Asian Journal of Pharmaceutical Technology and Innovation

Received on: 07-09-2013
Accepted on: 10-09-2013
Published on: 15-09-2013

Corresponding Author:

Suhas H. Lahane

M.pharm,
Department of Pharmaceutics,
MET's Institute Of Pharmacy,
Bhujbal Knowledge City,
Adgaon,
Nasik-422003
Mob no. +91-8983809997

*Email Id-
suhaschandralahane@gmail.com

Nanotechnology and Overview on Nanoparticle Drug Delivery: An Evolutionary Step toward Curing Cancer

Suhas H. Lahane

ABSTRACT

The scenario present in this article is to focus on areas of research in caner and its therapy. An outline is explained here related to cancer and its therapeutics. It is possible to design and construct targeted with least side effects system by application of nanotechnology. At Nano scale, novel properties are present with nanoparticle making them magic bullets to kill various diseases. Here it is explored that nanoparticles have so much potential to be used as carriers, selective, targeted system. In the recent years, due to lots of changes and advancement in technique, facility etc. scope for dosage form design has been widened.

Key-words:

Nanoparticle, Cancer, Nanotechnology, Tumor, Targeting

1. Introduction:

Nanotechnology is an emerging trend for creation of small scale nanostructure device that can be useful for diagnostic, therapeutic purpose. It refers to the interactions of cellular and molecular components and engineered materials-usually, bunches of atoms, molecules, and also molecular fragments into incredibly small particles—between one and 1000 nm. These incredibly small things have novel optical, structural and electronic properties that are not present usually at large scale[1,2].

One of the giants in science – Paul Ehrlich called this nanoparticle delivery system that would be used in this type of therapy "Zauberkugeln" – English "Magic Bullets"[3].

Mutation and alteration in gene's function would be consequences in to unrestricted growth of cell. Cancer is characterized by unlimited growth cell, basically classified into two types,

Hematologic: these are blood borne. e.g. Leukemia

Solid tumors: here solid palpable mass is observed. e.g. Breast cancer[4].

Current cancer therapy usually involves intrusive processes including application of catheters to allow chemotherapy, preliminary chemotherapy to reduce any existing cancer, surgery to then eradicate the tumors if possible, followed by more chemotherapy and radiation[5]. Most current anticancer agents do not greatly differentiate between cancerous and normal cells, resulting into systemic toxicity and adverse effects. This significantly restricts the maximum allowable dose of the drug[1,2]. Current research areas are providing development of carriers for the purpose of using alternative dosing routes, new therapeutic bull's eye such as blood vessels fueling tumor growth and targeted therapeutics that are more specific in their activity. Such nano scale particle, device, structure provide advantage of Targeted therapeutics and curing cancer with less side effects. Several research have done on novel nanodevices which are capable of detecting cancer at its premalignant stage, pinpointing cancerous tissue within the body while acting as vehicle to deliver antineoplastic drugs to the cancer cells. New agent and new ways are coming to move us away from cancer. Here this review primarily focuses on mechanism of nanoparticle and biologically utility of nanoparticle in cancer therapeutics. Before approaching toward therapy, it is important to understand basic of cancer, tumor and its characteristics.

1.1 Tumor Physiology

Tumor biology plays an important role in drug delivery. The impact on the ability of nanoparticle carriers is due to growth, structure and physiology of tumor. Development of more advances, effective and efficient providing fewer side effects can be done by understanding the beneficial aspect of tumor physiology.

1.2 Tumor Growth

A single cell leads to growth of tumor through mechanism of mutation. This results into uncontrollable proliferation of cell. Basically mutation is the cause that blocks its apoptotic signaling pathway[5]. As a single cancer

cell replicate at higher rate than other cell, it places lot of strain on nutrient supply and elimination of metabolic waste. Tumor cells will continue dividing until diffusion limited maximal size is reached as shown in Figure no.1[6].

