

Nanotherapeutics to Overcome Conventional Cancer Chemotherapy Limitations

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ABSTRACT - Cancer is one of the major causes of death worldwide and chemotherapy is a major therapeutic approach for the treatment which may be used alone or combined with other forms of therapy. However, conventional chemotherapy suffers lack of aqueous solubility, lack of selectivity and multidrug resistance. Nanotherapeutics is rapidly progressing aimed to solve several limitations of conventional drug delivery systems. Nonspecific target of cancer chemotherapy leads to damage rapidly proliferating normal cells and can be significantly reduced through folate and transferrin mediated nanotherapeutics which are aimed to target cancerous cells. Multidrug resistance is challenge in cancer chemotherapy which can be significantly reversed by solid lipid nanoparticles, polymeric nanoparticles, mesoporous silica nanoparticles, nanoparticulated chemosensitizer, nanoparticulated poloxamer and magnetic nanoparticles. Hydrophobic nature of chemotherapeutics leads to poor aqueous solubility and low bioavailability which can be overcome by nanocrystals, albumin based nanoparticles, liposomal formulation, polymeric micelles, cyclodextrin and chitosan based nanoparticles. This review focuses the role of nanotherapeutics to overcome lack of selectivity, multidrug resistance and lack of aqueous solubility of conventional cancer chemotherapy.

INTRODUCTION

Cancer is one of the major causes of the death worldwide. In India, cancer prevalence was estimated around 2.5 million with a growth of 8,00,000 new cancer cases and 5,50,000 cancer deaths every year. Cancer of oral cavity, lungs, oesophagus and stomach are common among Indian males whereas cancer of cervix and breast are common among Indian females (1, 2). In United States, one out of four deaths is due to cancer and it is seen in all age groups and in both sex. In 2010, about 1,529,560 new cancer cases and 569,490 cancer deaths are estimated in United States by Cancer Statistics Review. Death among children below 14 years in the United States is due to cancer, particularly acute lymphocytic leukaemia followed by brain cancer and non-Hodgkin lymphoma (3, 4). The three main approaches in cancer treatment are (a) Surgical excision, (b) Irradiation and (c) Chemotherapy. Comparative value of these approaches depends on tumor type and development stage of cancer. Major therapeutic approach for the treatment of localized and metastasized cancer is chemotherapy, which are used alone or combination with other forms of therapy (5, 6). However, conventional chemotherapy suffers some limitations (a) **Limited aqueous solubility**: Most chemotherapeutics either from plant source or synthetic are hydrophobic and requires solvents to formulate the dosage form which contribute to severe toxicity, (b) **Lack of selectivity of anticancer drugs**: Most chemotherapeutics lack

selectivity toward cancerous cells cause significant damage to rapidly proliferating normal cells and (c) **Multidrug resistance (MDR)**: MDR is mainly due to increased efflux pumps such as P-glycoprotein (Pgp) in the cell membrane which are responsible for transport of various anticancer drugs out of cells (7-10).

Nanotechnology literally means technology performed on a nanoscale. The nanoscale/nanoparticles are ultrafine particles in the size of nanometre from 1 nm to 1000 nm. Nanomedicine is an important area in nanotechnology which refers to highly specific medical intervention at the molecular scale for diagnosis, prevention and treatment of diseases (11). Nanotherapeutics are rapidly progressing field which are utilized to solve several limitations of conventional drug delivery system such as nonspecific biodistribution, lack of targeting, lack of aqueous solubility, poor oral bioavailability, and low therapeutic indices (12).

Some important technological advantages of nanotherapeutic drug delivery systems (NDDS) are (a) NDDS provides longer shelf life, (b) Both hydrophilic and hydrophobic substances can be incorporated in NDDS. (c) NDDS can be administrated through oral, nasal, parenteral, intraocular etc. (d) NDDS improve the biodistribution of cancer drugs.

