# Nanoparticles delivery to cancer: Approaches and limitation

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## Abstract:

Nanoparticles have received attention as promising delivery system of chemotherapy for cancer treatment. There are many mechanisms through which nanoparticles reaches the tumor site. Many nanoparticles delivery systems have been developed to solve problems associated with chemotherapeutic drugs such as solubility and stability or to increase tumor site specificity as by attachment of ligand to surface of nanoparticles. We provide a critical review about the factors affecting the delivery of nanoparticles to tumor site, mechanisms by which nanoparticles reach the tumor site, types of nanoparticles and limitation of nanomedicine.

**Key words:** Nanoparticles; nanomedicine; cancer targeting; nanoparticles delivery systems.

## Introduction:

Cancer is one of the worldwide deadliest disease , There is an estimated 18.1 million new cancer cases (17.0 million excluding nonmelanoma skin cancer) and 9.6 million cancer deaths (9.5 million excluding nonmelanoma skin cancer) in 2018(1). There are many advances in development of cancer therapeutics molecules. Chemotherapeutic agents are considered the major therapeutic approach for the treatment of cancer(2). However, administration of conventional anticancer drugs involves high patient risks because the drugs are not specific to cancer cells. Most patients must tolerate severe side effects, decreased quality of life, and repeated treatments. The inefficiency and side effects of chemotherapy have been primarily associated with the formulation and

biodistribution of the drug, toxicity to normal cells and the acquisition of drug resistance by the cancer cells. It has been found that nanomedicine can help to overcome these issues(2).

Chemotherapeutic drugs have different problems associated with their poor solubility. Poor water solubility is problematic because it limits the bioavailability of the compounds. Many other drugs have the same problem, due to the inclusion of lipophilic groups that show affinity toward the target receptor. These poorly water soluble drugs may cause embolization of blood vessels due to aggregation, and often show local toxicity because of high drug concentrations at the site of deposition. To overcome the solubility problems, surfactants have been used to solubilize the drug, but their formulations may cause the drug to precipitate in vivo, because their critical micelle concentrations in physiological fluids are too low to preserve micellar structures capable of maintaining the drug in solubilized state because of the dilution. So, Nanoparticles (NPs) have been used to overcome the solubility problems of drugs. For example, Paclitaxel, anticancer drug was first identified by the US National Cancer Institute in 1967, has been found to be a potent against a wide range of cancers, including head and neck, ovarian, lung, breast, and colon cancers. However, it has limitation in practical due to its high hydrophobicity and poor solubility in water (less than 0.5 mg/L). The available formulation for paclitaxel includes the use of Cremophor EL (polyethoxylated castor oil) as a solubilizer. However, Cremophor EL is known to be toxic and can cause serious side effects, including hypersensitivity reactions, nephrotoxicity and cardiotoxicity(3). Nanoparticles help to overcome the problems of solubility and toxicity of Paclitaxel via loading in poly lactic glycolic acid (PLGA) nanoparticles(4).

Another advantage of NPs is that they can protect anti-cancer compounds from biodegradation and/or excretion and thus influence the pharmacokinetic profile of a compound. For example, drugs cleaved enzymatically (e.g., siRNA by RNAses in the plasma, proteins by pepsin or trypsin in the stomach) can be prevented from being degraded by enzymes by loading in nanoparticles(5). Encapsulation of anti-cancer agents into nanocarriers or coupling of biodegradable compounds to synthetic polymers may overcome this problem.

Also, nanotechnology can improve the biodistribution of the chemotherapeutic drugs. Distribution of chemotherapeutic drugs within tumor is depending on their physicochemical properties and is limited by drug penetration into tumor tissue(6, 7). Nanomedicine can improve

drug penetration and target the compounds selectively to tumor cells by passive, active, triggered targeting strategies.

Finally, Nanomedicine can decrease the resistance of tumor against the anticancer drugs. Normally tumors develop many mechanisms to resist chemotherapeutic drug. By developing of targeted Nps which are able to interact with tumor cells receptors, the probability for chemotherapy drug resistance will be reduced(8-10).

Therefore, nanotechnology emerged recently as one of the most propitious fields in cancer treatment(11). It has been reported that nanoparticles with certain shape and size showed selective tumor accumulation more than free drug of the nanoparticles(12).

There are three main mechanisms through which nanoparticles reaches the tumor site: passive targeting, active targeting and triggered targeting.

