodology

Dendrimer tend to grow outwards from a core molecule outwards. The core interacts with monomer and contains one active and two dormant groups, which ultimately gives the first generation. So on this will form a complete dendrimer molecule.⁹ It is best suited for large quantity production of dendrimers. But incomplete reactions of terminals lead to defects, excess of reagent is also required to prevent side reactions that may also occur, which ultimately lead to difficulties in the purification of the dendrimer.¹⁰

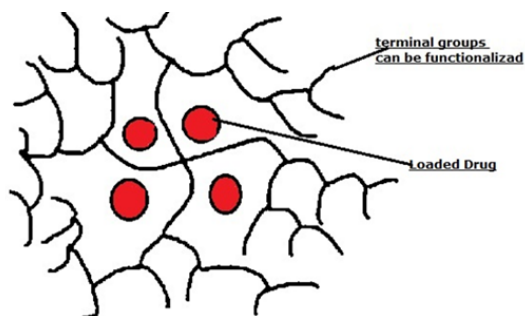


Figure 1 Dendrimer with drugs in it. The red spots showing the any loaded drug, entrapped inside a network of dendrimer, terminals can be functionalized.

In convergent methodology

Basically derived to overcome the drawbacks of divergent synthesizing technique. It starts from the end groups, and progress onwards, when the dendrons are large enough, they are attached to a core molecule, and hence a dendrimer through convergent technique will form. It has a drawback as it does not allow the formation of high generations because of the fact called steric hindrance, which occur in it.^{11,12}

It consist of 3 parts

- Core which initiates the dendrimer, and can be of a nanoparticle, polymer or some other dendrimers.
- Interior layers which are hollow and have enough interstitial sites for the drug to incorporate in them, moreover, the interior branching is a robust-covalent structure which connects the core to the surface groups.
- Exterior layers, which have the terminal sites which may or may not be functionalized, and can be anionic, cationic, neutral or hydrophobic groups.

Their synthesis is broadly categorized in to convergent and divergent methods of synthesis, every dendrimer can be synthesized by any of these methods, but depending on their application, their synthesis route is chosen. Outer membrane can be functionalized by various compounds which increase its versatility and usage good system or carriers.⁹ Drug and gene loading is very effective (because of huge voids in between dendrimers). Due to their hollow structure dendrimers have great physical and chemical properties, well define shape, size, molecular weight (which is almost impossible in case of polymers).

In gene delivery

PAMAM dendrimers can be used in delivery of genes, as they have amino groups at terminals; they react with the nucleic acids because of phosphate groups present in them. To improve the solubility and bio-compatibility of PAMAM dendrimers, they grafted with PEG on the surface of their synthesis, and encapsulated with anti-cancer drugs (methotrexate and adriamycin). These drugs are released slowly from the matrix in low isotonic solution, and control over drug release is yet to be done. Moreover, dendrimers can be used as vectors, as they act as carriers, in gene therapy.¹³⁻¹⁷ Vector transports genes from the cell membrane into the nucleus, and because of great bio-compatibility dendrimers will not do any bio-chemical reaction with organelles.

In drug delivery

Many studies have shown that due to larger size of traditional drugs, they take plenty of time to interact with cell, but dendrimers take One third time for cell and drug interaction to take place. Many molecules such as drugs and other therapeutic agents can be loaded both in interior void and at the surface to control the rate of release of the drugs.¹⁸ The use of dendrimers by encapsulating hydrophobic drugs is a potential way for delivering pharmaceutical compounds which are highly active, that are not is use may be because of their limited water solubility and resulting suboptimal pharmacokinetics. With the successive increasing generation in each dendrimer molecule, their drug carrying capacity increases by encapsulating drug in it and further research is advancing to use it as for specific cancer and other organ systems.^{19,20}

Caged Nanoparticles: In order to gain an efficient nano-mechanism for delivering of drugs to tissues, it should not compromise the following:

- Highly specific control over shape and size of particles used.
- High stability in physiological media to prevent aggregation of drug.
- Adequate drug carrying capacity in order to reach the target with sufficient concentration of drug.
- Effective active and passive targeted delivery.²¹

Keeping in mind all these points, gold nanoparticles seems to be compatible with these above requirements, as they have:

- Low cytotoxicity
- Good drug loading capacity
- No reactivity with other bio fluids
- Good cell permeability
- Affinity towards tumorous cells than healthy ones.