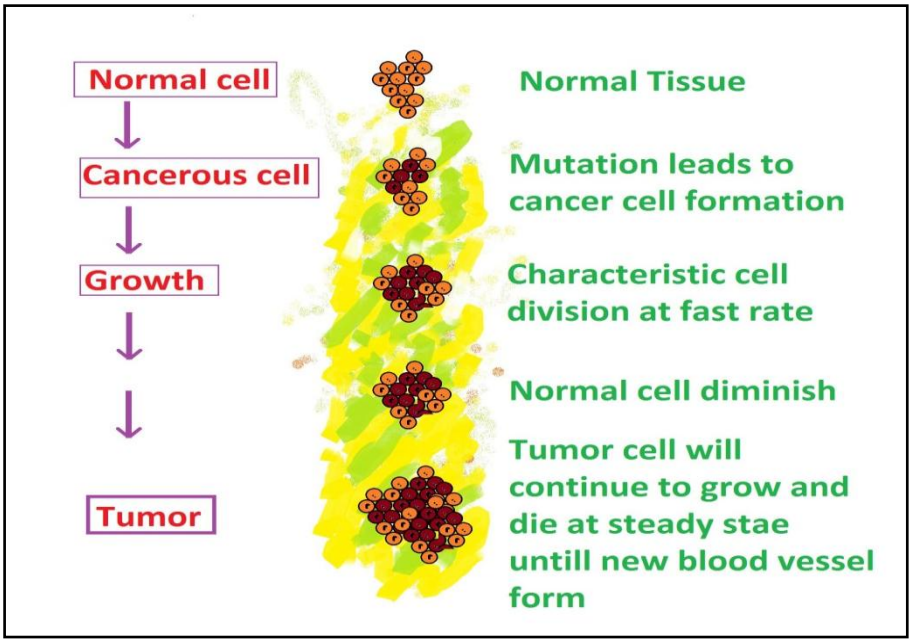

Figure.1: Tumor growth

It means at initial stage of tumor growth the cell depend mainly on diffusion working as main nutrient supply mechanism. A steady state of tumor is formed where rate of replication is equal to death rate; this diffusion limited maximal size of tumor is around two mm cub[7].

1.3 Angiogenesis

The growth of solid tumors is reliant upon the ability to generate an adequate blood supply.

A way to achieve tumor growth by overcoming the problem of diffusion limited maximal size limitation is to create new blood vessels to provide the nutrients necessary to fuel its continued expansion and whole process known as Angiogenesis[6]. Once a tumor mass is able to initiate angiogenesis, the blood vessels continue to rapidly grow producing an unorganized and aberrant vasculature. Angiogenesis is characterized by the invasion, migration and also proliferation of smooth muscle and endothelial cells, which degrade the basement membrane and form a new lumen structure.

Angiogenesis appears to be one of the most crucial steps in tumor translation to metastatic form, capable of spreading to other parts of the body[9].

1.4 Tumor vasculatures

An unorganized and aberrant vasculature is present in tumor. In the development process of tumor some part get adequate blood and nutrient supply while some not giving rise to extensive and poor vasculature[5]. Hence heterogeneous blood flow is present in tumor. The capillary endothelium in malignant tissue is more disorderly and thus more permeable towards macromolecules than the capillary endothelium in normal tissues. Tumor vessels are also inherently leaky due to abnormal basement membranes[1,9]. Also reduction in ability to drain fluid and waste from surrounding interstitial space is present in case of tumor[6]. Quickly proliferating tumor cells result into poorly defined lymphatic system further result into reduction in drainage[9].

As there is irregular vasculature with lack of nerve enervation and smooth muscle it leads to variable blood flow which becomes barrier to systemic drug delivery. It has been shown that there is no effect of drug where poor blood flow is present[5]. All the above information related to cancer and tumor is taken to decide which way should be followed for drug delivery, subsequent information given below, provides different drug delivery approaches for treatment of cancer.