## Passive drug targeting:

The most used mechanism to express the delivery of nanoparticles to tumor is passive targeting. Tumors are characterized by their leaky vasculature allowing the nanoparticles of the right size to extravasate through the vascular wall to tumor site and release its payload(13, 14). Also the lymphatic system inside the tumor is largely absent or dysfunctional which increase the retention time of the nanoparticles within the tumor site(15). The high permeability and lack of lymphatic drainage is called enhanced permeability and retention (EPR) effect which was first described by Matsumra and Maeda(16). Macromolecules and nanoparticles can target the tumor via EPR more efficiently than the small molecules as the extravasation of the nanoparticles occurs in tumor-specific manner (**Fig. 1**). Therefore; utilization of the high permeability of tumor tissues for nanoparticle delivery has become an important strategy for the design and development of new therapeutics for cancer treatment. Additionally, the acidic tumor microenvironment can also be utilized to deliver antitumor therapeutics selectively to the tumor tissues by designing of nanocarriers with pH-controlled response and drug release(17).

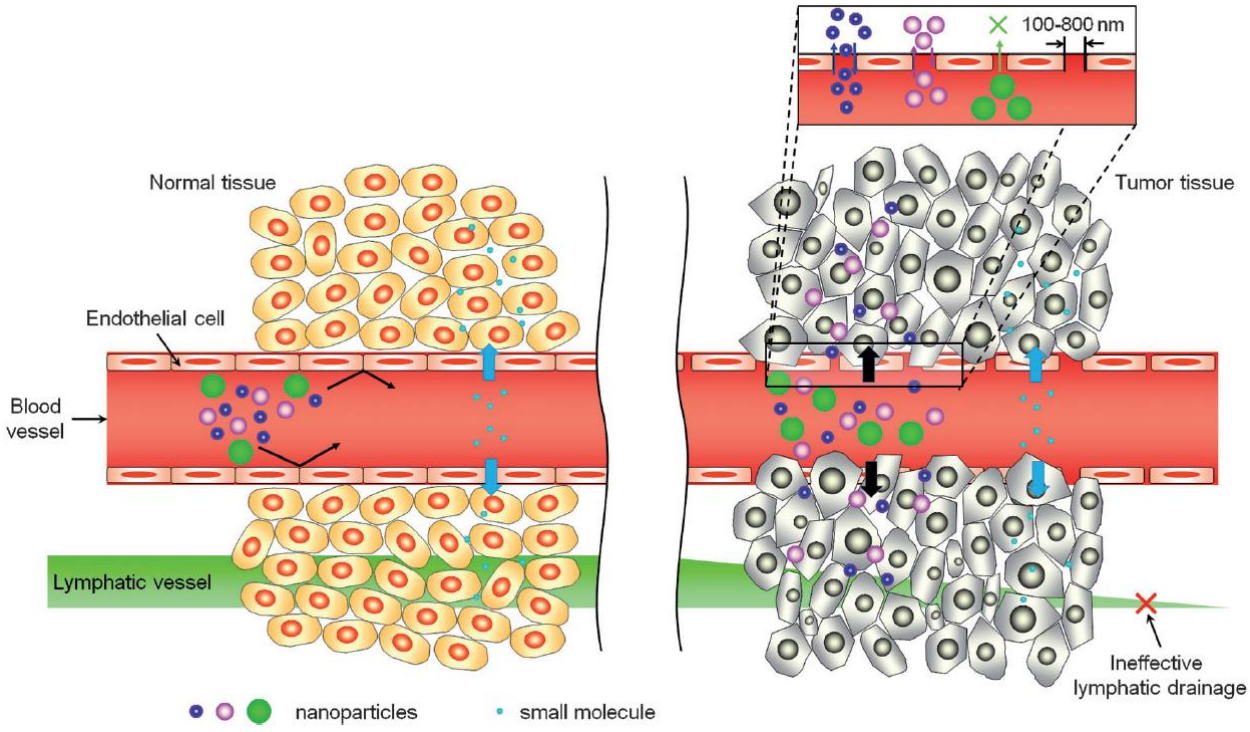


Fig. 1. Transport of nanoparticles with different sizes and small molecules through normal (left) and cancerous (right) tissues. The enhanced permeability and retention (EPR) effect is a unique feature of most tumors, allowing nanoparticles of appropriate sizes to accumulate more in cancerous tissues than in normal tissues(18).

## Active drug targeting:

Although passive targeting is the type of delivery most widely employed by nanoparticles, the EPR effect varies according to tumor type and patient condition, in addition, there could be huge differences in different areas of a single tumor(19, 20). Active targeting is used to overcome passive loading drawbacks. It relies on utilizing of the biochemical properties of cells to be targeted. Some of the receptors typically over-expressed on cancer cells, Therefore, by appropriately attaching ligands such as small molecules, peptides, antibodies and antibody fragments, and nucleic acids (e.g., aptamers) on the surface of the nanoparticles, their targeting efficiency can be improved. In active targeting, the ligand-receptor binding allows the nanoparticles to selectively and strongly bind to the cell. To achieve effective targeting of NPs to

their desired sites, it is essential to select the adequate targeting moiety, to be present in a sufficient quantity, and to have high affinity and specificity of coupling to cell surface receptors(21). In terms of cancer cells killing active targeting was found to be effective in vitro and in vivo to certain extent(22). For example, when nanoparticles are conjugated with target ligand, nanoparticles often show enhancement in internalization as this process is occurred by receptor-mediated endocytosis(23). On the other side, it has been found that nanoparticles with targeting ligand on the surface still rely on the EPR effect to pass the vascular gap in the vessel wall. It means that even in the presence of the targeting ligand, the retention and uptake of the nanoparticles by the cancer cells could be augmented as result of receptor mediated endocytosis but only after extravasation of the nanoparticles from the vasculature(24). Therefore, even with active targeting, it is believed that the accumulation of the nanoparticles is mediated by passive targeting.