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Whereas optimal size and surface characteristics of nanoparticles increases the circulation time of the drug, (e) NDDS provides control and sustain release of the drug both during the transportation and at the site of action and (f) NDDS increases the intercellular concentration of drug either by enhanced permeability and retention effect (EPR) or by endocytosis mechanism (13-14). This review focuses the role of nanotherapeutics to overcome lack of selectivity, multidrug resistance and lack of aqueous solubility of conventional cancer chemotherapy.

Nanoparticle drug delivery system to overcome lack of selectivity of anticancer drugs

Most cancer chemotherapeutics are administered either orally or intravenously to achieve systemic distribution for effective treatment. However, due to lack of selectivity these drugs cause significant damage to rapidly proliferating normal cells. The major goal of targeted therapies is to target the chemotherapeutics to cancer cell which ultimately reduce the side effects. Nanoparticles are targeted either passively or actively to specific sites.

Passive targeting

Size of nanoparticles and behaviour of tumor tissue vasculature plays a significant role in passive targeting (15). Solid tumor consists of tumor parenchyma and stroma, which in turn consist of vasculature and other supporting cells. Due to increased metabolic requirements of growing tumor cells, pre-existing blood vessels are subjected to angiogenic pressure and leads to the development of new capillaries to the tumor in a process called angiogenesis (16). Scanning electron microscopic studies revealed that the formed tumor capillaries are highly irregular and showed gross architectural changes. Normal tissue vasculatures are lined by tight endothelial

cells thereby preventing entry of nanoparticle whereas tumor tissue vasculatures are leaky (gaps as large as 200 to 2000 nm between adjacent endothelial cells) and hyper permeable. This defective vascular architecture induces an EPR and permits accumulation of nanoparticles in the tumor interstitial space (Figure 1) (17-23).

Accumulation of nanoparticles in tumor tissues depends on interstitial fluid pressure which is higher in tumor tissues than in benign tumor and normal tissues. In particular, interstitial pressure would be higher at the centre diminishing towards the periphery which is responsible for induction of drugs outflow from the cells which may leads to drug redistribution in some portions of the cancer tissue. Accumulation of nanoparticles in tumor tissues are also depends on size, surface character, circulation half-life of the nanoparticles and the degree of angiogenesis of the tumor (24-26). Selected delivery systems to achieve passive targeting are liposomes, polymeric nanoparticles, nanocrystals, inorganic nanoparticles, micelles, and dendrimers etc.

Active Targeting

Paul Ehrlich coined the term “magic bullet” which is an idealized package that would target and deliver drugs to a specific place in the body and this idea of active targeting was proposed even before a rational targeting ligand was discovered (27). Active targeting involves conjugation of targeting molecules (like antibodies, ligands, peptides, nucleic acids etc.) on the surface of nanoparticles with receptors over expressed on a tumor cell surface. Tumor targeting molecules on the nanoparticles bind to cell through an endosome-dependent mechanism (Figure 2) which bypasses the drug efflux pump leading to high intracellular concentration (23, 28-30).

