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ADVANCED MICRO AND NANO DRUG DELIVERY SYSTEM IN CANCER THERAPY

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ABSTRACT

The diagnosis of cancer is more affected if the delivery of any drug at the right time and in the target where it is needed and it is also necessary to known the required level of drug to appreciate the full potential of therapeutic molecules. These requirementsare already more important inthe case of cancer chemotherapies due to their high toxicity which could lead to serious side effects. Polymer conjugation is also a drug delivery system in the diagnosis of cancer as well as nano and micro delivery system. Both these methods are very important to diagnosis of cancer and improved the drug administrationand the efficiency and safety of conventional chemotherapies. It also revolutionized in the pharmaceutical andbiomedical industries in cancer therapy. In this review paper we have introduced the developments in nanotechnology which offer researchers opportunities to significantly transform cancer therapies. This technology has enabled the manipulation of the biological and physicochemical competence of nanoparticles to facilitate more efficient drug targeting and delivery.This technology provides a better result than traditional method in the treatment of cancer.

***Keywords*:**Cancer; Nanotechnology; Chemotherapy; Microand Nano particles;Treatment of Cancer by Therapy method

INTRODUCTION

After more than a decennary of research and development, micro and nanotechnology has reshaped the tradition thinking of using material for drug delivery in micro and nano range.[1]Nano and microscale molecules are smaller than human cells by 100 to 10,000 times but are similar in size to large biomolecules such as enzymes and receptors. Nano and microscale devices are very smaller size due to this these can easily enter most cells, and those smaller than 20 nm can move out of blood vessels as they broadcast by all the body. Nano and microdevices are applicable to serve as customized, targeted drug delivery vehicles to carry large doses of chemotherapeutic agents or therapeutic genes into malignant cells while sparing healthy cells means that micro and nano drug delivery are now showing much promise for numerous drug delivery application.[1]

Typically, micro and nanotechnology is defined as the use of material and system whose structures and components exhibit novel and significantly change properties when control is gained at the micro and nano scale.[1]The advanced development of drug delivery has improved therapeutic and toxicological properties of existing chemotherapies and facilitated the implementation of new one.[3] By including the drug in technologically optimized drug delivery system or conjugating the drug with different polymers, it is possible to modify the pharmacokinetics and bio-distribution of the drugs, improving the efficacy and security of the therapy.[3]

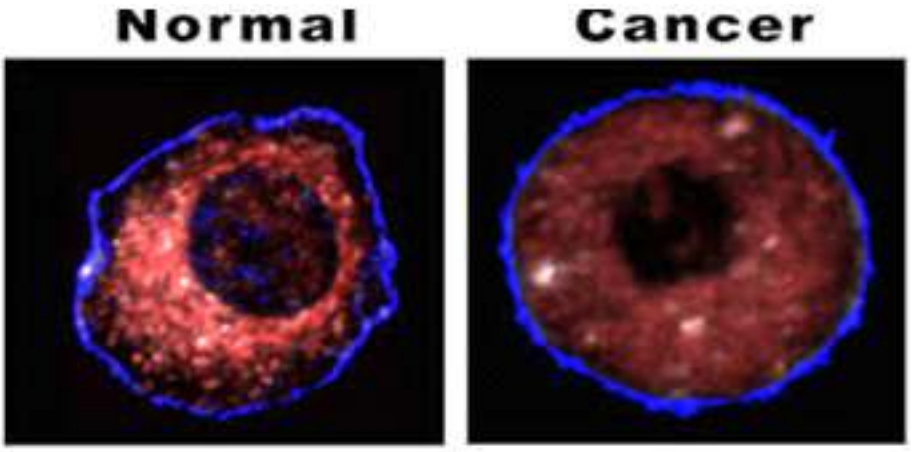
In cancer treatment, micro and nano particles can further rely on the enhanced permeability and retention effect caused by leaky tumor for better drug accumulation at tumor sites. These benefits have made therapeutic nano-particles a promising condition to replace tradition chemotherapy, where intravenous injection of toxic poses a serious threat to healthy tissue and result in dose limiting side effect.[1]

Table 1:

Late 1970	Current	Future
First nanoscale drug delivery system was lipid vesicles	Nowdays, liposome, cream, capsule, tablets, gel, aqueous solution, aerosols/spary delivery are used as form of delivery.	Nano and micro enabled technology will take the maximum share of the market up nearly 90% of drug delivery market.
Consider impossible to administer the pharmaceutical suspensions by intravenous means due to abvious risks of embolism.	15% of market uses nanoparticles for drug delivery system.	Safe, effective and without side effect. No wastages and increased bioavailabidity are going to be basis of future drug delivery.

CANCER

Cancers are abnormal cells which are different from healthy cells because these cells divide more rapidly than healthy cells. These cells found in collective behavior. Due to this behavior they form a mass of tissues is called a tumor. These cancerous cells that come in excess amount cause many problems to the bodies of patients. Figure-1, which shows below, shows the difference between normal and abnormal cell.