2 Drug delivery to Tumor

Current chemotherapy has lot of limitation due to poor blood circulation in tumor. These agents disrupt the normal functioning of cell by inhibiting replication or inducing apoptosis. Also there are lot of barrier that do not allow delivery of drug to tumor like RES, first pass renal filtering, heterogeneous blood flow as described above, high tumor interstitial pressure, extracellular matrix and intracellular transport[5].Selective drug delivery is an important approach with great potential for overcoming problems associated with the systemic toxicity and poor bioavailability of antineoplastic drugs. Nano medicine not only delivers antineoplastic agent to tumor in a targeted manner but also provide advantage of reduction in systemic toxicity of anticancer drug[10]. There are a variety of nanoparticle systems currently being explored for cancer therapeutics. The material properties of each nanoparticle system have been developed to enhance delivery to the tumor. The types of nanoparticles currently used in research for cancer therapeutic applications include dendrimers, liposomes, polymeric nanoparticles[8], micelles, protein nanoparticles , ceramic nanoparticles, viral nanoparticles , metallic nanoparticles, and carbon nanotubes[9]. Alternative approach has been provided by these nanomedicine. A promising active targeting carrier for tumor is through an approach of nanoparticle.

Nanoparticles also provide technique that can be used for detection, imaging of tumor cell, tumor and metastasis. Hence nanoparticle will play a major role in cancer therapeutics[11]. These will afford improved ability to identify site of cancer with improved drug delivery to tumor by overcoming barrier found in delivery of antineoplastic drug with low side effect and cellular toxicity.

2.1 Targeted delivery

2.2 Approach of bypassing RES/MPS

Reticuloendothelial system (RES) present in body which is clearance system of body that identify foreign body in blood circulation. The reticuloendothelial system (RES) also known as the mononuclear phagocytic system (MPS) are a group of organs and circulating macrophages whose primary function is to rid the body of foreign objects, such as bacteria. RES lower blood circulating time of foreign body hence of nanoparticle. By the process of opsinisation RES recognized foreign particle where opsonins, a class of protein coat foreign body so the macrophage engulf the particle by phagocytosis, ''cell-eating'' process[7].

Particles with longer circulation times, and hence greater ability to target to the site of interest, should be 100 nm or less in diameter and have a hydrophilic surface in order to reduce clearance by macrophages. e.g. Steric stabilized (stealth) nanoparticles etc[12].

2.3 Approach through enhanced permeability and retention

EPR effect is provided by defective vasculature architecture of tumor. Enhanced Permeation and retention effect (EPR effect) is due to leaky vasculature combine with poor lymphatic drainage. Such characteristic help to target tumors. Actually when large molecule leak out from the porous and leaking blood vessels during targeting either by actively or passively and enter to tumor interstitium leading to process known as extravasation. There is no possible way to return to circulation for these molecules. Obviously cause is large molecular size whereas smaller size molecules can return to circulation leading to known phenomenon 'EPR"[4].

2.4 Targeting through angiogenesis

As described before this process is vital for tumor and hence increasing amounts of research are focused on developing treatments to slow angiogenesis and limit tumor growth and dissemination. Some examples of therapeutic strategies include limiting endothelial proliferation and motility, increased expression of angiogenesis inhibitors and use of molecules such as soluble VEGF receptor to try and decrease the amount of angiogenesis stimulatory factors at the tumor site[6].

2.5 Tumor-specific targeting

Tumor-activated prodrug therapy uses the approach that a drug conjugated to a tumor-specific molecule will remain inactive until it reaches the tumor. The development of monoclonal antibodies and utilization of their targeting properties can be used for active targeting[13].

2.6 Passive targeting

Passive targeting is dependent on size shape, surface characteristics of tumor cell, tumor. As stated previously, a particle must be at least ten nm in diameter to avoid clearance by first pass renal filtration. Passive targeting results in insufficient drug concentrations at the tumor site and, consequently, little therapeutic efficacy[5].