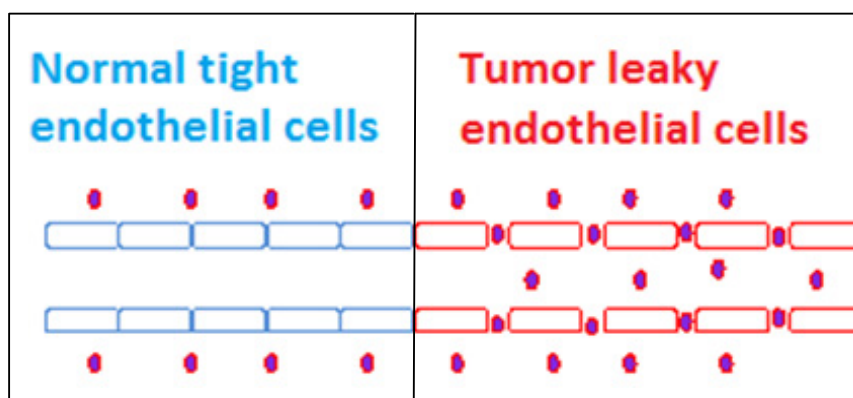


Figure 1. Nanoparticle accumulation in tumor tissue through EPR effect

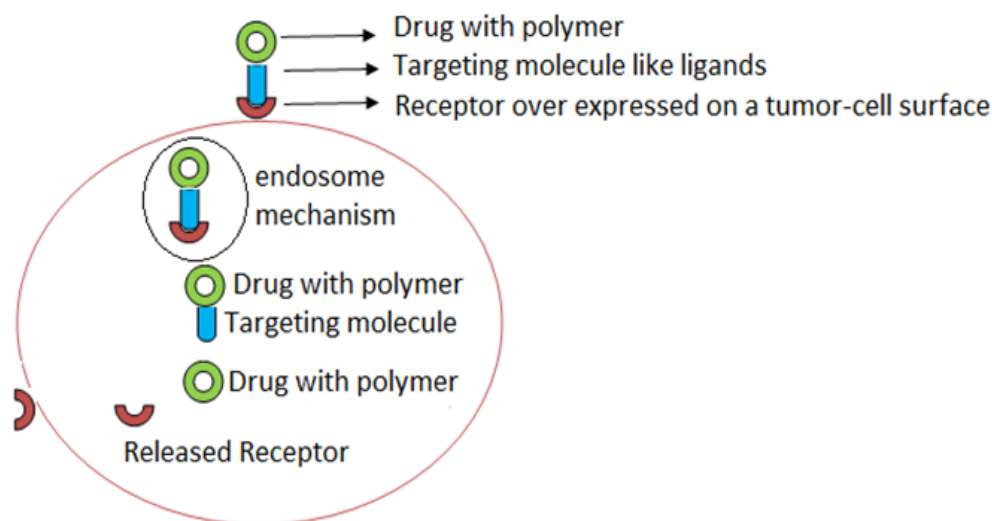


Figure 2. Endosome dependent mechanism of nanoparticles

Folate-Mediated Targeting

Folate receptor, a cell membrane associated glycosylphosphatidylinositol anchored glycoproteins involved in human growth and development, cell division and DNA synthesis, has been explored to target therapeutics into cancer cell due its over expression on malignant cancer cells. Binding of folic acid to folate receptor (FR- α and FR- β) initiates receptor-mediated endocytosis and internalization of folic acid. Most human tissues lack the folate receptor, except the placenta, choroids plexus, lungs, and kidneys; however, cellular activation and proliferation leads to over expression of high-affinity folate receptors in many cancers. Thus, Folate-mediated targeting has been used to deliver protein toxins, low-molecular weight chemotherapeutic agents, radio-imaging agents, MRI contrast agents, radio therapeutic agents, liposomes containing chemotherapeutic drugs, genes, antisense oligonucleotides, ribozymes, and immunotherapeutic agents to cancer cells (31-34). Many studies have been carried out to prove the enhancement of anticancer activity via folate mediated targeting.

To be specific, Zhaowu Zhang *et al.* utilized folate-conjugated nanoparticles on human cervixes carcinoma cells and found no cellular uptake of folate-conjugated nanoparticles in A549 cells which lacks folate receptor (35). Similarly Fabiana Canal *et al.* proved that antiproliferative activity of epirubicin markedly increased going from Folate Receptor (-) to Folate Receptor (++) cells with greater cellular internalization with the folate targeted conjugates than with their non-targeted analogues which was confirmed by

confocal microscopy studies (36). Chan Zhang *et al.* demonstrated uptake of folic acid conjugated doxorubicin up by HeLa cells and showed greater cytotoxicity compared to non-folate-mediated nanoparticles (37). Gene therapy for the treatment of cancer is a promising approach. However, clinical application of cancer gene therapy lacks vector that are safe, efficacious, and tumor-selective. Targeted gene delivery through cellular receptors, using either viral or nonviral vectors, is emerging as a novel approach. Folate receptor targeted liposomes have been evaluated for the targeted delivery of antisense oligodeoxyribonucleotides (ODNs) and shown impressive folate receptor selectivity in cell culture assays and shown promising tumor-specific gene transfer activity in several in vivo models (38).