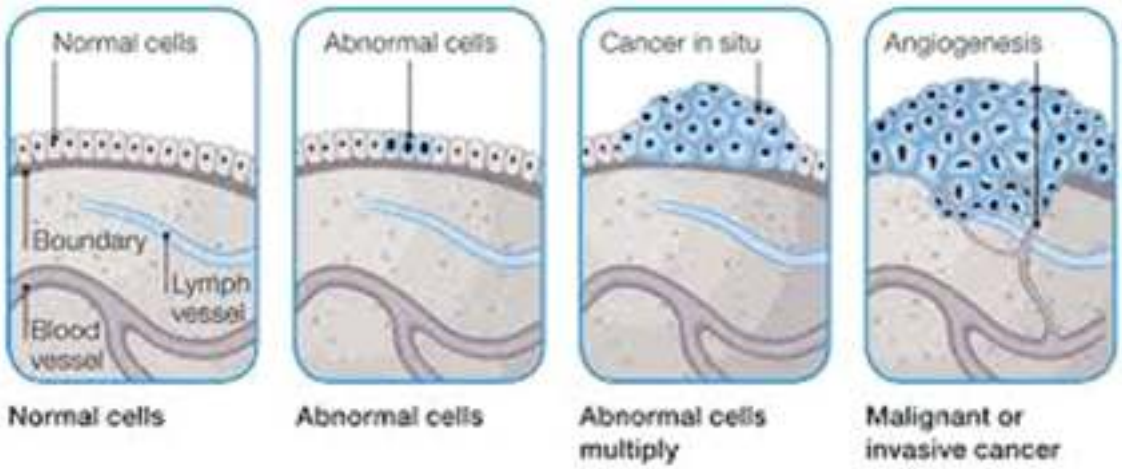
[Source- normal cell vs. bludder cancer cell ENCOGENCOGNITIVE COM- 254*148-SEARCH BY IMAGE]Fig-1

GENETIC OF CANCER

Before we know fully main issue of this report which deals with application of nanotechnology in cancer prevention, detection and treatment, we must indicate the underlying causes and the genetic mechanisms involved in cancer. Here we present an over-simplified text of what is known on the genetic of cancer for sake of brevity.[4]

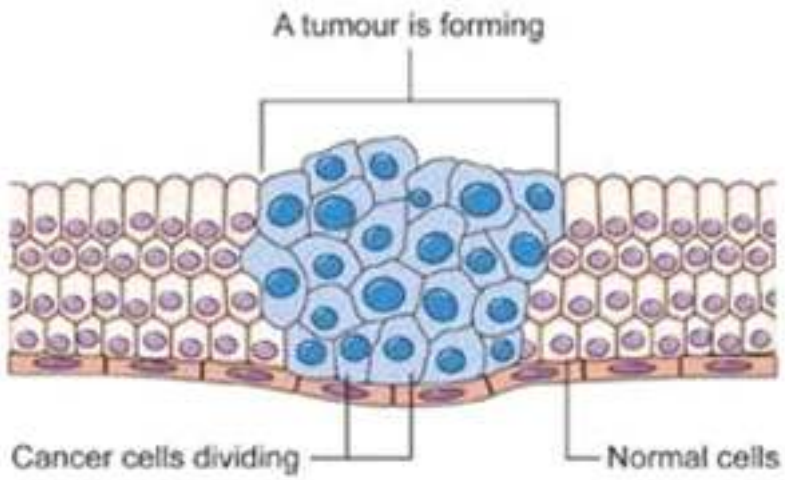
Cancer or neoplasm, on the other hand, aggregate tissues composed of cells that divide and grow abnormally. The intact number of geneticchanges required for these malfunctions remains unresolved for any cancer, but for adult cancers believed to range from 5 to 15 nano - meter.[5] The division of the abnormal cell is continues, and formed a large collection of cell. This type cluster of abnormal cells is known as a malignant tumour, and can furiously damage the surrounding tissue as it sucks up essential nutrients and displaces healthy cells.[6] Eventually, when the quantity of tumor is very large, then it creates more problems in the bloodstream and forming tumors in the other parts of body. This latest phenomenon is known as metastasis.

Effectively, it multiplies the cancer as well as its effects and eventually will prove fatal to the patient. In the below figure-2 and figure-3, show that how generate abnormal cell in our body and take a part of tumor which is called cancer.



[Source-CANCER CELL CANCER RESEARCH UK Cancer research UK 375*263-search by image]

Fig-2



[Source-CANCER CELL CANCER RESEARCH UKCancer research UK 375*263-search by image]

Fig -3

CHEMOTHERAPY

Chemotherapy is a type of treatment for cancer. It uses special drugs to kill cancer cell in body. Chemotherapeutic proxy work by destroying rapidly dividing cells, which is the main property of neoplastic cells.[17] Chemotherapy usually assigns to the use of medicines or drugs to treatment of cancer. The goal of chemotherapy is to stop or slow the growth of cancer cells.[8, 9]Chemo drugs target rapidly growing cancer cell, but they can also affect healthy cells that grow rapidly. To remove this problem a new method is created and is called radiation therapy. In this treatment drug is not used to treat a cancer. It gives a better result in comparison to other treatment.