## Triggered drug targeting:

Triggered drug targeting is one of the promising mechanisms for targeting drugs to tumor. It relies on using internal or external stimuli for triggering the release of the drug from the nanoparticles. The use of stimuli-responsive systems will reduce the nonspecific exposure to cytotoxic drugs and thereby reduce the side effects associated with the chemotherapeutic drugs.

Changes in pH, redox, ionic strength, and stress in target tissues are examples of internal stimuli(25). The difference in the pH of the intracellular organelles (endosomes and lysosomes) and the cytoplasm or blood(26) can trigger the release of the drug from the nanocarrier. For example, pH-responsive nanoparticles were used to trigger the release of the drug and therefore increase the therapeutic efficacy(27). Also, over expression of certain biomolecules and recognition of the host-guest interaction could be used as another internal stimulus. For example, numerous enzyme-based biochemical stimuli, including proteases and glucuronidases that are differentially expressed in normal cells and cancer cells, are useful for responsive systems(28). Another internal stimulus is tumor microenvironment which is hypoxic with low oxygen and high levels of reductive agents, such as glutathione(29). Nanocarriers with disulfide bonds may be used to target these types of tissue by carrying out redox reaction that oxidize glutathione which increases the cellular apoptosis(30).

Many external stimuli are also used as trigger for drug release. Physical stimulus is used as external trigger to release the drug from the nanoparticles. Local hyperthermia could induce the release of drugs from thermo-responsive nanocarriers. In addition, hyperthermia increases vascular permeability thus facilitating delivery of the anti-cancer agents deep into the tumor(31). Another example of external stimulus is using light source as ultraviolet or near infrared ranges(32). Magnetic and electric fields are other external stimuli. Paramagnetic nanoparticles (iron oxide nanoparticles) are responsive to an applied magnetic field. Thus, the nanocarrier can be guided to the tumor with high specificity and release its payload at the target site(33).

Difference between passive, active and triggered release are described in **Fig**. **2**.

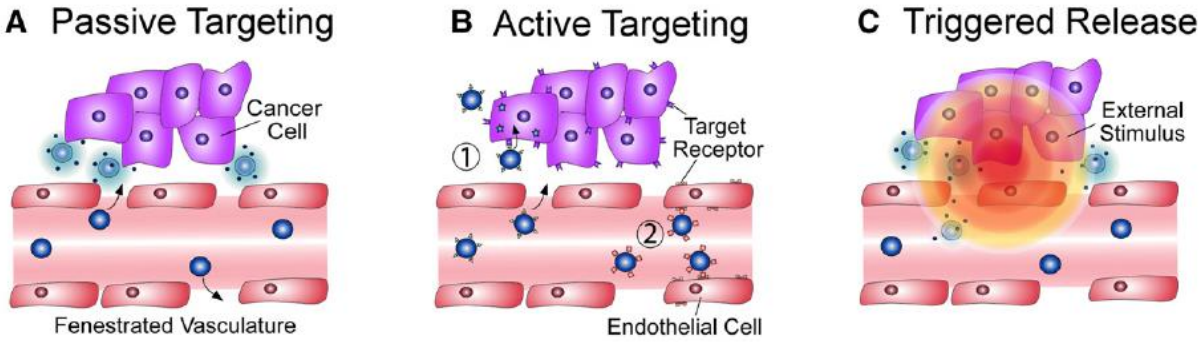


Fig. 2.Types of targeting for nanoparticle delivery to tumor tissue. **A)** Passive targeting relies on the leaky vasculature that is exhibited by tumors, allowing nanoparticles to travel through the fenestrations and reach tumors. **B)** Active targeting can be used when nanoparticles have ligands on their surface that can recognize and bind receptors that are overexpressed on tumor cells. **C)** Triggered release allows nanoparticles to congregate if exposed to an external stimulus such as a magnetic field or light(34).

## Factors affecting delivery of drug loaded nanoparticles to tumor:

### 1- Size

Particle size and size distribution are the most important characteristics of NPs. They determine the in vivo distribution, biological fate and toxicity, Also, size of nanoparticles showed to have impact on their other interactions with physiological barriers and tumor microenvironment.

