

Journal of Pharma Research

Review Article ISSN: 2319-5622

Available online through www.jprinfo.com

TARGETING OF ANTI CANCER DRUGS THROUGH NANOPARTICLES

Venkatesh Murukutla^{*}, Pusuluri Dharani Lakshmi Sai

Department of Pharmaceutics, SIMS College of Pharmacy, SIMS Group of Institutions, Mangaldas Nagar, Guntur,-522001, Andhra Pradesh, INDIA.

Received on: 19-04-2016; Revised and Accepted on: 02-06-2016

ABSTRACT

Prior studies suggested that nanoparticle drug delivery might improve the therapeutic response to anticancer drugs and allow the simultaneous monitoring of drug uptake by tumours. Cancer nanotherapeutics are rapidly progressing and are being implemented to solve several limitations of conventional drug delivery systems such as nonspecific bio distribution and targeting, lack of water solubility, poor oral bioavailability, and low therapeutic indices. To improve the biodistribution of cancer drugs, Nanoparticles have been designed for optimal size and surface characteristics to increase their circulation time in the bloodstream. They are also able to carry their loaded active drugs to cancer cells by selectively using the unique pathophysiology of tumers, such as their enhanced permeability and retention effect and the tumor microenvironment. In addition to this passive targeting mechanism, active targeting strategies using ligands or antibodies directed against selected tumor targets amplify the specificity of these therapeutic Nanoparticles. Drug resistance, another obstacle that impedes the efficacy of both molecularly targeted and conventional chemotherapeutic agents, might also be overcome, or at least reduced, using Nanoparticles. Nanoparticles have the ability to accumulate in cells without being recognized by P-glycoprotein, one of the main mediators of multidrug resistance, resulting in the increased intracellular concentration of drugs.multifunctional and multiplex Nanoparticles are now being actively investigated and are on the horizon as the next generation of Nanoparticles, facilitating personalized and tailored cancer treatment. Targeting methotrexate increased its antitumor activity and markedly decreased its toxicity, allowing therapeutic responses not possible with a free drug.

Key Words: Nanoparticles, drug delivery, targeting, drug release.

INTRODUCTION

 ${f N}$ anoparticles are defined as particulate dispersions or solid particles with a size in therange of 10-1000nm. The drug is dissolved, entrapped, encapsulated or attached to ananoparticle matrix. Depending upon the methodof preparation, nanoparticles, nanospheres or nanocapsules can be obtained. Nanocapsules are systems in which the drug is confined to acavity surrounded by a unique polymer membrane, while nanospheres are matrix systems in which the drug is physically and uniformly dispersed. In recent years, biodegradable polymeric nanoparticles, particularly those coated with hydrophilic polymer such as poly ethylene glycol (PEG) known as long-circulating particles, have been used as potential drug delivery devices because of their ability to circulate for a prolonged period time target a particular organ, as carriers of DNA in gene therapy, and their ability to deliver proteins, peptides and genes. The major goals in designing nanoparticles as a delivery system are to control particle size, surface properties and release of pharmacologically active agents in order toachieve the site-specific action of the drug at the therapeutically optimal rate and dose regimen. Though liposomes have been used as potential carriers with unique advantages includeing protecting drugs from degradation, targeting to site of action and reduction toxicity or side effects, their applications are limited due to inherent problems such as low encapsulation efficiency, rapid leakage of water-soluble drug in the presence of blood components and poor storage stability. On the other hand, polymeric nanoparticles offer some specific advantages over liposomes. For instance, they help toincrease the stability of drugs/proteins and possess useful controlled release properties.