Ordinarily, chemotherapy (chemo) hand over to the use of medicines or drugs to treat cancer. Therefore chemotherapy have important role in treatment of cancer. But knowing what chemotherapy is, how it works, and what to expect can often help calm your fears. It can also give you a better sense of control over your cancer treatment. [10]

1. How is Chemotherapy Used to Treat Cancer?

Chemotherapy is most impotent method for drug in treatment of any disease.

Chemotherapeutic agents work by destroying rapidly dividing cells, which is the main property of neoplastic cells. But mostly people think that chemotherapy is used for drugs in cancer treatment. It's often shortened to "chemo."[17]

Surgery and radiation therapy are also treatment methodsfor cancer, remove and kill, or damage cancer cells in a certain area, but chemo can work throughout the whole body. This means chemotherapy can kill cancerous cells that have elaboration (metastasized) to parts of the body far away from the original (primary) tumor.

2. Goals of chemotherapy treatment

The main goals for chemotherapy (chemo) in cancer treatment are three types which are following:

1. Cure
2. Control
3. Palliation

2.1. Cure

Normally chemotherapy destroyed the cancerous cell – it goes away and doesn't come back. But tradition method doesn't promiseto prevention, diagnosis and treatment of cancer therefore many doctors don't use the word "cure" except as a possibility or intention. So, when giving treatment that has a chance of remedying a person's cancer, the doctor may describe it as treatment with curative occasion.There are no guarantees, and though cure may be the goal, it doesn't always work out that way. It often takes many years to know if a person's cancer is really cured**.**

2.2. Control

When the treatment (cure) of cancer is not possible then the goal may be to control the disease. Chemo is used to shrink tumors and/or stop growing and spreading of cancer cells. Therefore it can help the person with cancer feel better and live longer.

2.3. Palliation

Chemotherapy can also be used torepel symptoms caused by the abnormal cells indite. This is called palliative chemotherapy or palliation. When cancer is in the last stage ie advanced stage, meaning that it is not under control and abnormal cells has spread from where it started to other parts of the body. In this condition the goal may be to improve the quality of life or help the person feel better. For instanter, chemo may be used to help shrink a tumor that's causing pain or pressure.

3. Limitations of conventional chemotherapies

Chemotherapy is one of the main important method for treatment of cancer but it has high toxicity due to this it has some drawback, which is proved harmful on the human body of cancer patients, which could lead to serious side effects,reducing the administrable and the therapeutic effect and the main drawback of conventional chemotherapy is that healthy cell are also affected because it cannot give selective action only to the cancerous cells.[18,19]

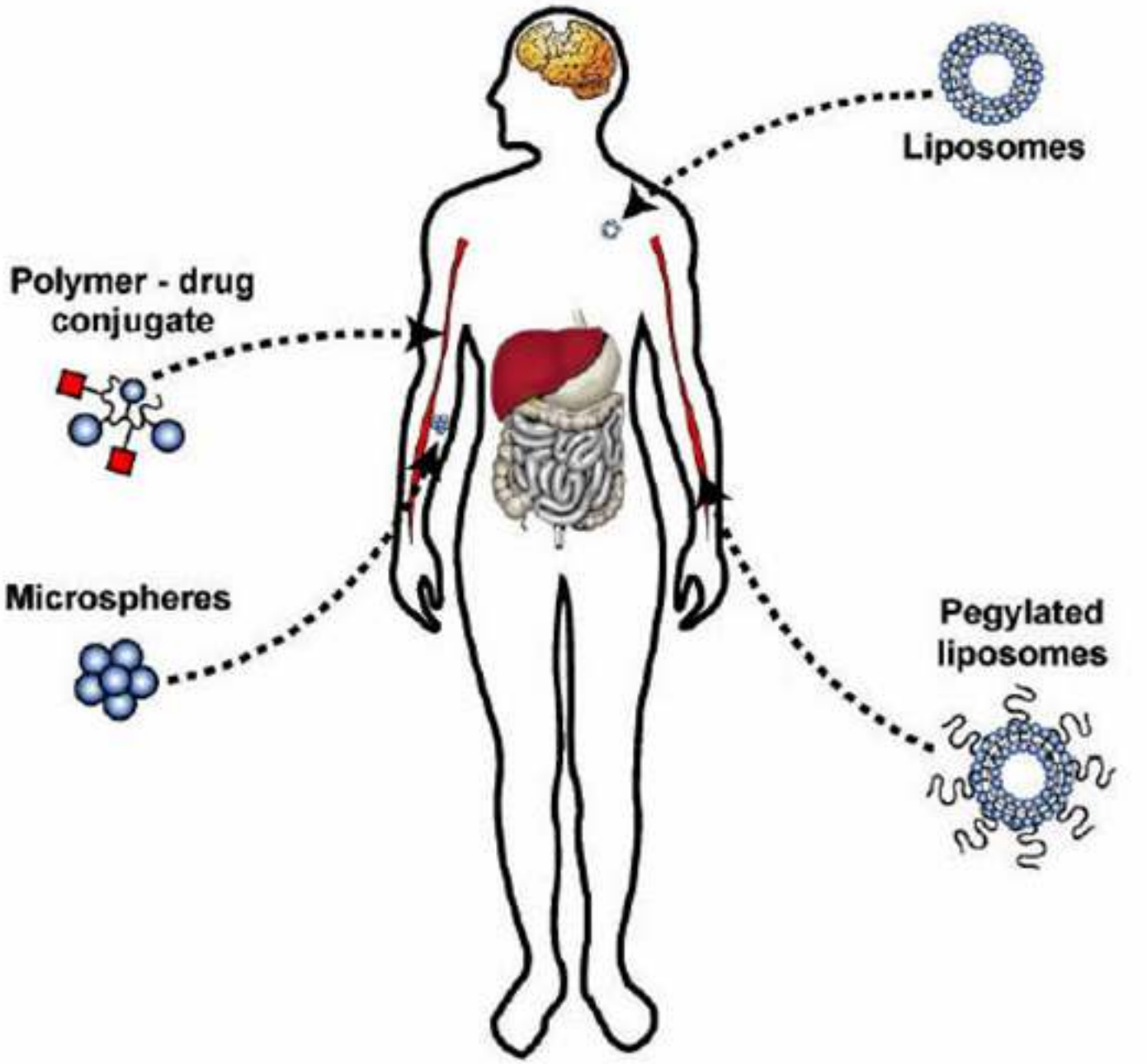
Traditional chemotherapeutic agents often get washed out from the circulation being devoured by macro and nano phase. Cancerous cell are not totally effective by chemotherapy because the circulation of chemotherapeutic agents for a very short time and cannot interact with the cancerous cells. The major drawback behind the failure of traditional chemotherapy is the poor solubility of the drugs. [20] Therefore the administered drugs remain unsuccessful or cannot bring the desired output.[21–22]