The optimal size of the NPs for chemotherapy delivery should be in the range of 10-100 nm(35). Ten nm is the estimated threshold to first pass elimination by the kidney(36). NPs with size above 200-400 nm in size were removed by hepatic clearance and splenic filtration(10, 37). Tang et al. have compared the biological profiles of silica nanoconjugates (NCs) with three different sizes (20, 50, and 200 nm). The 50-nm NCs demonstrated the highest tumor penetration, most efficient uptake by tumor cells and slowest tumor clearance, resulting in highest tumor tissue retention integrated over time and highest efficacy against both primary and metastatic tumors in vivo. However it was found that 200 nm particles tends to stay close to blood vessels not perfusing in the tumor(38). On the other hand it was found that particles with small size has difficulty in retaining the drug within the particles due to the large surface area compared to mass(39).

NPs size also contributes to the mechanism by which they enter cells. NPs with size greater than 500 nm are taken up by macrophages via phagocytosis. On the other hand, smaller-size particles ranging from 5 to100 nm are taken up by non-phagocytic cells including cancer cells via pinocytosis(40).

The size of the particles also affects the stealth effect of PEG covering the particles at comparable surface density. Chen et al.(41) have compared serum protein adsorption to gold NPs with diameter ranging from 15-90 nm with variable PEG surface density. They have found that at an equal PEG density, 15 nm NPs showed the greatest protein adsorption, due to the relatively large curvature that gave a greater steric freedom to each PEG molecule.

## 2- Surface properties of nanoparticles:

Apart from particle size, particle hydrophobicity increases the amount of opsonins that bind to its surface and thereby influence the phagocytosis of the nanoparticles(42). It was found that NPs without surface modification are rapidly opsonized and cleared by mononuclear phagocyte system MPS(43). It is critical to minimize the opsonization to prolong the circulation time of the nanoparticles. This was achieved by coating with hydrophilic polymers/surfactants or formulating nanoparticles with biodegradable copolymers with hydrophilic characteristics, e.g., polyethylene glycol (PEG), polyethylene oxide, poloxamer, poloxamine, and polysorbate 80 (Tween 80)(39). Several studies have shown that presence of PEG with brush -like shape on the surface of nanoparticles could be obtained at concentration > 8 % mol(44). The brush like shape could reduce

phagocytosis of the nanoparticles. On the other hand PEG at low concentration forms mushroom shape, which is not extending so far form the nanoparticles surface, increased the phagocytosis(45). However, excessive PEG content is not always helpful at least for liposomes, as the integrity of membrane can be compromised by the detergent effect of PEG-lipid conjugates(46).

## 3- Surface charge:

Surface charge and charge density of NPs influence their stability. Charged NPs repel each other in solution, lowering the possibility of flocculation and aggregation during storage. On the other side, particles with neutral charge have more tendency for aggregation(47).

Surface charge could also affect Np-cell interaction, circulation, half-life, and tissue retention. In terms of cell interaction positively-charged particles favor adhesion onto cell surface via electrostatic interactions with negatively charged lipids and sugar moieties in the cell membrane(48). On the other hand, positive charges, can lead to non-specific uptake of NPs due to interaction with negatively charged cells membrane(49).

Holl et al.(50) have been investigating the effect of positively charged dendrimers on lipid bilayers. It has been revealed that the positively charged nanoparticles destabilized the cell membrane and form holes or expand the preexisting defects. The formed holes caused diffusion of cytosolic proteins out of cells. Also, Harush-Frenkel et al.(51) have examined the endocytosis mechanisms of charged particles. Their results have shown that while negatively charged nanoparticles have displayed less efficient rate of endocytosis, positively charged nanoparticles internalized rapidly via a clathrin-mediated pathway.

On the other hand, internalization of negatively charged Nps is believed to occur through nonspecific binding and clustering of the particles on cationic sites on the plasma membrane (that are relatively rare than negatively charged domains) and their subsequent endocytosis(52). Therefore , negatively charged particles showed a longer circulation half-life and greater accumulation at the tumor than positively charged particles(53).

## 4- Shape of the nanoparticles:

The shape of the nanoparticles has been found to greatly influence the cellular uptake. Spherical shaped nanoparticles were taken up 5 times more than rod-shaped particles, which is explained by greater membrane wrapping time required for the elongated particles(54).

Godin et al.(55) have shown that after injection of NPs with similar diameter but with different shaped (discoidal and spherical), accumulation of discoidal particles in breast tumors were five times higher than spherical particles.

The shape of the nanoparticles also has been shown to dictate the interaction with the cell membrane. First, the shape of nanoparticles dictates their clearance by macrophages of reticuloendothelial organs. Recent studies have indicated that the oblate shape of particles has lower uptake by macrophage and thereby it has longer circulation in the blood and increases their chances to reach their target site(56-58). Besides macrophages, the nanoparticles shape is also important for endocytosis by normal and cancer cells.