To have more control over the drug, now, more efficient methods have been developed, such as, polymer caged nanoparticles release upon the treatment of laser. Strong absorption in the near infrared (NIR) has been used to generate thermal energy for release of drug.^{22,23} The surface of gold nano composite can be covered with a polymer or say a smart polymer and the drug loaded in it can be released in a controlled manner, using near infrared region laser.²⁴

The release of drug is dependent on laser power and time of irradiation. This method has been tested with doxorubicin (dox) which is a commercial chemotherapy for breast cancer treatment. On the exposure to NIR laser, absorbed light is converter to heat, which triggers the smart polymer to collapse and drug gets released (Figure 2). On switching off the laser, the polymer chains will again relax back to extended conformation and terminate the release of drug.²⁵

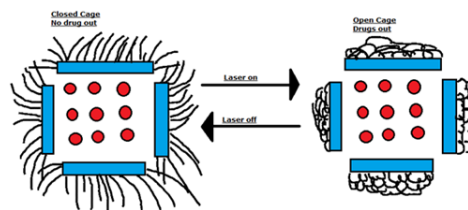


Figure 2 Caged Nanoparticles, with drugs in it, red spots display the drugs, entrapped inside the polymeric cage.

Carbon Nanotubes in cancer treatment: Carbon nanotubes are allotropes of carbon and structure of graphene sheets rolled at specific angles called chiral angles to produce a cylindrical structure called carbon nanotubes or CNT.^{6,11,23,26-30} They are black in color and can have very high aspect ratio and show inert nature to most chemicals. They have a hollow inner structure which act as a container to take drugs to specific sites for cancer treatment.

CNT can be:

- I. Single walled carbon nanotube
- II. Multi walled carbon nanotube

Moreover they can be capped as-well as uncapped tubes, the capped ones are generally capped with fullerenes at both ends. CNT have great potential in the field of drug delivery, biosensing applications, and imaging techniques. In the field of drug delivery, it can be used in cancer treatment. Till now in the research of cancer treatment, single walled as well as multi-walled carbon nanotubes are being used as a drug carrier (Figure 3). CNT's in any form are difficult to dissolve and disperse in polar as well in non-polar solvents, and are resistant to wetting, their toxicity is an issue for drug-delivery applications. To over-come these solubility issues, other entities is made to interact with CNT to change their chemical properties, according to the need.³¹ This functionalization is generally done at the region of higher chemical instability, which is at defect sites, or at open-closed ends or near the sp^2 - sp^3 interactions. These functionalization techniques can be broadly categorized by the method of type of reaction between CNT and the ligand or drug.

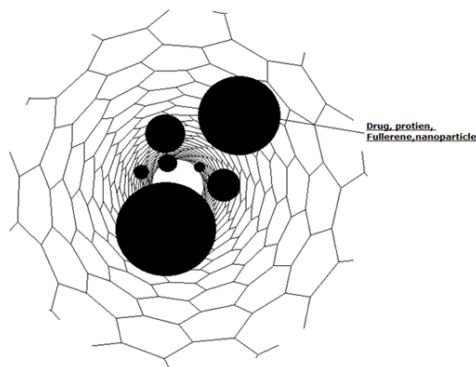


Figure 3 CNT in Drug Delivery (Inside CNT view). Black spots are the drugs which are inside the CNT.