In this review paper weare addressingthat the treatment of cancerous cell is possible by nano and micro drug delivery in chemotherapy which is more effectively than traditional chemotherapy. To improve the output for treatment of cancer it is essential to transport the therapeutically active molecule mainly to the target where it is needed and at therequired time and level.[10] This could be achieved by embedding the drugs into nontoxic and biodegradable polymers from which the drug will be released in a sustained manner. [11]

RADITION THERAPY

One of the most common treatments for cancer is Radiation therapy. It uses high-energy particles or waves, such as x-rays, gamma rays, electron beams, or protons, to destroy or damage cancer cells. Other names for radiation therapy are radiotherapy, irradiation, or x-ray therapy. [28]

Radiation can be used or used with other treatments, such as surgery or chemotherapy. In fact, definite drugs are known to be radio sensitizers (RAY-dee-oh-SENS-it-tie-zers). This means they can actually make the cancer cells more sensitive to radiation, which helps the radiation to better kill cancer cells.[28]

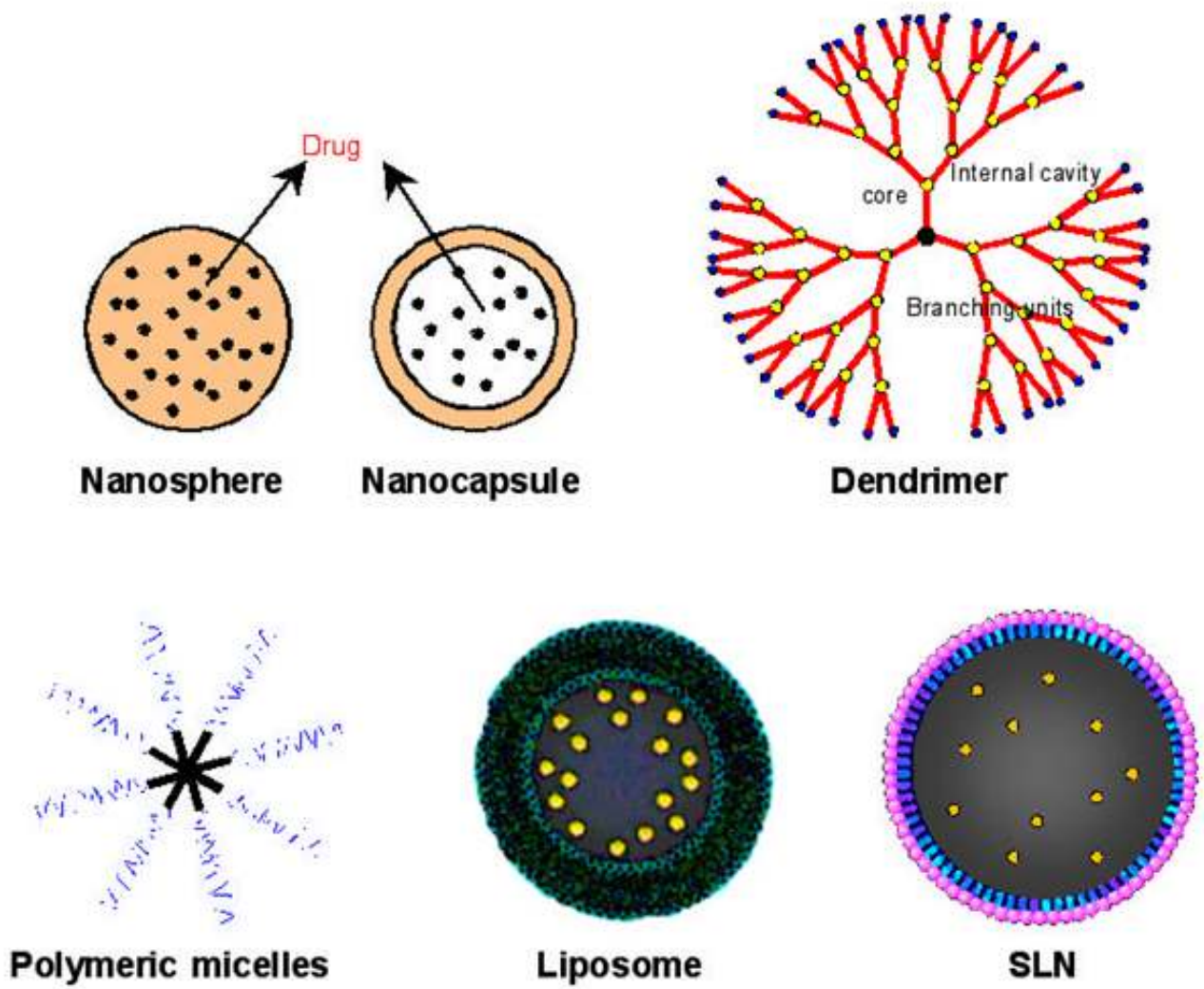


Examples of different drug delivery approaches that are FDA-approved or are in clinical development as anti cancer treatments. Reproduced from Moses et al, 2003 with kind permission from Cancer Cell. Figure 4

MICRO AND NANO - TECHNOLOGIES

The dreadful opportunities exist for using micro and nanoparticles as controlled drug delivery systems for cancer treatment.[32]The term "microparticle" refers to a particle with a diameter of 1- 1000 mm, while "nanopaticle" is used when the particle is <1 mm in size. However, under this term it is possible to distinguish several reservoirs including micro/nanocapsules, micro/nano spheres, liposomes, etc. All these devices differ not only in the structure (Figure 5) but also in their biopharmaceutical cretic and therapeutic uses . [33]The manufacturing protocol of each molecule differs also considerably and the scale-up could be a challenge for some of these devices. An important issue to be considered when manufacturing these systems is the drug load that the reservoir can carry. This drug load depends on the size and the structure of the device, ranging from some few molecules of the drug to a few

tens. Therefore, selection of drugs with potent pharmaceutical activity is necessary in order to have therapeutic effects in the released dose. Furthermore, it is essential that the drug will not be altered during the fabrication process and the storage. Finally, interactions between drug and the reservoir must be optimized to facilitate drug release only in the target where it is needed and at the desired kinetic-release. Natural and synthetic polymers including albumin, fibrinogen, alginate, chitosan and collagen have been used for the structure of micro and