3 Nanoparticle-An emerging trend for curing cancer.

Nanoparticles are colloidal carriers with dimensions on the nano scale.

Why nano-

A little thing always has importance as by creating smaller structure a big achievement can be obtained. When we are dealing with small creators like cellular and molecular components and engineered materials-typically, bunches of atoms, molecules, and molecular fragments have incredibly small size between one and 1000 nm, definitely we should have some material of same size so it could fit there and work there. Nano size gives high surface area to volume ratio, pharmacokinetic properties, quantum effects which are beneficial without changing active compound. Obviously as size decreased, surface area increased. There are some properties like reactivity, electrical and in-vivo properties that have different behavior at nano level[14].

As given in Table no.1, various biochemical molecules size and found that all are having comparable size with nanoparticle reinforcing interest in nanoparticle.

Hence drug delivery is focused toward biochemistry[15]. So there is so much interest have been increased at nanoscale manipulation or engineering of drug delivery system.

TABLE 1: TYPICAL SIZE OF VARIOUS BIOCHEMICAL MOLECULES

OBJECT	SIZE (nm)
Carbon atom	0.1
DNA	3
Ribosome	10
Red blood cell	5000

Nanoparticle has lot of advantages like

- Large surface-to-volume ratio resulting boosted interaction sites
- Surface functionalization for directing
- Suitable encapsulation
- Release drugs in controlled manner
- More efficient uptake by cells

Conventional or micro scale carriers may do not have unique properties like nanoparticle or nanoparticulate drug delivery system[16].

3.1 Synthesis of nanoparticle

There are so many techniques such as milling and homogenization techniques, spray drying, ultra sonication, polymerization etc. by which we can synthesis nanoparticle. But the basic principles behind all these technique are two as given below: (shown in Figure no.2)

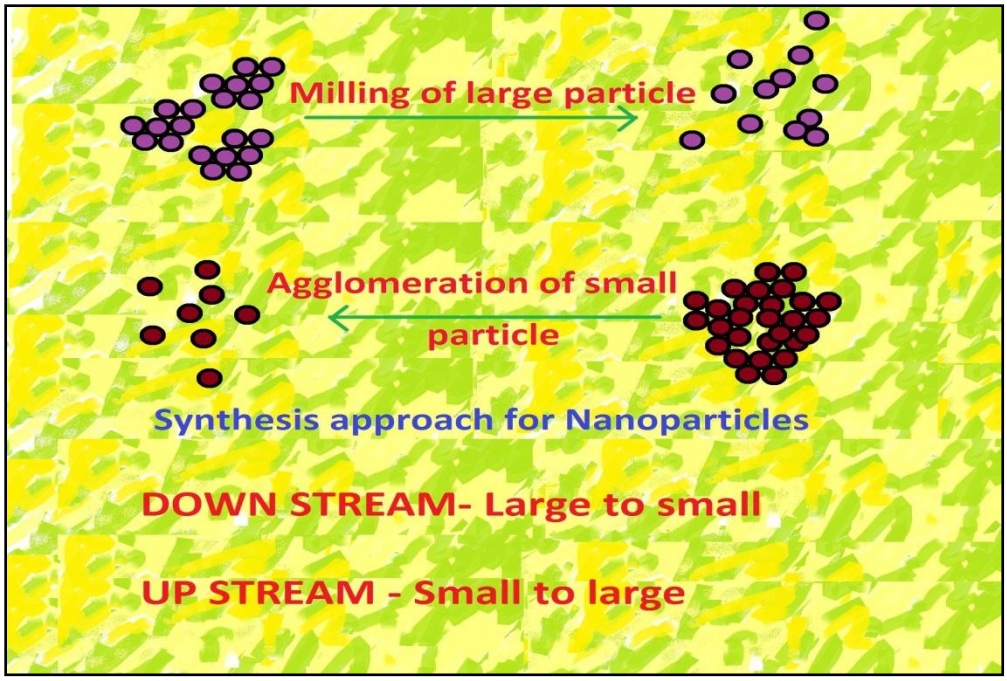

Figure.2: Processes for nanoparticle preparation

3.1.1 Breaking down process

Here, the drug and excipients are subjected to stress resulting into breaking of it into smaller size tending toward nano scale. A lot of energy is required to go down further for nano size[13].