*Corresponding author:

Venkatesh Murukutla Department of Pharmaceutics, SIMS College of Pharmacy, SIMS Group of Institutions, Mangaldas Nagar, Guntur,-522001, Andhra Pradesh, INDIA. *E-Mail: brahmaiahmph@gmail.com The advantages of using nanoparticles as a drug include the following:

- 1. Particle size and surface characteristics of nanoparticles can be easily manipulated to Achieve both passive and active drug targeting after parenteral administration.
- 2. They control and sustain release of the drugduring the transportation and at the site of localization, altering organ distribution of thedrug and subsequent clearance of the drug soas to achieve increase in drug therapeutic efficacy and reduction in side effects.
- 3. Site-specific targeting can be achieved by attaching targeting ligands to surface of particlesor use of magnetic guidance.
- 4. The system can be used for various routes of administration including oral, nasal, parenteral, intra-ocular etc.

Cancer:

Development of abnormal cells that divide uncontrollably which have the ability to infiltrate and destroy normal body tissue.

Cancer arises as a result of series of genetic and epigenetic changes

- Inactivation of tumor suppressor gene
- The activation of oncogenes Cancer cells differs from normal cells
- Uncontrolled proliferation
- Ability to undergo metastasis
- High interstitial pressure at the center
- Solid tumours have a pore size of 100nm to 2um.

Preparation of Nanoparticles:

Nanoparticles have been prepared most frequency by three methods:

- 1. Dispersion of preformed polymers
- 2. Polymerization of monomers
- 3. Ionic gelation or concervation of hydrophilic polymers.

However, other methods such as supercritical fluid technology and particle replication in non-wetting templates have also been described in the literature for production of nanoparticles. The latter was claimed to have absolute control of particle size, shape and composition, which could set an example for the future mass production of nanoparticles in industry(Van vlerken*et al* 2006).

Dispersion of preformed polymers:

Dispersion of preformed polymers is a common technique used to prepare biodegradable Nanoparticles from poly lactic acid (PLA), polyglycolic acid(PLG), poly (D, L-lactide-co-glycolide) (PLGA) and polycyanoacrylate (PCA), this technique can be used in various ways as described below(Tice *et al* 1985).

Solvent evaporation method:

In this method, thepolymer is dissolved in an organic solvent suchas dichloromethane, chloroform or ethyl acetate which is also used as the solvent for dissolving the hydrophobic drug. The mixture of polymer and drug solution is then emulsified in anaqueous solution containing a surfactant or emulsifying agent to form an oil in water (o/w)emulsion. After the formation of stable emulsion, the organic solvent is evaporated either byreducing the pressure or by continuous stirring. Particle size was found to be influenced by the type and concentrations of stabilizer, homogenizer speed and polymer concentration. In order to produce small particle size, often ahigh-speed homogenization or ultrasonication may be employed.

Spontaneous emulsification or solvent diffusionmethod:

This is a modified version of solventevaporation method. In this method, the water miscible solvent along with a small amount of the water immiscible organic solvent is used as anoilphase. Due to the spontaneous diffusion of solvent saninter facial turbulence is created between the two phases leading to the formationof small particles. As the concentration of water miscible solvent increases, a decrease in thesize of particle can be achieved. Both solvent evaporation and solvent diffusion methods can be used for hydrophobic or hydrophilic drugs. In the case of hydrophilic drug, a multiple w/o/w emulsion needs to beformed with the drug dissolved in the internal aqueous phase (Nah J.W.*et al*2006).

Polymerization method:

In this method, monomers are polymerized toform nanoparticles in an aqueous solution. Drugis incorporated either by being dissolved in the polymerization medium or by adsorption onto then a noparticles after polymerization completed. The nanoparticle suspension is then purified toremove various stabilizers and surfactants employed for polymerization by ultracentrifugation and re-suspending the particles in an isotonic surfactant-free medium. This technique has been reported for making polybutyl cyanoacrylateor poly alkyl cyanoacrylatenano particles. Nanocapsule formation and their particle sizedepends on the concentration of the surfactants and stabilizers used.

Coacervation or ionic gelation method:

Much research has been focused on the preparation of nanoparticles using biodegradable.

