Drug carrier systems for anticancer agents: A review

Renu Chadha1*, V K Kapoor1, Deepika Thakur1, Rupinder Kaur1, Poonam Arora1 and D V S Jain2

1University Institute of Pharmaceutical Sciences, 2Department of Chemistry, Panjab University, Chandigarh 160 014

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Poor aqueous solubility and adverse effects in cancer treatment using cytotoxicity or hormone therapy are frequently encountered during formulation and usage of conventional drugs. This paper reviews application of various solubilizers and carriers (polymers, cyclodextrins, dendrimers and proteins and amino acids) being used for improving therapeutic efficacy of these agents. Preparation of microspheres, microcapsules and nanospheres to improve aqueous solubility, and potential of liposomes and nanoparticles as effective drug delivery tools have been discussed.

Keywords: Anticancer agents, Cyclodextrin, Liposomes, Nanoparticles, Polymers, Solubility

Introduction

Physiological events regulating proliferation, apoptosis, differentiation, and cell arrest, modulate correct homeostasis and functionality of all tissues. A disorder in these sequential events, which results in alteration of the ratio between cell death, cell differentiation and cell proliferation, leads to an increase in the number of dysregulated cells. Recent advances in tumorigenesis and metastasis have provided unique opportunities to design novel compounds that rationally act on abnormal molecular and biochemical signals leading to cancer. However, major progress achieved in cancer treatment results from conventional drugs used for cytotoxic therapy. Most of anticancer drugs are water-insoluble, delaying their clinical effectiveness. Moreover, a number of anticancer drugs such as camptothecin, paclitaxel, and etoposide are lipophilic, polar and unstable in aqueous media and undergo less potent decomposition through hydrolysis. These characteristics make their design formulation difficult.

This review presents potentialities of various anticancer drug carrier systems for providing therapeutically effective concentration on tumor.

Effective Drug Delivery

Effective drug delivery has been achieved by considering advantage of distinctive tumor pathophysiology. Effective tumor chemotherapy requires directive action of anticancer drug at molecular level of tumor. Undirective distribution of the drug within living system reduces therapeutic effectiveness and increases risks of side effects and toxicity (Fig. 1). As few anticancer drugs are self-directive, a major approach is to carry drug in a particulate carrier that is capable to deliver drug at tumor location. Various methods have been developed for enhanced solubility and effective delivery, by considering advantage of leading drug carrier technologies.

Solubilizers

Majority of anticancer agents show poor solubility. Efficiency of a solubilization technique is determined by physio-chemical properties of the drug. Various agents generally used are Sorporol 230, Sorporol 120Ex, Aceporol 345-T, Aceporol 460 and Riciporol 335.
hydrotropic agents such as sodium benzoate, sodium o-hydroxybenzoate (sodium salicylate), sodium 2,5-di-hydroxybenzoate (sodium gentisate), and sodium salts of 2,4-di-hydroxy- and 2,6-di-hydroxybenzoic acid and of 2,4,6-tri-hydroxybenzoic acid.

Paclitaxel, an antitumor agent, is widely used in treatment of advanced breast and ovarian cancer but has a very low aqueous solubility (<1 μg/ml)\textsuperscript{11,12}. Loos \textit{et al.}\textsuperscript{8} and Fugimoto\textsuperscript{9} has demonstrated that alteration of drug distribution in blood occurred in all carriers studied but it changed significantly in Cremophor EL. However, no difference in the affinity of paclitaxel for tested solubilizers was found during equilibrium dialysis experiments. Different carriers were distinguished by a different rate of esterase-mediated breakdown, which was correlated with the fatty acid content of solubilizers. Activation of complement cascade was less pronounced for all solubilizers, except Riciporol 335, as compared to Cremophor EL. Darwish \textit{et al.}\textsuperscript{10} established that, out of all hydrotropes used as solubilizers, sodium benzoate showed weakest interaction and sodium 2,4,6-tri-hydroxybenzoate (STB) showed strongest interaction with etoposide. However, use of STB is limited for poor aqueous solubility. Hydrotropic solubilization of STB showed a promising increase in aqueous solubility for formulating aqueous parenteral etoposide.