e.g. High shear milling, High pressure homogenization

3.1.2 Building *up process*

Here initially nuclei formation takes place which further subjected to grow in size through agglomeration and coagulation[15].

e.g. supercritical fluid process, Emulsification-diffusion process.

3.2 Various types of nanoparticle for cancer

3.2.1 Passively targeted liposome

These are the lipid bilayer vesicular system enclosing an aqueous phase. Here drug is either entrapped in the lipid bilayer part or encapsulated in aqueous region. To avoid clearance it is coated with poly ethylene glyco[17].

e.g. Stealth liposome.

3.2.2 Actively targeted liposomes

By coupling with targeted moieties to surface of liposome, active targeting by liposome is done. Selectively these liposomes go to the tumor[17].

e.g. Folate targeted liposomes.

3.2.3 Polymeric micelle

Here the self-assembly of amphiphilic block copolymers forms polymeric Micelles. Hydrophobic core and a hydrophilic surface are present to in it. Fundamental properties of micelle like thermodynamic stability, hydrophilic surface and small size make them ideal system for drug delivery and it remains more time in circulation as becomes unrecognized by RES[17].

e.g. Dox loaded micelle.

3.2.4 Polymeric Nanoparticle

These are nano level aggregates of biocompatible or biodegradable polymers[17].

e.g. Transferrin targeted PEG coated polycyanoacrylate nanoparticle for delivery of drug 'Palclitaxel'.

3.2.5 Biological ghost delivery system

In this system, natural particles from endogenous cells, bacteria, or viruses are used as ghost by removing membrane vesicles by removing its contents. These are potential carriers as they are biocompatible, biodegradable and non-immunogenic[17].

e.g. Folate targeted erythrocyte ghost.

3.2.6 Lipid based nanoparticle

These particles contain lipids, well known as solid lipid nanoparticles. General constituents of SLNs are surfactant, glyceride mixture, waxes etc[17].

3.3 Surface engineering of nanoparticle

There is need to reach at nano size and manipulate at that level by applying various approach for designing its surface, to modify its properties. Nanoengineering of drug delivery system is becoming a new important aspect for disease therapy. Due to nanoengineering various benefits are obtained like enhanced duration of time interval with increased efficacy, patient compliance is increased, toxicity is minimized, less cost etc[16].

3.4 Modification by polymer

Drug carrier is modified through engineering of drug delivery system so that it contains one or more polymer that results into drug release controlled system. Biodegradable polymers are used to have controlled over drug release. An example of such system is poly (D,L-lactide-co-glycolide) i.e. PLGA. It act by mechanism of erosion by hydrolysis. A triggered release system is developed by using various combinations or blending of polymers[16].

3.4.1.1 Lipid based modification

At nanoscale lipid based material has unique properties such fluidity of lipid domain that provides mechanism for controlling water influx. Spray dried lipid coat over nanoparticle gives sustained effect to drug release from nanoparticle. Altering phase transition in case of lipid chain is also important application in triggered release system of nanoparticle[16].

3.4.1.2 Other strategies

Nanonizition is another one, it itself provide increased surface area resulting in enhancement of dissolution, solubility. Modifying nanoparticle with electrostatic and steric stabilizing agent is used to provide stability for such systems in storage. Passive targeting thorough application of poly ethylene glycol i.e. long circulated PEGylated nanoparticle well known as stealth liposomes are example of passive targeting strategy. The bioconjugation of ligands to nanocarrier surface is example for active targeting. Ligands used are antibodies, proteins, or peptides[16].