Transferrin-Mediated Targeting:

One of the characterized ligands to be exploited for targeting tumor cells is transferrin which plays an essential role in iron homeostasis and cell growth. Inherent characteristic of some cancer cells is over expression of transferrin receptor. However, high expression of transferrin receptor is seen hypothalamus and medulla oblongata compared to other part of brain and many in vivo studies showed that transferrin increases brain delivery of nanoparticles (39). Uptake of transferrin into cells is mediated by transferrin receptors which are cell membrane associated glycoprotein. Binding of transferrin to transferrin receptor initiates receptor mediated endocytosis and interlization of transferrin. Whereas in presence of inhibitors, transferrin mediated

nanoparticles interact with the cells in a specific manner and enter the cells via the caveolae pathway (40, 41). Many studies have been carried out to prove the enhancement of anticancer activity via transferrin mediated targeting.

To be specific, Yu Zheng *et al.* studied the activity of transferrin-conjugated lipid-coated poly (d,l-lactide-co-glycolide) (PLGA) nanoparticles carrying the aromatase inhibitor, 7 α -(4'-amino)phenylthio-1,4-androstadiene-3,17-dione on breast cancer cells and results showed that aromatase inhibition activity of the transferrin nanoparticles was enhanced relative to that of the non-targeted nanoparticles, which was attributable to transferrin receptor mediated uptake (42). Similarly, Rohit S. Mulik *et al.* studied the anticancer activity of transferrin conjugated solid lipid nanoparticles of curcumin on MCF-7 breast cancer cells and results showed that the cell uptake and cytotoxicity increased considerably with transferrin conjugated solid lipid nanoparticles compared to curcumin solution. Transferrin conjugated nanoparticles enhance the antitumor activity via active target mechanism and also contributes to the photo stability and sustain release of drug (43).

Nanoparticle drug delivery system to overcome multidrug resistance

A major problem in cancer chemotherapy is multidrug resistance. Cancers such as non-small cancer, lung cancer, and rectal cancer may not respond to standard chemotherapy from the beginning which is called primary resistance or natural resistance. Whereas some sensitive tumors respond well to chemotherapy drugs in the beginning but develop acquired resistance later. The cell membrane, cytoplasm, and nuclear protein participate in resistance mechanisms. The mechanisms with known clinical significance are: a) activation of transmembrane proteins effluxing different chemical substances from the cells; b) activation of the enzymes of the glutathione detoxification system; c) alterations of the genes and the proteins involved into the control of apoptosis (especially p53 and Bcl-2). However, multidrug resistance is mostly due to increased efflux pumps in the cell membrane. The most common efflux pump in the cell membrane is P-glycoprotein (Pgp) and it transports various anticancer out of cells by using ATP.

Pgp is one of the membrane transporter superfamily having the ATP-binding cassette (ABC) with well-preserved homology of the site where ATP binds. Other efflux pumps of the mammalian cell membrane in ABC superfamily include multidrug resistance-associated proteins

(MRP) and breast cancer resistance proteins (BCRP). Acidic organelles in multidrug resistance cells are also contribute to developing resistance to chemotherapeutic drugs. Since most anticancer drugs are in an ionisable form, the pH of extracellular matrix and intracellular compartments are critical factors in determining drug partitioning and distribution. In some instance higher dose may be required to overcome multidrug resistance which in return, may enhance the toxicity of the treatment. To decrease the toxicity and to enhance the selectivity of existing drugs, many drug delivery systems have been developed in recent years (44-52). Various nanoparticulate drug delivery systems to overcome multidrug resistance are highlighted in this review.