Hydrophilic polymers such as chitosan, gelatine and sodium alginate. Calvo and co-workers developed a method for preparing hydrophilic chitosan nanoparticles by ionic gelation method. The method involves a mixture of two aqueous phases, of which one is the polymer chitosan, adi-block co-polymer ethylene oxide or propylene oxide (PEO-PPO) and the other is a polyanion sodium tripolyphosphate. In this method, positively charged amino group of chitosaninteracts with negative charged tripolyphosphate to form coacervates with a size in the range of nanometre. Coacervates are formed as a resultof electrostatic interaction between two aqueousphases, whereas, ionic gelation involves the material undergoing transition from liquid to gel due to ionic interaction conditions at room temperature.

Active Targeting:

• Conjugating the nanoparticle to the targeted organ, tumor or individual cells for Preferential accumulation. Active tumor targeting of nanoparticles involves attaching Molecules, known collectively as ligands, to the outsides of nanoparticles. These ligands are special in that they can recognize and bind to complementary molecules, Orreceptors, found on the surface of tumor cells.

Examples for ligands

- Folate, Biotin, Thiamine, Transferin(Fenget al 2003).
- Lecithin, Antibodies, Antibody fragments.
- Galactose, Apotamase.

Passive Targeting:

The surface of the drug or polymer nanoparticle is coated with hydrophilic PEG orPLGA that reduces the hydrophobic interactions with the Reticulo Endothelial system (krang D.M.*et al* 1995).

- The drug circulates in the blood for a long time.
- E.g. paclitaxil



Fig. 1: Development of abnormal Cancer cells

Table No. 1: Different polymer-Drug conjugates using as Nanoparticles.

S.No.	Polymer-drug conjugate	Disease	Company
1.	PEG-Asparginases	Acute lymphpoblastic anemia	Enzon
2.	HPMA coplymer-Doxorubicin	Lung and breast cancer	Pfizer
3.	PEG-Paclitaxil	Clinical evaluation of solid tumours	Enzon

The nanoparticle drug delivery improve the therapeutic response to anti-cancer drugs:

1. Acetylateddendrimers were conjugated to folic acid as a targeting agent:

Eg: methatrexate,

Foliate receptor is over expressed in breast, ovary, endometrium, kidney, lung, head, neck, brain & myeloid cancers (Kommareddy*et al* 2005).

2. Twin nanoparticle shows effective at targeting, killing breast cancer cells:

Treatment of breast cancer by twin nanoparticle by binding one gold nanoparticle with an iron oxide nanoparticle.A synthetic protein anti-body was attached to the iron oxide nanoparticle act as a targeting agent, on another end cis-platin was attached to the gold nanoparticle. The attached anti-body binds to the antigen protein located on the surface of the malignant cell, the drug release occurs at the malignant cell and kills it.

Venkatesh Murukutla et al., J. Pharm. Res. 2016, 5(6), 151-154

3. Carbon Nanotubes Target Tumor Cells:

The Platinum-IV can incorporate into carbon nanotubes which has the capability to attach tumor targeting agent -Folic acid. The carbon nanotubes rapidly enter the target cell. There enzymes within the cell convert Platinum-IV to toxic Platinum-II which reacts with DNA and eventually kills the tumor cell (Hainfeld*et al* 2005).

4. Thermal cytotoxicity in malignant cells:

The SWNTs targeted to cancer cells may allow noninvasive RF field treatments to produce lethal thermal injury to the malignant cells. The RF field can be used 13.56 megahertz.

5. Remote magnetic field triggers nanoparticle drug release:

To the nanoparticle a short piece of DNA, one or more anticancer drugs were added. The nanoparticle and drugs are complimentarily attached to the DNA. At body temperature, the complimentary strands of DNA form the famous and strong double helix. When the nanoparticle becomes warm as a result of an applied oscillating magnetic field the bonds of DNA become weak and drug molecule diffuses out.

6. Enhanced cytotoxicity of monoclonal anticancer antibody:

Doxorubicin loaded long circulating liposomes were modified with the nucleosome specific monoclonal antibody 2c5(mAb 2c5) as a result higher cytotoxicity towards various cancer cells (Esenaliev*et al* 2005).

7. Magnetic nanoparticle targeting human cancer cells:

Nanoparticles are functionalized with ligands that bind with high affinity to the EphA2 receptor in the ovarian cancer.