There are covalent interactions and non-covalent interactions. The covalently bonded CNT-entity is obtained by oxidizing the CNT with strong acids, such as H_2SO_4 , HNO_3 . During this process $-COOH$ groups are formed at the terminals, and at the defects of the CNT walls. After their functionalization, due to free reactive sites, CNT becomes hydrophilic and compatible to react with DNA, proteins, enzymes, genes, drugs etc.

Due to fact that, CNT can easily penetrates through nuclear and cytoplasmic membrane; anticancer drugs can be liberated *in situ* with the unchanged concentration. Many anticancer drugs such as doxorubicin (dox), cisplatin, quercetin, methotrexate, paclitaxel, and epirubicin have been tested *in vitro* and *in vivo* successfully. Moreover, chemotherapeutic agents can be linked or bound to a complex formed by carbon nano tubes and antibody against antigen over expressed on the surface of cancerous cell. By the antigen-antibody interaction, CNT can be taken up by tumor cell prior the anticancer drug is cleaved off CNTs, thus the targeted drug gets released in the tumor

cell.³² In case of *vivo*, administration of SWCNT paclitaxel conjugate in a murine breast cancer model has been studied with high efficiency in suppressing tumor growth along with low toxic effects to other organs. The lower side effects along with higher therapeutic efficiency could be attributed to the higher tumor uptake, prolonged circulation of blood, and slower release of drug from SWCNTs.

Single-walled Carbon Nanotubes in the treatment of cancer: The CNT along with etoposide and dexamethasone (anti-cancer drugs) was being used on HeLa and Panc1 cells and results were calculated, which show that at high concentrations CNT with anti-cancer drugs were more effective to cause an increase in etoposide than the drug without CNT was used. The etoposide produces sDNA and dsDNA breakages, which causes delay progression through late S or early G2 phase of the malignant cell cycle. The etoposide induces redox reactions with production of derivatives that binds with the DNA, thus DNA damaging is caused by these anti-cancer agents with the drug carrying ability of CNT.³³

Multi-walled Carbon Nanotubes in the treatment of cancer: CNTs are able to absorb light of near infrared region, results in heating of tubes. This ability of carbon nanotube is used to kill cancerous cells by supplying thermal energy to them, similar to that of magnetic hyperthermia. The length of nanotube is such that, is it half of the wavelength of the light being used in the treatment (according to principle of antenna theory). Multi-walled Carbon nanotubes are being used as they have high chances of having defects and have high number of electrons ultimately will generate higher thermal energy.³⁴⁻³⁶ The dopants of group III and can be used. N-doped MWCNT is being used to kill cancerous cells in kidney In the presence of near infrared-light.

Conclusion

Although they will prove better than the traditional methods of treatment, but their methods of synthesis, pending tests will take some time for their approval to use on humans. Moreover, their current methods of synthesis are still not very cost effective. The new trends discussed here seem very much promising and many of them are in the stage of animal testing. In dendrimers, its stabilization in different pH solvents, precise control in its shape and size, and terminal group functionalization is still difficult and research is going on to develop new and better methods for their synthesis.

Compatibility of drug with the carrier is also an also an issue faced by drug carriers. Not all the drugs are compatible with all the drug delivery carriers. To overcome this hurdle, one approach can be finding out and using different more bio-compatible and drug-compatible carriers, other approach is to functionalize the carrier according to the drug, by in-situ or ex-situ functionalization. Earlier, toxicity of CNTs was an issue, but by functionalizing SWCNT will prevent it from being cytotoxic and altering the function of immune cells. Although CNT are good choice for cancer treatment, but their insolubility with water is a problem. However, it can be concluded that the current research goes in the correct path, but modifications and their application is still to be done.

The future research may be focused on, making these drug delivery methods more efficient and reliable. May be now, the functionalization of these materials such as carbon nanotubes, dendrimers etc. to change their undesired effects needs to be done, to make it more bio-compatible and safe for their application. Even now, some more polymeric or carbon based materials can be developed which may have better properties for drug delivery than these existing ones.

Acknowledgments

None.

Conflicts of interest

None.

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