Chemosensitizers through NDDS

Drugs such as verapamil and immunosuppressant Cyclosporine A would inhibit or reverse resistance by functioning as competitive substrates of Pgp and are called chemosensitizers. Clinical studies also showed that these drugs could reverse resistance to anticancer drugs. Xiang Rong Song *et al.* studied the effect of chemosensitizer (verapamil) using PLGA vincristine nanoparticles and found the following (a) administration sequence of vincristine and verapamil was significant for maximal therapeutic efficacy, (b) Highest reversal could be achieved when vincristine and verapamil administration simultaneously, (c) PLGA nanoparticles showed moderate MDR reversal activity on MCF-7/ADR cells, (d) Normal tissue drug toxicity and fewer drug-drug interactions are seen when vincristine and verapamil co-encapsulated (53).

Mesoporous Silica Nanoparticles

Mesoporous silica nanoparticles (MSNs) were first reported by Kuroda and co workers in 1990 in Japan and later developed by Mobil Corporation laboratories and named as Mobil Crystalline of Materials, or MCM-41. Silica nanoparticles with much larger (4.6 to 30) nanometer pores were produced at the University of California and named Santa Barbara Amorphous type material, or SBA-15. Some of the advantages of MSNs are (a) Particle sizes of MSNs can be tuned from 50 to 300 nm, (b) Stable and rigid frame of MSNs allows for resistance to pH, mechanical stress, and degradation, (c) Pore diameters of MSNs can be tuned between 2 and 10 nm allowing for different drug loadings, (d) MSNs have a high surface area and large pore volume allowing high loadings of drugs and (e) The interior and exterior surfaces of MSNs can be

selectively functionalized with different moieties on either surface (54-57).

Alex M. Chen *et al.* studied the activity doxorubicin and Bcl-2-targeted siRNA on multidrug resistant A2780/AD human ovarian cancer cells utilizing MSNs and results showed that by delivering Doxorubicin and Bcl-2 siRNA simultaneously into cancer cells, the Bcl-2 siRNA can effectively silence the Bcl-2 mRNA and significantly suppress the non pump resistance and substantially enhance the anticancer action of Doxorubicin and result also suggest that the Doxorubicin delivered by MSNs has minimal premature release in the extracellular environment, which can greatly eliminate side effects of Doxorubicin (58).

Solid lipid nanoparticles (SLN)

SLN are colloidal drug carrier systems and are similar to nanoemulsions. However, the liquid lipid used in nanoemulsions is replaced by a solid lipid in SLN. SLN can be administered through parenteral (intravenously, intramuscularly or subcutaneously), oral, Rectal, ophthalmic and topical (59). Many studies have been carried on SLN which proves to provide controlled drug delivery, enhancement of bioavailability of entrapped drugs, improvement of tissue distribution and targeting of drugs. To be specific, Keon Wook Kang *et al.* studied doxorubicin-loaded solid lipid nanoparticles on MCF-7/ADR cells (doxorubicin-resistant breast cancer cell line) and result showed that Doxorubicin-loaded solid lipid nanoparticles efficiently enhanced apoptotic cell death through the higher accumulation of doxorubicin in MCF-7/ADR cells in comparison with free doxorubicin (60).

Polymeric nanoparticles

When the free drugs are administered, they enter the cell by diffusion through the plasma membrane and are recognized by the Pgp pumps whereas these drugs are conjugated to macromolecular carriers, the drug in the form of polymeric prodrug is taken up by endocytosis and subsequently efflux pumps are circumvented in turn reducing the multidrug resistance. Doxorubicin, when conjugated with polymeric dextrans of various molecular weights, its cytotoxicity significantly higher than free doxorubicin when studied on human carcinoma KB-3-1 cells and its multidrug-resistant subclone KB-V-1 cells (61). Similarly, Yang Liu *et al.* demonstrated that paclitaxel nanocrystal formulation using D- α -tocopheryl polyethylene glycol 1000 succinate have significant advantages over Taxol in achieving better therapeutic effect

in Taxol-resistant cancer cells both in vitro and in vivo (62).