nanoparticles. However, among all of them, lactic-glycolic acid copolymers are the most frequently employed materials due to their biocompatibility and biodegradability. Following a multiple emulsion process, a drug can be entrapped into a poly (lactic-co-glycolic) (PLGA) microsphere and released at a zero-order kinetic by diffusion of the drug through the polymer reservoir and the slow degradation of the polymer matrix. These advantages resulted in the first two PLGA microparticle extended-release formulations that were approved by the US Food and Drug Administration (FDA). One of themreleased the recombinant humangrowth hormone (rhGH)[1] whereas the other microparticle-based drug delivery system released the euteinizing-hormone-releasing hormone (LHRH) agonist leuprorelin acetate.[34] The latter is currently on the market under the name of Lupron® Depot and it is approved in the United States for the palliative treatment of advanced prostate cancer. However, there are still few microencapsulated structure on clinical trials addressing cancer treatments. In fact, a recent review of National Cencer Institute revealed that from the 1200 open clinical trials in the United States only one to be testing a microparticulate system for controlled drug delivery. [35]Experts, however, predict that within the next 5-10 years some of the structure currently understudy might progress to the clinical evaluation and perhaps become marketed therapy not so far.[36]



Schematics of different nano technology based drug delivery systems for cancer therapy. Reproduced from Sahoo and Labhas et.war, 2003 with kind permission from Drug Discovery Today. **Figure 5**:

Although the total drug-load is reduced considerably and the manufacture process is more complex, the nano-scale devices present some advantages over the micro-systems. In fact, submicron systems show higher intracellular uptake than microsized particles, thereby allowing drug-release in different cellular compartments such as cytoplasm and nucleus. Nanoparticles can be also easily conjugated with a ligand to favour a targeted therapeutic approach and as it has been reported, some nanoparticles can cross the blood-brain barrier (BBB). For example, doxorubicin bound to polysorbate-coated nano-particles can cross the intact BBB, reaching therapeutic concentrations in the brain. When these particles were administered in gliobla-stoma-bearing rats, a very aggressive human cancer with short survival times, significantly higher survival times were observed in the treated animal group compared with all other groups. [37]Depending on the elaboration method and the materials employed different nanosystems can be distinguished including micelles, nano-capsules, dendrimers, nano-spheres, solid lipid nano particles and ceramic nano-particles. The principal characteristics and some of the recent research using eachnano-systems is reviewed in Table 2.