Various oil/water (o/w) emulsions have also been utilized for paclitaxel. Formulated emulsion [paclitaxel, 0.75 mg/ml; oil blend, 10% (w/v); EPC, 4% (w/v); and Tween 80, 3% (w/v) in glycerol, 2.25% (w/v)] has very good stability when stored at 4°C. Paclitaxel-emulsion displayed cytotoxicity against HeLa cells with IC50 at 30 nM. Formulated emulsion was found to be a promising carrier for paclitaxel and other lipophilic drugs\textsuperscript{13}. Lipiodolized w/o emulsion or w/o/w multiple emulsions containing doxorubicin hydrochloride (Adriamycin HCl) with different emulsifiers was prepared. Dissolution studies indicated that the release of doxorubicin HCl was significantly sustained for both emulsions when HCO-60 [polyoxyethylene (60) hydrogenated castor oil] was used as an emulsifier. Lipiodol and HCO-60 seemed to play an important role in prolongation and selective retention of w/o or w/o/w emulsions, \textit{in vitro} and \textit{in vivo}\textsuperscript{14}.

Dolan \textit{et al.}\textsuperscript{15} observed that O-6-benzylguanine, when given in PEG 400 than cremophor-EL, is more effective enhancer of antitumor activity of BCNU. Aqueous nanocrystalline drug suspensions prepared by wet milling technology of four anti cancer agents [piposulfan (alkylating agent), etoposide (topoisomerase II inhibitor), camptothecin (topoisomerase I inhibitor) and paclitaxel (antimitotic agent)] have been demonstrated to be stable and efficient\textsuperscript{16}. A sterile preparation of methyl CCNU, a water insoluble drug, which was made by first dissolving in absolute alcohol and slowly adding to a fat emulsion, Intralipid, was found stable for 8 h at room temperature and 7 days under refrigeration. On administration of the preparation to 100 patients, no significant side effects were attributed to the fat emulsion\textsuperscript{17}.

Self-emulsifying drug delivery formulations (SEDDS) are widely used in enhancing oral absorption of poorly soluble drugs\textsuperscript{21,22}. Supersaturable SEDDS (S-SEDDS) formulations have been developed to avoid side effects of these systems\textsuperscript{22}. S-SEDDS generates a protracted supersaturated solution of drug when the formulation is released from an appropriate dosage form (capsule) into an aqueous medium. S-SEDDS contains a reduced surfactant level and a polymeric precipitation inhibitor to yield and stabilize a temporarily supersaturated drug. HPMC and related cellulose polymers have been used to inhibit crystallization and thereby generate and maintain supersaturated state for prolonged time\textsuperscript{22,23-28}. SEDDS\textsuperscript{29} and S-SEDDS of paclitaxel have been developed using hydroxyl propyl methylcellulose as a precipitation inhibitor\textsuperscript{12}.

Recently, two new synthetic antitumor agents, XK-469 and PPA, have been solubilized by pH adjustment coupled with cosolvency, micellization, or complexation\textsuperscript{7}. At pH 4.55, neither cosolvency micellization nor complexation has much effect on solubility of PPA. However, these techniques can significantly increase solubility of XK-469.