Also, it was found that targeting nanoparticles using receptor-ligand systems is also governed by shape. Compared to nanospheres, oblong-shaped nanoparticles are able to form a greater number of multivalent occurrences(59).

## Nanoparticles based drug delivery system:

Nanocarriers used for medical applications should be biocompatible with the ability to integrate with the biological system without eliciting immune response and be nontoxic. Undesirable effects of nanoparticles strongly depend on their hydrodynamic size, shape, amount, surface chemistry, the route of administration, uptake of nanoparticles by macrophages and granulocytes.

Nanocarriers with optimized physicochemical and biological properties are taken up by cells more easily than larger molecules, so they could be used successfully as delivery tools for drugs(60). There are many nanoparticles delivery systems used for chemotherapy such as liposomes, solid lipids nanoparticles, dendrimers, polymers, silicon or carbon materials and magnetic nanoparticles Fig. 3.

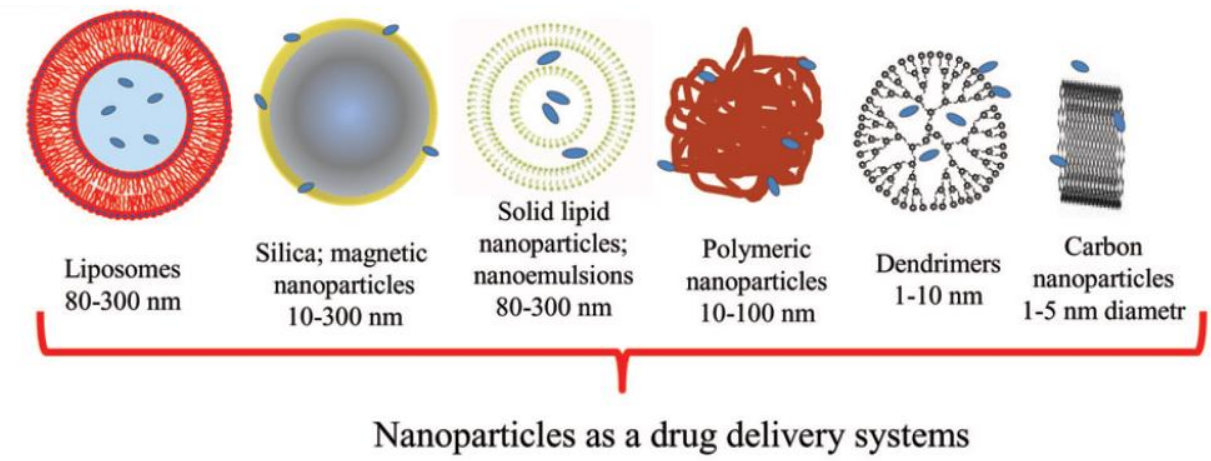


Fig. 3. Types of nanoparticles drug delivery systems.

## 1- Liposomes:

Liposomes are the first FDA approved nanoparticles in the market under the name of Doxil® which is liposomal Doxorubicin(61). They are nanoparticles with 80-300 nm size range(62). They are spherical bilipid vesicles mainly composed of phospholipid and steroid, e.g., cholesterol. Liposomes are formed spontaneously because the amphiphilic phospholipids self-associated into bilayers upon hydration with aqueous media. The lipid bilayer closes in on itself due to interactions between water molecules and the hydrophobic phosphate groups of the phospholipids. Liposomes can encapsulate both hydrophobic and hydrophilic drug moities in the lipid layer and aqueous phase respectively(63). Drug loading into liposomes could be achieved through (i) liposome formation in an aqueous solution saturated with soluble drug; (ii) the use of organic solvents and solvent exchange mechanisms; (iii) the use of lipophilic drugs; and (iv) pH gradient methods(64). Liposomes have been reported to increase the solubility of drugs and improve their pharmacokinetic properties; such as the therapeutic index of chemotherapeutic agents, rapid metabolism, reduction of harmful side effects and enhancement of *in vitro* and *in vivo* anticancer activity(65). The release of a drug from liposomes can be modified to depend on stimuli such as liposome composition, pH(66), osmotic gradient, temperature(67) and the surrounding environment(68). Liposomes have many mechanisms of interaction with cells such as a adsorption, fusion, endocytosis, and lipid transfer(69). Liposomes also have the potential to combat the increasing problem of multidrug resistance (MDR) acquired by cancers. Ogawara et al.(70) have tested the antitumor effect of Doxil® in male mice bearing colon cancer (C26) cells or

their doxorubicin-resistant (MDR) subclone, which overexpresses P-gp efflux pumps. Results showed that PEG liposomal doxorubicin had anti-tumor effects on both doxorubicin-resistant and non-doxorubicin-resistant C26 cells. With increasing incidence of resistance to chemotherapy, the use of liposomes offers an effective treatment without the need for the costly discovery of new chemotherapeutic drugs because current drugs can be reformulated.