Poloxamers

Poloxamers was invented by Irving Schmolka in the year 1973, which belong to polypropylene oxide (PPO) and polyethylene oxide (PEO) triblock copolymers family which are widely used nanoparticulate engineering for drug delivery systems (63). Due to its amphiphilic structure, poloxamers acts as surfactant and can be used to increase the water solubility of hydrophobic, oily substances and increase the miscibility of two substances with different hydrophobicities. Poloxamers is a potent chemosensitizer of multidrug resistant cancers and its activity includes inhibition of Pgp, inhibits complex I and complex IV of the mitochondria respiratory chain, decreases oxygen consumption and causes ATP depletion in multidrug resistant cells (64, 65). Yangqing Zhang *et al.* studied the cytotoxicity of paclitaxel-loaded poly (ϵ -caprolactone) (PCL) / Poloxamer 188 nanoparticles on paclitaxel resistant human breast cancer cell line and found PCL/Poloxamer 188 nanoparticles achieved a significantly higher level of cytotoxicity than both of PCL nanoparticle formulation and Taxol[®], which indicates Poloxamer 188 nanoparticles could overcome MDR in human breast cancer cells (66).

Magnetic nanoparticles (MNPs)

Chemotherapeutic agents bound to a magnetic carrier will be injected in the vascular system and under the influence of an external magnetic field this compound will be held in the targeted area and concentrated at the specific site. MNPs have been studied extensively for targeted delivery of pharmaceuticals. Bao-an Chen *et al.* evaluated the cytotoxicity of daunorubicin (DNR)-loaded magnetic nanoparticles of Fe₃O₄ (MNPs-Fe₃O₄) on K562-n/VCR cells in mice of different groups and found weight was lower in group which received DNR-MNPs-Fe₃O₄ than in other groups. Similarly transcriptions of Mdr-1 and Bcl-2 gene were significantly lower in group which received DNR-MNPs-Fe₃O₄ than in other groups. However, there was no difference in the expression of P-glycoprotein. Result indicates DNR-loaded MNPs-Fe₃O₄ can overcome MDR in vivo (67).

Nanoparticle drug delivery system to overcome aqueous solubility

Drug substances are considered highly soluble when the largest dose of drug is soluble in <250mL water throughout the physiological pH

range from 1 – 8 but most of the anticancer drugs show poor aqueous solubility. Poor aqueous solubility chemotherapeutics both from plant source and synthetic often demonstrate decreased bioavailability, increased chance of food effect, more frequent incomplete release from the dosage form and higher interpatient variability. However, administration of poor water soluble drugs through systemic route requires solvents like Cremophor EL, Tween (polysorbate)-80, etc. which in turn, lead to severe adverse effects, including acute hypersensitivity reactions, fluid retention, and peripheral neuropathy (68-72). There are two basic approaches to overcome the poor water solubility and poor bioavailability problems (a) Increase of saturation solubility (by complex formation) and (b) Increase of dissolution velocity (Dissolution velocity can be increased by increasing the surface area of the drug powder, i.e. nanonisation) (73).

Nanocrystals

Nanocrystals increases the dissolution velocity by surface area enlargement (size reduction leads to an increased surface area) and increases the saturation solubility (74). Nanocrystal of hydrophobic drugs like paclitaxel and camptothecin shows significant cytotoxicity by inhibiting the tumor growth in human lung cancer and murine breast cancer than its counter free paclitaxel and camptothecin. The nanocrystals encapsulated over 99% of the drug with a high ratio of drug to excipient. These nanocrystals also showed significant therapeutic effects via oral administration (75).