Biomimetic nanoparticle is the one in which biomimetic ligands such as albumin is used. Sialic acid also serves the same purpose. Nanoparticles are incorporated with magnetite so that they are magnetically guided to tumor. Tomato pea lectin, asparagus pea lectins becomes adhesive in bioadhesive nanoparticle and serves as ligands for targeting.

4 Nanoparticles application in cancer

Presently there are varieties of nanoparticle systems having ability to be used in cancer therapy. Research is on progress to develop material properties so that they are enhanced and diverted toward tumor. A simple example to explain all this is stealth nanoparticle. In this surface properties are modified to hydrophilic characteristics so nanoparticles spend longer circulation time. Also it is found that if surface properties are changed to positively

charged surface, endocytosis of nanoparticles are enhanced. There are various types of nanoparticle are present that have wide application in research and cancer therapeutics such as liposomes, dendrimers, polymeric nanoparticles, metallic nanoparticle, micelles, protein nanoparticle, ceramic nanoparticle etc. Carbon nanotubes are also developed. Although large variety of nanoparticles are developed for curing cancer, only few number of nanoparticle are approved for therapy of cancer by U.S. Federal Drug Administration and European Medicines Agency[9].

4.1 Nanoparticles as carriers

Nanoparticles have the power of addressing and resolving some of the most noteworthy boundaries of old-style chemotherapy such as, its absence of specificity and narrow window of therapeutic efficacy. Their small size, diverse composition, surface functionalization, and stability made them attractive for cancer treatment. Enhanced cytotoxic effect obtained as there is increased nano size particle transport to the intracellular organelles. Polyalkylcynocrylate nanoparticles are ultrafine, degradable that are able to associate with drugs. Nanoparticls shows new area for treatment with controlled release of drug[18].

4.2 Diagnostic work by nanoparticles

For investigating that cancerous tumor is present or not, simply a basic principle is considered i.e. common similarity, features etc. Hence scientist found out some common features in tumor physiology. Common characteristics that differ from normal cell, tissue etc. is the way by which they show rapid growth. As for further growth blood supply is necessary as stated earlier, hence in characteristic way disorganized blood vessels development takes place and this is another common characteristics. Nacrosis, hypoxia may be having importance. These characteristics might be form basis of selective therapy of cancer. Also inefficient supply of blood to tumor tissues has vital implication in therapy. Nacrosis, hypoxia may be having importance.

4.2.1 Imaging of cancer

It is very important to ensure that drug delivery is specific and selective. Same techniques which are used for targeting cancerous cell can be applied for imaging. Radionucliotide like Tc99 are being used for imaging of cancer. In a liposome having size ~100 nm encapsulate radionucleotide, accumulate in cancerous part and imaging is done. Early stage detection of cancer is very necessary. This would help to prevent advanced cancer by treating it in primary stage and as early as possible.

4.2.2 Tracer uptake study

It is done to measure tumor blood flow. There are many methods are present which are based on quantifying the tumor uptake. Tracer is administered systemically and tracers are quantified. Also rate of clearance of tumor is another strategy[19].

e.g. Rb86, Xe133 are widely used tracers for washout study.

4.2.3 Tumor targeting by Nanoparticles

A system which has pharmaceutical and therapeutical use and also capability of escaping phagocytic clearance becomes beneficial for tumor targeting. Nanoparticles have advantage of extravasation phenomenon. Also biological engineering is done on nanoparticles which reinforce its targeting ability. For anchoring nanoparticle to tumor, specific ligands are added by employing engineering that tangle to specific cells within tumor[20].

4.3 Delivery of few anticancer agents

4.3.1.1 Paclitaxel

It has anticancer activity. This antineoplastic agent has activity in breast, colon, primary epithelial ovarian carcinoma and lung cancer. The mechanism behind its activity is that it disrupts the dynamics needed for cell division. Specifically it is observed that it enhance polymerisation of tubulinin resulting into cell death[6].