Table 2: Examples of different nanoparticles and their applications as cancer treatments

Nanoparticle	Description	Recent applications	Reference
Nanocapsules	Vesicular systems in which the drug issurrounded by a polymeric membrane	Stability of the cisplatin nanocapsules has been optimized by varying the lipidcomposition of the bilayer coat	Velinova et al. 2004 [39]
Nanospheres	Matrix systems in which the drug is physically and uniformly dispersed	Bovine serum albumin nanospheres containing 5 fluorouracil show higher tumourinhibition than the free drug	Santhi, et al. 2002 [40]
Micelles	Amphiphilic block copolymers that canself - associate in aqueous so lution	Micelle delivery of doxorubicin increasescytotoxicity to prostate carcinoma cells	McNaealy, et al. 2004 [41]
Ceramic nanoparticles	Nanoparticles fabricated using inorganiccompounds including silica, titania…	Ultra fine silica based nanoparticles releasingwater insoluble anticancer drug	Roy, et al. 2003 [42]
Liposomes	Artificial spherical vesicles producedfrom natural phospholipids andcholesterol	Radiation - guided drug delivery of liposomal cisplatin to tumor blood vessels results inimproved tumour g rowth delay	Geng, et al. 2004 [43]
Dendrimers	Macromolecular compound thatcomprise a series of branches around aninner core	Targeted delivery within dendrimers improved the cytotoxic response of the cells tomethotrexate 100 - fold over free drug	Quintana, et al. 2002 [44]
SLN particles	Nanoparticles made from solid lipids	SLN powder formulation of all - trans retinoicacid may have potential in cancerchemoprevention and therapeutics.	Soo - Jeong, et al. 2004 [45]

Nano-technology can be used for more efficient drug delivery system to tumor. Nano-particles can control the basic functions of cells, and potentially kill cancer cells, by virtue of their size alone without the need for drugs. One of the important mission of passive lipo-somal drug delivery is to cancer. Lipo-somes are one of the most well-known drug delivery carriers employed in the treatment of cancer. Due to their advantages, lipo-somal formulations provide a substantial increase in anti-tumor efficacy comparing with the free drug or standard chemotherapy regimens. [38] Liposomes are composed of a double lipid bilayer which encloses an aqueous space that can be employed to transport anticancer drugs.

The shape of liposome is a spherical vesicle having at least one lipid bilayer. Liposome can be used as a administration of nutrients and pharmaceutical drug. Liposomes are nano-particles ranging from 20 nm to 500 um in diameter. They are small spheres, the wall that separates the internal media from the external environment is a lipid bilayer. Given that they are comprised of both a lipid fraction and an aqueous fraction, liposomes can incorporate lipophilic substances and hydrophilic substances. [30] Figure 6 schematically shows liposomes with the two types of load.