## 2- Solid lipid nanoparticles:

Solid lipid NPs (SLNs) have been first described by Müller et al.(71), also referred to as lipospheres or solid lipid nanospheres. They are prepared with wide range of lipids including mono-, di- and triglycerides, fatty acids, waxes and combinations of them which were stabilized by surfactant to form administrable emulsion(72). They remain in a solid state at room temperature and human physiological temperature (37 °C) and their size range from 50 to 1000 nm. SLNs are biodegradable and biocompatible and could be used in humans because of their low toxicity(73).

Drugs are loaded in the lipophilic matrix for subsequent release. There are many factors affecting the drug loading into the SLN matrix such as a) the drug lipophilicity, b) the physical and chemical properties of the used lipids, c) the crystalline properties of the lipids at the biological temperature, d) the polymorphic forms of the used lipids.

SLNs have been investigated for the delivery of various anticancer drugs, with promising results in preclinical mouse trials showing that SLNs might help to overcome MDR in cancers(74). Kang et al.(75) have shown that SLN loaded with Dox enhanced apoptotic cell death through the higher accumulation of Dox in MCF-7/ADR cells. Therefore, SLN-Dox could be used as a potential therapeutic approach to overcome the chemo resistance of Adriamycin-resistant breast cancer. Serpe et al.(76) also have shown the benefit of SLNs for delivery of Dox, cholesteryl butyrate and paclitaxel using colorectal cancer cell line.

## 3- Polymer Based Nanoparticles:

Polymeric nanoparticles (PNPs) have attracted considerable interest due to their unique properties and behaviors resulting from their small size(77). They have as a wide range of applications such as diagnostics and drug delivery(78). They have many advantages including-controlled drug release, the ability to combine both chemotherapeutic and imaging agents

(theranostics), protection of drug molecules, specific targeting, improvements of drug therapeutic index.

As a class of molecules, their designs are similar polymer backbone which are formed from biodegradable monomer which are biocompatible and functional moieties for active targeting(79). A wide variety of therapeutic agents such as low-molecular-weight lipophilic or hydrophilic drugs, high-molecular-weight DNA or antisense DNA, could be loaded inside NPs. Drug loading could be achieved by either entrapment of aqueous drug phase using the polymer to form nanoscale structure such as cages and capsules(80), or chemical linking of the drug molecules to the polymer backbone via hydrolysable link such as ester or amide bond. The entrapped moiety in the polymeric matrix can be released in sustained manner by diffusion or degradation of the polymer matrix(81).

PNPs is formed from synthetic polymer such as polycaprolactone(82), polyacrylamide(83) and polyacrylate(84). The most widely used are biodegradable polymers including polylactide (PLA)(85), poly(D,L-lactide–co-glycolide)(PLGA)(86) and PEG(87).

PNP surface can also be modified with ligand for active targeting. Ligands can be presented on the Nps either by covalent linkage to polymer backbone or by the use of biologically inert spacer groups(88).

Several studies have investigated the intracellular drug delivery mechanisms. It has been known that the PLGA NPs are taken by endocytosis followed by intracellular drug release. Many studies demonstrated rapid and efficient cellular uptake of PLGA NPs, based on microscopic observation of PLGA NPs encapsulating a fluorescent probe and/or measurement of the intracellular level of the probe(89-91).

PLGA nanoparticles loaded with Paclitaxel was formulated with 70% encapsulation efficiency and similar apoptotic level to Taxol® when tested with Hela cancer cells. Theses formulated Paclitaxel NPs showed no in vivo toxicity associated with cremophor vehicle used in Taxol® Manufacturing(4).

Another example of anticancer drug which have been loaded in PLGA NPs is cisplatin. Cisplatin loaded NPs have shown less cytotoxicity than free cisplatin solution. *In-vivo* study has shown that cisplatin blood levels was prolonged and sustained compared with free drug solution(92).

However, there are many issues associated with polymeric nanoparticles including limited shape and wide size distribution(34). Polymeric nanoparticles are typically spherical, while a wide variety of different sizes may be generated during formulation. New techniques are currently being investigated to resolve these issues. The most recent approach is particle replication in nonwetting templates (PRINT). PRINT allows for the creation of uniform polymeric nanoparticles, allowing the customization of properties such as shape and size. Thus, the aesthetic properties of the nanoparticles, as well as the amount, rate, and pathway used for cellular uptake of the encapsulated drug molecule, may be tailored(93).

## 4- Dendrimer nanoparticles:

Dendrimers have been first reported in the 1980s(94). Dendrimeric nanoparticles are three dimensional, immensely branched, well organized macromolecules typically 5000-500,000 g/mol(95).