**Polymers and Drug Conjugates**

Polymer-drug conjugates\textsuperscript{30} (PDCs) produce an improved pharmacokinetic profile of an antitumor agent and in addition as soluble carriers can achieve either first-order (organ specific) or second-order (tumor specific) drug delivery (Fig. 2). PDCs are usually administered intravenously. Soluble polymeric carriers have potential to improve the activity of conventional antitumor agents\textsuperscript{31}. PDCs selectively accumulate within tumour tissue, which leak through the disorganized vasculature\textsuperscript{32,33}. Clearance from tumour tissue is delayed due to poor lymphatic drainage. Tumour accumulation of PDCs enhanced permeation and retention effect\textsuperscript{14}. On intra-venous administration, PDCs are taken up by tumour cells and
active drug released intracellularly. PDCs delivery on passive tumour is influenced by the nature of polymer backbone. Most of the polymeric backbones explored are prepared from non-biodegradable materials. Treatment of malignant tumors is hampered by problem of drug delivery in tumor bed due to blood brain barrier. So, biodegradable polymers that can release chemotherapeutic agents against malignant gliomas have been developed. Although, care must be taken to ensure that biodegradation does not hamper accumulation of PDCs in tumour tissue. Various polymers used are HPMA, poly (glutamate), poly ethylene glycol. Daunorubicin, doxorubicin, cisplatin and 5-fluorouracil have been linked to polymer to form drug polymer conjugates.

A thermoplastic biodegradable polymer (an oligomer of microcaprolactone) drug depot of camptothecin has been prepared. This system was heated to a temperature at or above physiologic temperature whereupon it would form a low viscosity melt. The drug containing polymer melt is then injected to form a semi solid depot upon cooling.

A novel solid formulation for oral delivery of pH-sensitive, scarcely water-soluble etoposide has been designed, characterized, and tested. Solid formulation was developed by grinding drug with a cross-linked polymeric carrier (crospovidone) under controlled process conditions (mechano-physical drug activation), and subsequently incorporating selected oil/surfactant (o/s) blends into polymer particles. Physio-chemical characterization (thermal analysis, drug dissolution kinetics, drug o/w partition studies) provided information on drug-polymer interaction at solid state, and on formulation performance in vitro, resulting in enhancement and modification of etoposide solubilization process. Such solid formulation was considered equivalent, in vitro, to the current marketed product.

Four types of in vivo degradable polylactic acid (PLA) [mol wt: 1500 (1500DL), 2200 (2200DL), 2800 (2800DL) and 3500 (3500DL)] were used for preparations of bleomycin-containing solid forms (polymers). In vitro release of bleomycin from polymers suggested that polymers containing BLM could be useful for the site of drug administration or anti-cancer release pattern. HPMA copolymer-doxorubicin, HPMA copolymer-doxorubicinalactose, HPMA copolymer-platinate, and poly(L-glutamic acid) (PG)-paclitaxel have entered phase I and II trials. HPMA copolymer-paclitaxel, and HPMA copolymer-camptothecin, dextran-doxorubicin failed because of inadequate polymer drug linkage and toxicity. Cisplatin, an antineoplastic, is extremely hydrophilic. As controlling the release rate through micropores on ethyl cellulose is difficult, a gel-forming polymer was formulated. An oral sustained release cisplatin preparation was prepared by combining microporous water insoluble polymer, ethyl cellulose, a membrane and gel forming agent polymer, poly(acrylic)acid (carbopol).

Three potent anticancer drugs [bleomycin, mitomycin C and 5-fluorouracil (FU)] were entrapped in hydrogel matrix prepared by copolymerization of collagen and poly hydroxyethyl methacrylate (HEMA). HEMA hydrogels can serve as ideal carriers for controlled release of anticancer drugs. Intravenous administration of paclitaxel is hindered by poor water solubility of the drug. Currently, paclitaxel is dissolved in a mixture of ethanol and Cremophor EL; however, this formulation (taxol) is associated with significant side effects, which are considered to be related to the pharmaceutical carrier. A new water-soluble polymer-conjugated derivative of paclitaxel, PNU166945 is in phase I study. A polyanhydride matrix containing BCNU was in phase III evaluation for treatment of glioma multiforme.