Applications of Nanoparticulate Delivery Systems:

The rationale of using nanoparticles for tumor targeting is based on

- 1) Nanoparticles will beable to deliver a concentrate dose of drug in the vicinity of the tumor targets via the enhanced permeability and retention effect or active targeting by ligands on the surface of nanoparticles.
- 2) Nanoparticles will reduce thedrug exposure of health tissues by limiting drug distribution to target organ (Cho B.K. *et al* 1997).
 - Verdun et al demonstrated in mice treated with doxorubicin incorporated into poly (Isohexylcyanoacrylate) nanopsheres that higher concentrations of doxorubicin manifested in the liver, spleen and lungs than in mice treated with free doxorubicin
 - Studies show thepolymeric composition that of such astype, hydrophobicity nanoparticles and biodegradation profileof the polymer along with the associated drug's molecular weight, its localization in then anospheres and mode of incorporation technique, adsorption or incorporation, have agreat influence on the drug distribution pattern in vivo. The exact underlying mechanism is notfully understood but the biodistribution of nanoparticles is rapid, within 1/2 hour to 3 hours, and it likely involves MPS and endocytosis/phagocytosis process reported the biodistribution and pharmacokinetics (PK) of a cyclic RGD doxorubicin-nanoparticle formulation in tumour bearing mice. Their biodistribution studies revealed decreasing drug concentrations overtime in the heart, lung, kidney and plasma and accumulating drug concentrations in the liver, spleen and tumour. The majority injected dose appeared in the liver (56%) and only 1.6% in the tumour at 48 hrs post injection, confirming that nanoparticles have a great tendency to becaptured by liver. This indicates the greatest challenge of using nanoparticles for tumour targeting is to avoid particle uptake by mononuclear phagocytic system (MPS) in liverand spleen. Such propensity of MPS forendocytosis/ phagocytosis of Nanoparticles provides an opportunity to effectively deliver therapeutic agents to these cells. This bio-distribution can be of benefit for the chemotherapeutic treatment of MPSrich organs/tissues localized tumours like hepatocarcinoma, hepatic metastasis arising from digestive tract or gynaecological cancers, broncopulmonary tumors, primitive tumors and metastasis, small cell tumors, myeloma and leukemia. It has been proved that using doxorubicin loaded conventional Nanoparticles was effective against hepatic metastasis modelin mice. It was found there was greater reductionin the degree of metastasis than when free

drugwas used. The underlying mechanism responsible for the increased therapeutic efficacy of the formulation was transfer of doxorubicin from healthy tissue, acting as a drug reservoir to the malignant tissues

- Histological examination showed а considerable accumulation of nanoparticles in the liposomal vesicles of Kupffer cells, whereas Nanoparticles could not be clearly identified in tumoral cells. Thus Kupffer cells, after a massive uptake of nanoparticles by phagocytosis, were able toinduce the release of doxorubicin, leading to agradient of drug concentration, favourable for aprolonged diffusion of the free and still activedrug towards the neighbouring metastatic cells When conventional nanoparticles are used as carriers in chemotherapy, some cytotoxicity against the Kupffer cells can be expected, whichwould result in deficiency of Kupffer cells and naturally lead to reduced liver uptake and decreased therapeutic effect with intervals ofless than 2 weeks administration (Charlton D.E. et al 2006)
- Moreover, conventional nanoparticles can also target bone marrow (MPS tissue), which is an important but unfavourable site of action for most anticancer drugs because chemotherapy with such carriers may increase myelosuppresive effect. Therefore, the ability of conventional nanoparticles toenhance anticancer drugs efficacy is limited to targeting tumors at the level of MPSrich organs.Also, directing anticancer drug-loaded nanoparticles to other tumoral sites is not feasible if a rapid clearance of Nanoparticles occurs shortly after intravenous administration.