4.3.1.2 5-Fluorouacil

Dendrimers of poly (amidoamine) modified with mPEG-500 is used for inclusion of 5-Fluorouracil[6].

4.3.1.3 Doxorubicin

Well known and potent, also widely used anticancer agent is doxorubicin. Its mechanism is to inhibit or stop synthesis of nucleic acids in cancerous cell. It has very narrow therapeutic index due to its number of not required side effects. Several research have been done to diminish side effects of it such as cardiotoxicity and myelosupression[6].A potential carrier system for doxorubicine have been used in breast cancer. These dedronized heparin-Dox conjugate based nanoparticle systems have advantage of high antitumor activity with low side effects. Very less toxicity was noted in healthy tissues in experiment with mice bearing tumor and normal mice[21].

e.g. Doxorubicin encapsulated in chitosan nanoparticles, doxorubicin conjugated with PLGA nanoparticle, Heparin Dox conjugated nanoparticle etc.

4.3.1.4 Antineoplastic agents

Anticancer agents such as camptothecin based drugs like camptosar and topotecan, 5-fluorouracil, doxorubicin, paclitaxel etc. single and in combinations are used in cancer therapy. These drugs are incorporated in nanoparticles having size range 100 nm to 900 nm and are being used in therapy[9].

4.4 Specific organs cancer targeting

Selectively and successfully to target and transport nanoparticle to organs or tissue is great challenge. Targeting agent or ligands having capability to weld with surface of nanoparticle drug delivery system, helps a lot for this specificity.

4.4.1 Breast cancer

Two antibodies (f5 and C1) are identified to the breast tumor cell line SK-BR-3. This is bind to growth factor that is common inhuman breast carcinoma (20-30%). Doxorubicin is encapsulated in liposome[9].

4.4.2 Folate receptors

In normal cell receptor for folic acid in cell surface are not accessible. Exactly opposite is the case in cancer cell surface where it is exposed. This feature provide possible target for cancer therapy in various types of cancer. Folic acid derived antibodies are used for targeting cancerous cell[9].

4.4.3 Liver carcinoma

We can rely on Asialoglycoproteinreceptor for liver targeting[9].

5 Theranostic agent on framework of nanoparticle

The term is combination of therapeutic and diagnostic function, hence 'Theranostic'. In this in a single agent is working for both functions. The nanotechnology has reinforced power for diagnosis and therapy more than past. Nanoparticle based theranostic agents are framework which is modified to carry out both functions. This agent provides advantage of imaging not only before and after but also at intermediate stage. Zhang group has welded methotrexate, an anti-cancer agent on surface of iron oxide nanoparticle. In another example, acrylates polymeric nanoparticle along with prostate specific membrane antigen targeting antibody is used to target tumor area into prostate cancer bearing mice. Quantum dot aptamer-DOX conjugate is used for cancer imaging, therapy and for its monitoring. Gold nanoparticle, silica nanoparticle and carbon nanotubes have potential used for theranostic purpose[22,23].

6 Conclusions

Evidences reinforcing a belief that we are travelling towards aim of achieving specific and targeted anticancer agents system delivery. Superior diagnosis and treatment can be provided with help of nanoparticle drug delivery. Undoubtedly nanoparticle and nanotechnology is becoming a superior system for curing cancer. Hopefully a successful with diminish side effects therapy would be there in next era for cancer.