**Polymeric Micelles**

Using amphiphilic, solubilizing agents, Cremophor EL, can increase water solubility. However, a number of problems associated with its use were overcome by developing poly(N-vinylpyrrolidone)-block-poly (D,L-lactide) copolymer that formed polymeric micelles (Fig. 3) in water and solubilized anticancer drugs (paclitaxel, docetaxel, teniposide and etoposide). Doxorubicin was physically loaded into micelles prepared from polyethylene glycol (PEG)-poly(β-benzyl-L-aspartate) block copolymer by an o/w
emulsion method with a substantial drug loading. This system showed high antitumor activity compared to free doxorubicin\(^48\). Diblock copolymer poly(DL-lactide)-block-methoxy PEG as an intravenous delivery carrier for paclitaxel was developed. Cremophor paclitaxel or polymeric micellar paclitaxel (PMP), tested in mice, indicated that PMP could be a clinically useful chemotherapeutic formulation\(^49\). Adriamycin, an anthracycline anticancer drug, was bound to poly(aspartic acid) chain of PEG-poly(aspartic acid) block copolymer by amide bond formation between an amino group of adriamycin and carboxyl groups of poly(aspartic acid) chain. High anticancer activity of this micelle-forming polymeric drug was observed in comparison with free adriamycin, due to its low toxicity\(^50\).

Organometallic Compounds

Rh(I) complexes appeared to be promising drugs because of their solubility in aqueous polymer. Rh(I) show a similarity to cisplatin in reducing tumor growth. Poly (oxyethylene) was used to solubilize these poorly water-soluble compounds. Both Rh(I), A \([\text{Rh}(\text{NBD})(2,4N)]\text{ClO}_4\] and B \([\text{Rh}(\text{NBD})(3,4N)]\text{ClO}_4\], were found good candidates for tumor control growth\(^51\).

Cyclodextrins

Cyclodextrins, carbohydrate macrocycles, have ability to form molecular inclusion complexes (Fig. 4) with a wide range of hydrophobic molecules\(^52\). Many drugs such as melphalan and carmustine form inclusion complex with \(\beta\)-cyclodextrins (\(\beta\)-CDs). However, use of \(\beta\)-CDs is limited due to its low solubility and significant renal toxicity after parenteral administration. Thus cyclodextrin derivatives, sulfobutyl ether \(\beta\)-cyclodextrin ((SBE)\(_7\)–\(\beta\)-CD or Captisol) and hydroxypropyl \(\beta\)-cyclodextrin (HP-\(\beta\)-CD) were synthesized due to their minimal toxicity\(^53\). In addition, \(\gamma\)-CDs and HP-\(\gamma\)-CDs were used to form an inclusion complex with doxorubicin, which had poor blood brain barrier permeability. Increased delivery resulted at high concentrations as a result of disruption of the membrane\(^54\). The complexes formed by doxorubicin and daunorubicin were analyzed by liquid chromatography, circular dichroism and absorption spectroscopy\(^55\).
An inclusion complex of γ-CDs with aphidicolin has poor solubility in water. Complex was used for systemic treatment of xeno transplanted parental and vincristine-resistant UKF-NB-3 tumours. β-Cyclodextrin-PEG-folic acid conjugate (CD-PEG-FA) increased solubility of chlorambucil. CD-PEG-FA displayed a reduced hemolytic effect as compared to unmodified β-CD. Also, heptakis(2,6-di-O-methyl)-β-cyclodextrin and β-CD of chlorambucil increased solubility and stability of chlorambucil. DIMEB was found more efficient than β-CD.