Albumin based nanoparticles

Albumin is a natural carrier of endogenous hydrophobic molecules (such as vitamins, hormones, and other water-insoluble plasma substances), that are bound in a reversible non-covalent manner and enhances penetration by albumin receptor-mediated (gp60) endothelial transcytosis. The albumin coating that surrounds the active drug assists in the transport of the nanoparticles to the interior of the tumor cell that preferentially takes in albumin as a nutrient through the gp60 pathway. Albumin that binds to therapeutic peptide or protein covalently or physically enhances the stability and half-life of the drug (76-83).

Franco Dosio *et al.* studied paclitaxel–albumin conjugate with two different conjugate populations (with 6 or 30 average molecules of drug linked to each albumin molecule) and found the following (a) Conjugates were stable in physiological solution and in serum whereas the

presence of proteases or liver extract released the paclitaxel in a linear fashion, (b) Conjugates maintained high cytotoxicity with efficient cell binding and internalization followed by release of the paclitaxel inside three different tumor cell lines, (c) Both paclitaxel–albumin conjugate followed a bicompartamental model but elimination of the conjugate from the plasma was much slower than the free paclitaxel, giving a relevant rise in area under the curve and mean residence time values after IV administration, (d) The conjugate also released of paclitaxel continuously to the plasma over prolonged periods, thus providing a depot effect and (e) The acute toxicity noted with the standard formulation of taxol was strongly reduced in albumin-conjugated preparation (84).

Liposomal formulation

Liposomes are biodegradable, non-toxic vesicles that have been used to deliver both hydrophilic and hydrophobic agents. Liposomal formulations of several active molecules are currently in pre-clinical and clinical trials with promising results. The key problems in drug therapy are biodistribution throughout the body which can be overcome by using liposomal formulations. Liposomes protect encapsulated molecules from degradation and can passively target tissues (85). Inclusion of paclitaxel in liposomal formulations has proved to be a good approach to eliminating Cremophor EL and ethanol, improving the drug's antitumor efficacy. Allen Zhang *J et al.* developed a lyophilized liposome-based paclitaxel (LEP-ETU) with a mean particle size of 150 nm which increases the solubility (0.25 mg/ml) without drug precipitation or change in particle size. In vitro drug release study of LEP-ETU in phosphate-buffered saline (pH 7.4) showed that less than 6% of the entrapped paclitaxel was released after 120 hours, which indicates that the drug is highly stable in an entrapped form at physiologic temperature. Stability data indicated that the lyophilized LEP-ETU was physically and chemically stable for at least 12 months at 2-8 °C and 25 °C (86).

Polymeric micelles

Polymeric micelles are nanosized particles that are made up of polymer chains and are usually spontaneously formed by self-assembly in a liquid, generally as a result of hydrophobic or ion pair interactions between polymer segments. BBSKE is an organic selenium compound chemically named (1, 2-[bis (1, 2-benzisoselenazol-3(2H)-one)] ethane) with significant antitumor activity. However, BBSKE

is poorly soluble in water (2.57 µg/mL) and its bioavailability by oral administration is also considerably low. Xinru Li *et al.* prepared a series of monomethoxy poly (ethylene glycol)-poly (lactide) (mPEG-PLA) diblock copolymers and fabricated with mPEG-PLA micelle. BBSKE was efficiently encapsulated into the micelles by the dialysis method, and the solubility of BBSKE in water was increased up to 82 µg/mL. BBSKE-loaded polymeric micelle showed enhanced antitumor efficacy and reduced toxic effect compared with BBSKE-HP-β-CD inclusion at the same dose in H₂₂ human liver cancer cell bearing mouse models. These results suggested that mPEG-PLA polymeric micelle nanoparticles had great potential as nanocarriers for effective solubilization of poorly soluble BBSKE and further reducing side effects and toxicities of the drug (87).

Cyclodextrin based nanoparticles

Cyclodextrins were used to enhance aqueous solubility and chemical stability of drugs in the beginning and these functionalities were related to their ability to form drug-cyclodextrin inclusion complexes. Cyclodextrin have been shown to participate in various types of non-inclusion complexes with organic salts and water-soluble polymers. Cyclodextrin have also been shown to form aggregates, either alone or in combinations with other excipients which can form dispersed drug delivery systems such as micro and nanoparticles (88).