7 References:

1. Sinha R, Kim G, Nie S, Shin D. Nanotechnology in cancer therapeutics: bioconjugated nanoparticles for drug delivery. *Mol Cancer Ther*2006; 1909-17. [Online August 23, 2006.]
2. Baker N, Pappu R, Thomas D. Nanoparticle ontology for cancer nanotechnology research.*J of Biomed Info* 2011;44:59–74.
3. JorgKreuter. Nanoparticles-a historical perspective. *Int J Pharm*2007; 331:1–10.
4. Bapat V, Bhagvatkar H. Novel methods of drug delivery to solid tumors. In: Jain N K, ed. *Progress in controlled and novel drug delivery system,* CBS publishers;2004:1,5,6.
5. Peppas N, Moore M, Steichen S. A review of current nanoparticle and targeting moieties for the delivery of cancer therapeutics. *Eur J Pharm Sci*2012; www.ScienceDirect.com.
6. Peppas L, Blanchette J. Nanoparticle and targeted systems for cancer therapy, *Adv Drug Deliv Rev* 2010; 64: 206–12.
7. Jones A, Harris A. New developments in angiogenesis: a major mechanism for tumor growth and target for therapy, *Cancer J Sci Am* 1998;4: 209–17.
8. Saltzman W, Patel T,Piepmeuer J, Zhou J. Polymeric nanoparticles for drug delivery to the central nervous system, *Adv Drug Deliv Rev*2012 ;www.ScienceDirect.com.
9. Peppas L, Tania B, Byrne J. Active targeting schemes for nanoparticle systems in cancer therapeutics. *Adv Drug Deliv Rev* 2008;60:1615–26.
10. Acharya S, Dilnawaz F, Sahoo S. Targeted epidermal growth factor receptor nanoparticle bioconjugates for breast cancer therapy. *Biomaterials* 2009;30:5737–50.
11. McDougal S, Singh M, Feldman A. The potential of nanoparticle-enhanced imaging. Urologic Oncology: Seminars and Original Investigations 2008; 26: 65–73.
12. Jain R K. Transport of molecules, particles and cells in solid tumors. *Ann Rev Biomed Eng*1999; 1:241–63.
13. Lobenberz R, Roa W, Azarmi S. Targeted delivery of nanoparticles for the treatment of lung diseases. *Adv Drug Deliv Rev* 2008; 60:863–75.
14. Thasssu D, Pathak Y, Deleers M. Nanoparticulate Drug-Delivery system: An overview. In: Thassu et al.,ed. *Nanoparticulate Drug Delivery system*. Informa Publication; 2007:1-24.
15. Gupta R. B. Fundamentals of nanoparticles. in: Gupta et al., editor. *Nanoparticle Technology for Drug Delivery*, Taylor & Francis Group;2006:1-12.
16. Jaygapal A, Shastri V. Nanoengineering of drug delivery system. in: Thassu et al., ed. *Nanoparticulate Drug Delivery System* . Informa Publication;2007:99-107.
17. Li Y, Lee C. Drug delivery: Tumor Targeted system. in: Swarbrick et al. ed. *Encyclopedia of pharmacy*, Informa healthcare, Newyork 2006:1332-36.
18. Singh U V, Shenoy B, Udupa N. Novel carriers in cancer chemotherapy. in: Jain N K, Ed. ,*Advances in controlled and novel drug delivery*,CBS;2001:51.
19. Ching L, Wilson W, Baguley B. Inhibition of tumor blood flow. Methods in molecular medicine. in: Francis G.E. et al., ed. Vol.25: *Drug targeting: Strategies, Principles and Application*, Human press Inc.; 2000:133,134,142-5.
20. PaciottiG, Tamarkin L. Biological and engineering considerations for Developing Tumor-Targeting Metallic Nanoparticle Drug-Delivery Systems. in: Thassu et al., editor. *Nanoparticulate Drug Delivery system* .Informa Publication; 2007:1-24.
21. Luo K, Gu Z, She W, Li N et al. Dendronized heparin-doxorubicin conjugate based nanoparticle as pH-responsive drug delivery system for cancer therapy. *Biomaterials;* 2012:1-13.
22. Xie J, Lee S, Chen X. Nanoparticle-based theranostic agents. *Adv Drug Deliv Rev* 2010; 62:1064–79.
23. Mackay A, Janib S, Moses A. Imaging and drug deliver using thernostic nanoparticles. *Adv Drug Deliv Rev* 2010; 62:1052–63.