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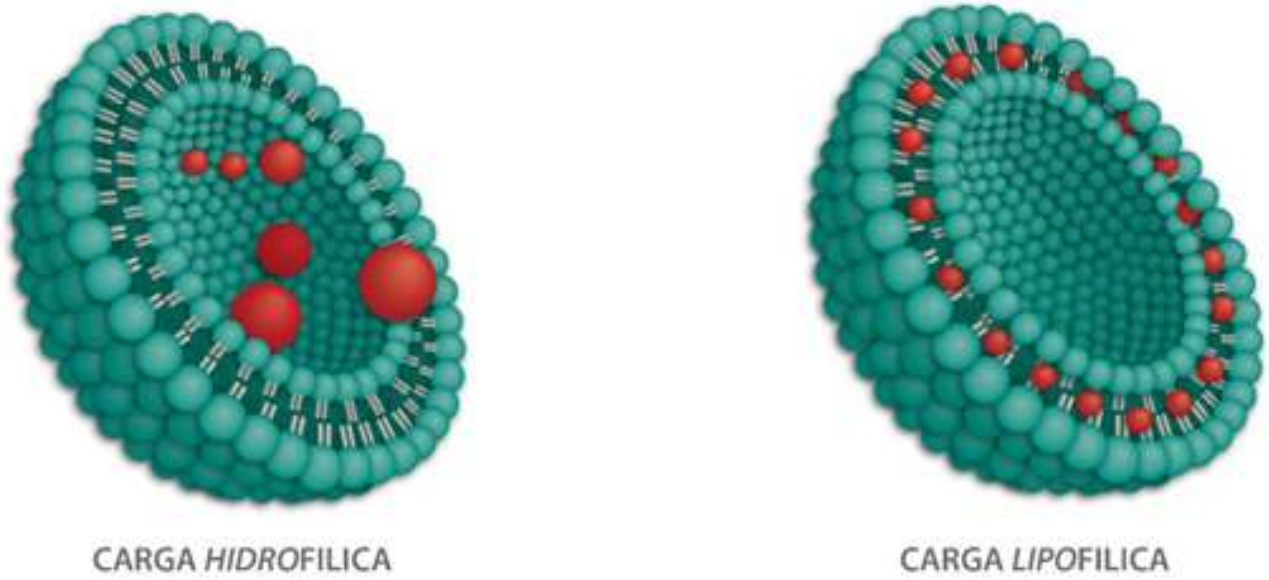
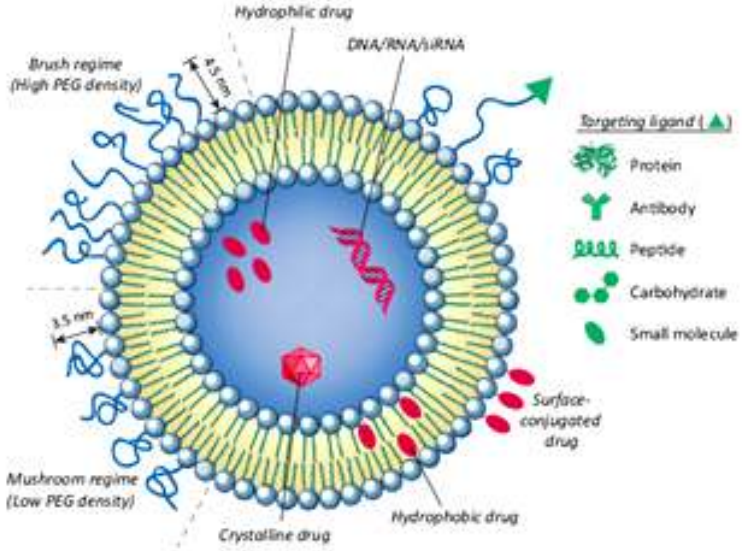


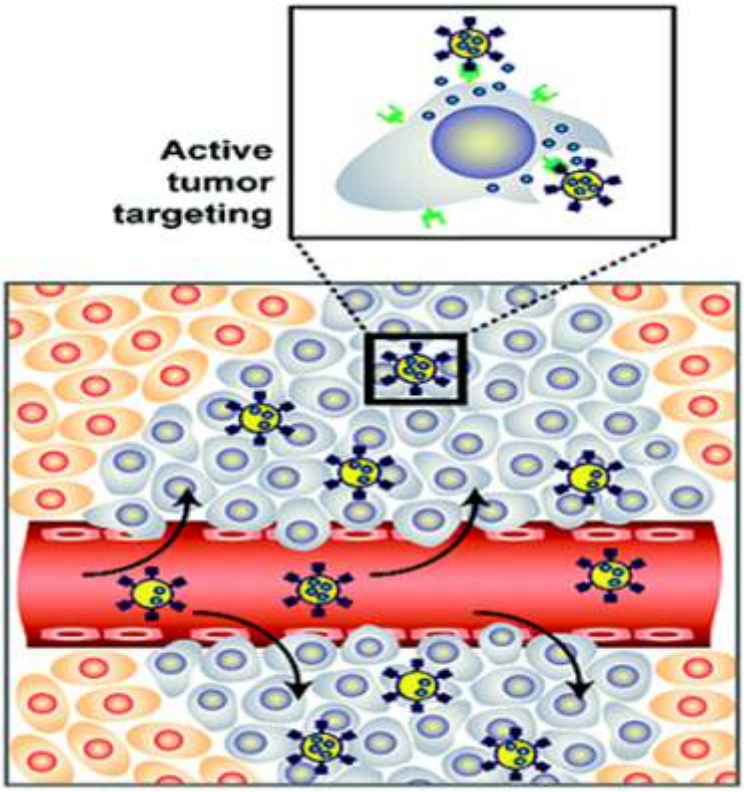
[Source-http://www.lipomize.com/en/liposome] **Figure6**

Liposome molecules are easily diffused into the cells, since their structures and cell membrane structure can interact very well while drug uptake process. The enhanced permeation and retention (EPR) effect is the concept that liposomes remain in the bloodstream for a long time and are collected passively from tumor cell. Through the EPR effect, concomitant in toxicity problem of therapy is relatively solved as lower and repeated dose of liposome drug. The uses of EPR effect allow up to 10 times the amount of drug to be delivered to the tumor than the free drug method.[31] The characterization of liposome molecule is give in fig.7