They are spherical macromolecules with many branches originating from central point called dendrimer. They are composed of the following elements; core, dendrons, and surface-active groups. The core is single atom or molecules that dendrons are attached to it. Dendrons are molecules of monomer linked with the core, forming layers and building successive generations(96).

By using specific initiator cores, the size and degree of branching of the dendrimer can be easily manipulated and the polydispersity of the nanoparticles will be minimized. By carefully planning the scheme of cores and branching units, the molecular weight, size, branch density, flexibility, and water solubility can be specified (97). Biocompatibility and physicochemical properties of dendrimers are determined by surface functional groups. Dendritic architecture is one of the most popular structures observed throughout all biological systems like: glycogen, amylopectin, and proteoglycans(98).

Dendrimers cytotoxicity are depending on the core material and surface nature. The presence of surface functional groups enables the interaction with cell receptors and enhance the biological activity(96). Drugs could be loaded in the dendrimer by encapsulation in the internal structure of the dendrimer(99), chemical attachment or physical adsorption on the dendrimer surface(100). To improve target selectivity of the nanoparticles many ligands could be attached on

the dendrimer surface such as folic acid(101), epidermal growth factors(102), antibodies(103), cyclic targeting peptides – arginine-glycine-aspartic acid (RGD)(104), selective A3 adenosine receptor(105), or poly(ethylene glycol) (PEG)(106).

In one example, Minko et al.(107) have used poly propylenimine tetrahexacontaamine dendrimer generation 5 (PPIG5) to load siRNA against B-cell lymphoma (BCL, anti-apoptotic) mRNA. The PPIG5-siRNA dendrimer was coated with PEG for steric stabilization and then a synthetic analogue of luteinizing hormone-releasing hormone (LHRH) peptide as the targeting motif. Targeted LHRH-PEG-DTBP-PPIG5-siRNA showed extensive cellular uptake for LHRH-positive A2780 human ovarian carcinoma cells, but not for LHRH-negative SKOV-3 cells. On the other side non-targeted nanoparticles did not show significant intracellular accumulation in either of the two cell types.

## 5- Inorganic nanoparticles:

Inorganic nanoparticles comprise an important category of drug delivery systems. There are many types of inorganic nanoparticles as silica nanoparticles, carbon nanotubes, noble metals e.g. gold nanostructure and porous silicon.

Silica xerogel is one type of silica nanoparticles which is produced by Sol-gel technique. Modification of synthesis conditions such as ratio of reagents, temperature, concentration of the catalyst, and pressure of drying, allows to alter properties of xerogels used in controlled drug release(108, 109). Many chemotherapeutic drugs have been loaded in silica nanoparticles using sol-gel technique such as doxorubicin(110) and cisplatin(111).

Mesoporous silica (MSN) is another type of silica Nps which have been developed and described by Kresge et al.(112). MSN have size in the range of 50-300 nm and have several advantages including biocompatibility, highly porous framework, enormous surface area and an ease in terms of functionalization(113). In comparison with xerogels, MSN have more homogenous structure, lower polydispersity and higher surface area for adsorption of therapeutic agents. It is able to incorporate both small molecules as carboplatin(114), large molecules(115) and in combined therapy as well(116).

Gold nanoparticles (GNPs) are another type of inorganic nanoparticles which can be synthesized using $NaBH_4$ to reduce $AuCl_4$ salts in the presence of thiol containing moieties that

subsequently form a monolayer around the core gold atom, depending on the stoichiometric gold/thiol ratio to give GNPs with diameter of 1-150 nm(117, 118). Studies have shown that gold NPs are not toxic at the cellular level in many human cell lines(119). Drugs can be conjugated to the surface of solid Au nanostructures (e.g., nanospheres and nanorods). Also, Au structures with hollow interiors (e.g., nanoshells(120) and nanocages(121) allow for a much enhancement of encapsulation efficiency of drugs within their cavities. Many studies showed the efficiency of GNPs when functionalized with anticancer drug such as Paclitaxel. Combination GNPs with Paclitaxel showed enhanced antiproliferation on tumor due to the disruption of the cell adhesion by GNPs(122).

Patra et al. have described another demonstration of the potential of multifunctional GNPs for delivery of GNPs covalently bound to cetuximab, as an active targeting agent and Gemcitabine as a chemotherapeutic agent in pancreatic cancer(123). It has been demonstrated that high intratumoral gold concentrations (4500 mg/g) could be achieved with using of cetuximab as active targeting agent compared with 600 mg/g with untargeted GNPs. With that combination of GNP–cetuximab– Gemcitabine nanocomplex was superior to any of the agents alone or in combination in vitro and in vivo. Low doses of complex Gemcitabine (2mg/ kg) led to inhibition of 80% tumor growth in an orthotopic pancreatic cancer model compared with 30% inhibition using the non-conjugated agents in combination(124).