Yu Liu *et al.* studied the inclusion complexation behaviour of paclitaxel with a series of oligo (ethylenediamino) bridged bis (β-cyclodextrin) possessing bridge chains in different length of 1 - 4 to improve the water solubility of paclitaxel and found bis(β-cyclodextrin) 1 and 2 are able to solubilize paclitaxel to high levels up to 2 and 0.9 mg/mL, respectively. Result also revealed that the cytotoxicity of these complexes assessed using a human erythroleukemia K562 cell line indicates that the antitumor activity of bis(β-cyclodextrin) 1-paclitaxel complex is better than that of free paclitaxel (89). Similarly, Agüeros M *et al.* encapsulated paclitaxel (PTX) as a complex with three different cyclodextrins β-cyclodextrin (CD), 2-hydroxypropyl-β-cyclodextrin (HPCD) and 6-mono-deoxy-6-mono-amino-β-cyclodextrin (NHCD) and studied the oral bioavailability paclitaxel in rats with a single dose of 10 mg paclitaxel per kg body weight and result showed that the plasma curves were characterised by a plateau of paclitaxel concentration close to the C_{max} from T_{max} till 24 h post-administration. For PTX-CD NP and PTX-

HPCD NP, these sustained levels of the anticancer drug were found to be between 27 and 33-fold higher than the reported value of drug activity whereas the relative oral bioavailability of paclitaxel was calculated to be higher than 80% (90). These fact shows that cyclodextrin based nanoparticles can significantly alter the solubility and bioavailability and can be utilized to deliver cancer therapeutics with low solubility and bioavailability.

Chitosan based nanoparticles

Biodegradable polymer that has received a good deal of attention towards oral drug and gene delivery systems is chitosan. Chitosan is nontoxic and biodegradable, with an oral LD₅₀ in mice of over 16 g/kg. Major factors contributing to chitosan widespread evaluation as a component of oral dosage forms are its safety, its ability to extend residence time in the gastrointestinal tract through mucoadhesion, and its ability to improve absorption by increasing cellular permeability. Absorption enhancement of chitosan was found to depend on both molecular weight and degree of deacetylation (68). Can Zhang *et al.* studied the possible utilization of amphiphilic N-octyl-N-trimethyl chitosan (OTMCS) derivatives in solubilization and controlled release of hydrophobic anticancer drug, 10-hydroxycamptothecin (10-HCPT) and the results showed the solubility of 10-HCPT in aqueous fluid was increased about 80,000-fold from 2 ng/ml in water to 1.9 mg/ml in OTMCS micellar (degree of octyl and trimethyl substitution is 8% and 54%, respectively) solution. In addition, OTMCS was able to modulate the in vitro release of 10-HCPT and improve its pharmacokinetic properties and lactone ring stability in vivo. These data suggested the possible utilization of the amphiphilic micellar chitosan derivatives as carriers for hydrophobic drugs for improving their delivery and release properties (91).

CONCLUSION

Nanoparticulate drug delivery systems are being studied to overcome limitation of conventional oral dosage form in many therapeutic areas particularly in cancer chemotherapy where most of the anticancer drugs have limited aqueous solubility, lack of targeting cancer tissues and multidrug resistance. Nanoparticle drug delivery system such as folate mediated targeting, transferring targeting are the most studied targeting approach in cancer chemotherapy. However, many other targeting approaches are

under investigation. Major problem in cancer chemotherapy is multidrug resistance which can be effectively circumvented via Mesoporous Silica Nanoparticles, Solid lipid nanoparticles, Polymeric nanoparticles and Magnetic nanoparticles. Poor aqueous solubility and low bioavailability of cancer chemotherapeutic can be effectively overcome by nanocrystals, albumin based nanoparticles, liposomal formulation, Polymeric micelles, cyclodextrin and chitosan based nanoparticles.

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