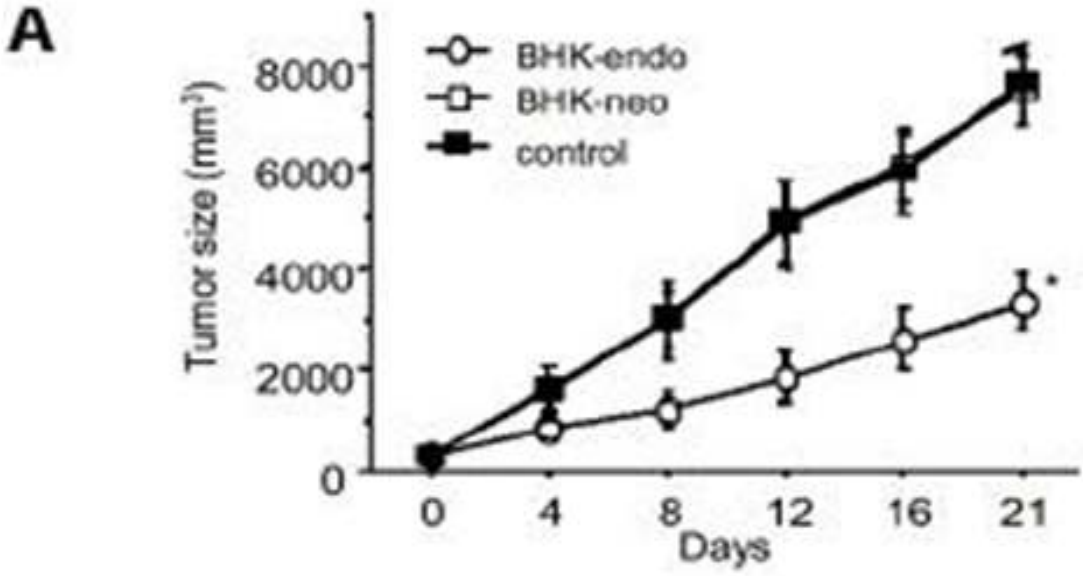
Source- liposomes as as potential drug carrier system Intech-760*456-search by image]

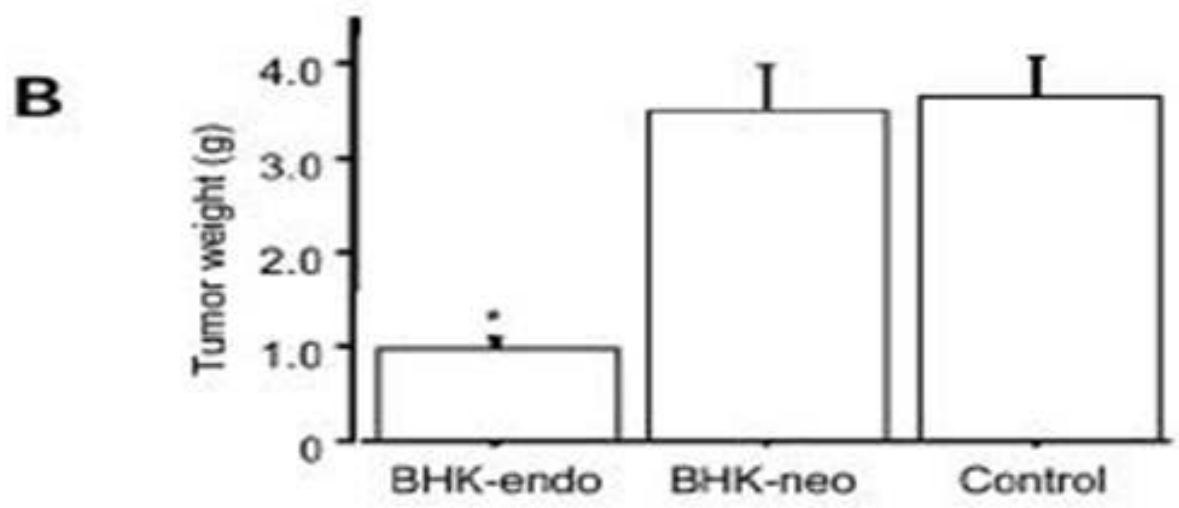
In the below figure no 8, we are addressing the process of working of nanoparticle drug delivery to target the tumor and the way how can remove the tumor and controlled the abnormal cell.



[Source-http://pubs.acs.org/doi/abs/10.1021/nn900002m]

Figure 8





CONCLUSION

Buy reviewing of this article, it is clear that "nanotechnology is the key word of human life." Every field is affected by the nanotechnology. Nanotechnology changes the definition of many object and has already revolutionized cancer therapy in many aspects and is radically changing the treatment pattern. Nanotechnology gives a better result in the treatment of cancer.Nowadays the treatment of cancer is very easily available in comparison to past time. The treatment of cancer by traditional method is very harmful for patient, but by nano and micro drug delivery in therapy, it is harmless. There are more advantages in the treatment of cancer. The present paper reviews the use of micro and nanotechnology as well as macromolecular conjugation as strategies to deliver existing chemotherapies and novel therapeutic molecules in a controlled manner to malignancies. These technologies come along with other exciting drug delivery approaches such as patches, microchips and osmotic pumps. In general, the technologies described here improve significantly the pharmacokinetics and bio-distribution of the free drugs and reduce considerably their side-effects.

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