## 6- Hydrogels:

Hydrogels are three-dimensional, cross-linked networks of hydrophilic polymers which are able to retain water or physiological fluids in large quantities(125). Typical examples of naturally occurring polymers used for hydrogels include chitosan, hyaluronic acid, dextran, alginate, collagen, and gelatin. These natural occurring hydrogels are biodegradable. However; most synthetic hydrogels are not biodegradable, but enzymatic, hydrolytic, and stimuli responsive components can be added into the hydrogel matrix in order to create nanoparticles that are degradable under certain conditions(126). Hydrogels possess unique advantages such as the high water content makes them resembles biological tissues, thus reducing interfacial tension with biological fluids and promoting biocompatibility(127). The porosity of the hydrogel can be controlled by changing the density of cross-linking in the gel matrix which affects the drug loading and release rate. Hydrogels have a positive surface charge and therefore can interact with the

negatively charged cell membranes, increasing cellular uptake of the nanoparticles drug payload. Since serum proteins also are negatively charged, hydrogels may aggregate to serum proteins, decreasing the circulation time of the nanoparticles(97). To solve the aggregation problem with serum protein Wang et al. have developed charge-converting nanogels that could be activated in the acidic tumor conditions(128). They have formulated nanogel with 100 nm size and zeta potential of +30 mV. To solve the positive charge issue, they have added a layer of 2,3 dimethyl maleic anhydride (DMMA) to the surface of the nanogels, which changed the zeta potential of the gels to -17 mMA). After incubation in acidic conditions (pH 6.8), the DMMA groups were gradually cleaved to convert the surface charge of the nanogels from negative to positive. The charge converting nanogels elicited more accumulation in tumor cells (MDA-MB-435s) in vitro at pH 6.8 than at pH 7.4. When loaded with doxorubicin, DMMA nanogels also caused higher cytotoxicity for (MDA-MA-435s) cells in vitro in a pH-dependent manner.

## Limitation of current nanomedicine formulation:

One of the most important limitation of the current nanomedicine formulation is only 0.7% of the injected nanomedicine dose reach the tumor(129). This limited fraction of drug reaching the tumor site attributes to limited success of clinical translation of cancer nanomedicine.

Another limitation of nanoparticles is there limited capacity of drug loading with typical few weight percent of active pharmaceutical ingredients (API). This made most of the nanoparticles are composed of inactive ingredients. High drug loading nanoparticles are a potential strategy for circumventing many of issues that plague nanotherapeutics. Since most nanocarriers have low drug loadings, a large amount of nanoparticle is needed to deliver a clinically relevant dose of a therapeutic, leading to the use of a large amount of excipients, which may cause undesirable side effects and drive up the cost of a nanotherapeutic(130).

There are many benefits gained from increasing the drug loading in nanoparticles. First, nanoparticles will be able to avoid immediate recognition and clearance by Monocytic phagocytic system (MPS), its circulation time is independent on the total nanoparticle dose(131, 132). Second benefit, high loaded nanoparticles are more efficient in delivery of therapeutics as it can deliver more API per tumor. Therefore, the total dose of nanoparticles needed to deliver a given amount of API is reduced. In addition, a high drug loaded nanoparticle will requires fewer non-API components, it not only lowers potential adverse effects of excipient agents, but also has a potential

to reduce the manufacturing cost of the nanotherapeutic(130). High loaded NPs are needed for chemotherapy not only for increasing the efficiency of chemotherapy but also to decrease toxicity. Mayer, L.D et al.(133) have compared $LD_{50}$ of liposomal Dox with different drug to lipid ratios. The decrease of the drug to lipid ratio from 0.28:1 to 0.038:1 has decreased the $LD_{50}$ from 57 to 39 mg/kg. Also have increased the amount of Dox accumulated in the heart by 1.8-fold. This increased toxicity due to the increased drug leakage from the liposomes caused by the extended exposure to the blood components and accumulation of the free doxorubicin in the tissues.

Another limitation of the current NPs is the scaling up of the nanoparticles for commercialization. Because they are limited by high production costs and persistent manufacturing issues such as scalability to multikilogram batches and batch-to-batch consistency. The toxicological impact and biological persistence of many nanoparticles remain poorly investigated, posing long-term issues from exposure to these materials(134).

## Future perspective:

The field of nanomedicine has grown in the past decades. There are many nanoparticles delivery systems have been developed to overcome problems associated with chemotherapy such as solubility and stability. Also, they have been used to improve the accumulation and release of chemotherapeutic agents from nanoparticles in the tumor site by using of mechanisms such as active and triggered release mechanisms. However, the limited fraction of nanoparticles reaching tumor site stays an obstacle against translation of nanomedicine to clinical stages. There is indeed need to achieve 10% of the injected dose reaching the tumor, understand interactions of the nanoparticles with tissues and organs, understand the relation between the physicochemical properties of nanoparticles and the biological system(135).

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