Long circulating Nanoparticles:

- To be successful as a drug delivery system, nanoparticles must be able to target tumour swhich are localized outside MPS-rich organs. Inthe past decade, a great deal of work has been devoted to developing so-called "stealth Nanoparticles".
- particles or PEGylated nanoparticles, which areinvisible to macrophages or phagocytes major break through in the field came when theuse of hydrophilic polymers (such as polyethylene glycol, poloxamines, poloxamers, and polysaccharides) to efficiently coat conventional nanoparticle surface produced an opposing effect to the uptake by the MPS.
- These coatings provide a dynamic "cloud" of hydrophilic and neutral chains at the particle surface which repel plasma proteins.
- As aresult, those coated nanoparticles become invisible to MPS, therefore, remained in the circulation for a longer period of time. Hydrophilic polymers can be introduced at the surface in two ways, either by adsorption of surfactants or byuse of block or branched copolymers for production of nanoparticles.
- Studies show nanoparticles containing a coat of PEG not only have a prolonged half-life in the blood compartment but also be able to selectively extravasate in pathological sites suchas tumours or inflamed regions with a leaky vasculature.
- As a result, such long-circulating nanoparticles have increased the potential todirectly target tumors located outside MPS-richregions.
- The size of the colloidal carriers aswell as their surface characteristics are thecritical to the biological fate of nanoparticles. Asize less than 100 nm and a hydrophilic surface are essential in achieving the reduction of opsonisation reactions and subsequent clearance by macrophages.
- Coating conventional nanoparticles with surfactants or PEG to obtain a long-circulating carrier has nowbeen used as a standard strategy for drugtargeting *in vivo*.
- Extensive efforts have been devoted toachieving "active targeting" of nanoparticles inorder to deliver drugs to the right targets, basedon molecular recognition processes such asligand-receptor or antigen-antibody interaction. Considering that fact that folate receptors are over expressed on the surface of some human malignant cells and the cell adhesion moleculessuch as selectins and integrins are involved inmetastatic events, nanoparticles bearing specificligands such as folate may be used to target the cells.

• ovarian carcinoma while specific peptides or carbohydrates may be used to target integrins and selectins (Brannon *et al* 2004).

Nanoparticles for oral delivery of peptidesand proteins:

• Significant advances in biotechnology and biochemistry have led to the discovery of a large number of bioactive molecules and vaccines based on peptides and proteins. Development ofsuitable carriers remains a challenge due to the fact that bioavailability of these molecules islimited by the epithelial barriers of the gastrointestinal tract and their susceptibility to gastrointestinal degradation by digestive enzymes. Polymeric nanoparticles allow encapsulation of bioactive molecules and protect them against enzymatic and hydrolytic degradation. For instance, it has been found thatinsulin-loaded nanoparticles have preserved insulin activity and produced blood glucose reduction in diabetic rats for up to 14 days following the oral administration.

Targeting of nanoparticles to epithelial cells:

In the GI tract using ligands:

- Targeting strategies to improve the interaction of nanoparticles with adsorptive enterocytes andM-cells of Peyer's patches in the GI tract can beclassified into those utilizing specific binding toligands or receptors and those based on nonspecific mechanism (Wiener EC *et al* 1997).
- The surface of enterocytes and M cellsdisplaycell-specific carbohydrates, Which may serveas binding sites to colloidal drug carriers containing appropriate ligands. Certain glycoprotein's and lectins bind selectively to this type of surface Structure by specific receptor-mediated mechanism. Differentlectins, such as bean lectin and tomato lectin,have been studied to enhance oral peptideadsorption.
- Vitamin B-12 absorption from the gut under physiological conditions occurs via Receptor-mediated endocytosis. The ability toincrease oral bioavailability of various peptides (e.g., granulocyte colony stimulating factor, erythropoietin) and particles by covalent couplingto vitamin B-12. For this intrinsic process, mucoprotein is required, which is prepared by the mucus membrane in the stomach and binds specifically to cobalamine. The mucoprotein completely reaches the ileum where resorption is mediated by specificreceptors.

Nanoparticles for drug delivery into the brain :

The blood-brain barrier (BBB) is the most important factor limiting the development of new Drugs for the central nervous system. The BBBis characterized by relatively impermeable Endothelial cells with tight junctions, enzymatic activity and active efflux transport systems. Iteffectively prevents the passage of water-soluble molecules from the blood circulation into theCNS, and can also reduce the brain concentration of lipid-soluble molecules by thefunction of enzymes or efflux pumps consequently, the BBB only permits selective transport of molecules that are essential for brainfunction (Bhadra*et al* 2002).

The foregoing show that nanoparticulate systems have great potentials, being able to convert poorly soluble, poorly absorbed andlabile biologically active substance into promising deliverable drugs. The core of this system can enclose a variety of drugs, enzymes, genes and is characterized by a long circulation time due to the hydrophilic shell which prevents recognition by the reticular-endothelial system. To optimize this drug delivery system, greater understanding of the different mechanisms of biological interactions, and particle engineering, is still required. Further advances are needed inorder to turn the concept of nanoparticle technology into a realistic practical application as the next generation of drug delivery system.

CONCLUSION

REFERENCES:

- 1. Bhadra D, Bhadra S, Jain P, Jain NK. Pegnology: a review of PEG-ylated systems, *Pharmazie*, **2002**; 5(2): 5-29.
- Brannon-Peppas L, Blanchette JO. Nanoparticle and targeted systems for cancer therapy, *Adv. Drug Deliv. Rev.*, 2004; 3(6): 16-26.
- 3. Charlton DE, Booz, J. A Monte-Carlo Treatment of the Decay of 1225.
- 4. Cho BK, Roy EJ, Patrick TA, Kranz DM. SinglechainFv/folate conjugates mediate efficient lysis of folate receptor-positive tumor cells, *Bioconjug. Chem.*, 1997; 8(3); 38–46.
- Disis, M. Tumour immunology. June 6, 2006. www.meds.com/immunotherapy/tumor_immunology.html.
 Esenaliev R.O. US20006165440A (2000).
- Esenanev R.O. 052000105440A (2000).
 Hainfeld J.F, Slatkin D.N. US2005256360A1 (2005).
- Kommareddy S, Tiwari SB, Amiji MM. Long-circulating Polymeric nanovectors for tumor-selective gene Delivery, *Technol. Cancer Res. Treat.*, 2005; 4(6): 15-25.
- Kranz DM, Patrick TA, Brigle KE, Spinella MJ, Roy EJ. Conjugates of folate and anti-T-cell-receptor antibodies specifically target folate-receptor-positive tumor cells for lysis, Proc. Natl. Acad. Sci., USA, **1995**; 57–61.
- Micelle nanotechnology. October 20, 2006. http://www.maelor.plc.uk/mice.phpe anticancer drug paclitaxel (Taxol(R)): PLGA.
- 11. Mu L, Feng SS. A novel controlled release formulation for the nanoparticles containing vitamin ETPGS, *J. Control Release*, **2003**; 8(6): 33-48.
- 12. Nah J.W, Jung T.R, Jang M.K, Jeong Y.I. US2006013885A1 (2006).
- Tice TR, Gilley RM. Preparation of injectable controlledrelease microcapsules by a solvent-evaporation process, *J. Control Release*, **1985**; 2(4): 343-52.
- 14. Van Vlerken LE, Amiji MM. Multi-functional polymeric nanoparticles for tumour-targeted drug delivery, *Expert Opin. Drug Deliv.*, **2006**; 3(3): 05-16.
- Wiener EC, Konda S, Shadron A, Brechbiel M,Gansow O. Targeting dendrimer-chelates to tumorsand tumor cells expressing the high-affinity folate receptor, *Invest. Radiol.*, 1997; 3(2): 48–54.

How to cite this article:

Venkatesh Murukutla, Pusuluri Dharani Lakshmi Sai. TARGETING OF ANTI CANCER DRUGS THROUGH NANOPARTICLES, J. Pharm. Res., 2016; 5(6): 151-154.

Conflict of interest: The authors have declared that no conflict of interest exists. Source of support: Nil