Proteins and Amino Acids as Carrier Systems

Folic acid has been widely investigated as a delivery molecule for active anticancer drug delivery systems. Folate-based carriers are radionuclide deferoxamine-folate complexes for radiopharmaceutical imaging, liposome-folate-encapsulated drugs, liposome-folate-encapsulated polylysine-DNA, and cytotoxin-folate conjugates. Therapeutic application of folate conjugates is often limited by their large size. An alkylating nitrogen mustard agent that utilizes D-alanine as a drug carrier for three chloroethyl substituents (CICH₂CH₂-) was synthesized. Synthetic approach utilizes (CICH₂CH₂-) 1,2-dichloroethane reaction with primary amine of D-alanine resulting in chloroethyl substituents. A nitrogen mustard agent showed alkylation activity in aqueous solution directed toward a nucleophilic primary amine group. D-alanine mustard agent has good bioavailability. Serum albumins of different species were used as carrier proteins, mostly of bovine (BSA), human (HSA) or rat (RSA) origin to form complexes with anticancer drugs. New groups of synthetic biodegradable branched chain polypeptides have been used to elucidate structural and functional properties required for the selection of macromolecular carriers for targeting/delivery of antitumor agents (daunomycin, methotrexate, boron derivatives).

Dendrimers

Dendrimers have unique characteristics including monodispersity and modifiable surface functionality, along with highly defined size and structure. Drug delivery can be achieved by coupling a drug to polymer through one of two approaches. Hydrophobic drugs can be complexed within hydrophobic dendrimer interior to make them water-soluble or drugs can be covalently coupled onto surface of the dendrimer. Poly(amideamine) (PAMAM) has emerged as potential dendrimer to act as targeted drug carrier. PAMAM has been modified by partial acylation to act as multifunctional cancer therapeutic nanodevices, which were synthesized by conjugation of remaining nonacetylated primary amino groups with fluorescein isothiocyanate (FITC, an imaging agent), folic acid and methotrexate (a chemotherapeutic drug). Nanodevices are being used for delivery of chemotherapeutic and imaging agents to specific cancer cells.

A PAMAM dendrimer generation 3.5 with a sodium carboxylate surface was conjugated to cisplatin giving a dendrimer-platininate (dendrimer-Pt; 20-25 wt% platinum), which was highly water soluble and released platinum slowly in vitro. Dendrimer-Pt was also less toxic (3- to 15-fold) than cisplatin and thus has potential for further investigation as a novel antitumor agent. Single-chain Fv (scFv) fragments, multi-drug carriers, were linked dendrimer molecules bearing up to nine chlorambucil residues at the branch ends.

Prodrugs

Two-step ADEPT (Antibody Directed Enzyme Prodrug Therapy) has been developed for directing antitumor agents (Fig. 5). First an enzyme is directed at the tumor cell surface as a fusion protein followed by injection of a non-toxic prodrug hydrolyzed by this enzyme, thus enabling the release of anticancer agent. More solubility and encouraging serum stability and enzymatic hydrolysis led to development of prodrug of...
etoposide (vepeside\textsuperscript{9}). Prodrugs were also developed for taxol (taxotere\textsuperscript{8}) and camptothecin (irinotecan\textsuperscript{8})\textsuperscript{70}.

A novel method for creating water-soluble prodrugs of cisplatin analogues bearing chelating diamines has been introduced. When 2-(aminomethyl)aniline is reacted with K\textsubscript{2}PtCl\textsubscript{4} at pH 6-7, neutral chelated complex as compound 1 is isolated. On the other hand, when complexation occurs under acidic conditions (pH 3), zwitterionic, “open-ring” form is obtained, as compound 2. Compound 2 has a solubility of 10 mM in acidic aqueous medium; that is 20 times more than that of 1. Both compounds (1 & 2) are equally effective at halting the growth of three different human cancer cell lines in vitro, indicating that prodrug is quantitatively converted to the parent drug in a complex, biologically relevant medium. Etoposide (Vepeside) is a widely used drug in a variety of neoplasms. Etoposide phosphate (Etopophos) has been developed as a prodrug. In comparison to the parent compound, etoposide phosphate is highly soluble in water and can be readily formulated for intravenous use, resulting in higher clinical application\textsuperscript{71}.

Three new prodrugs of 5-FU, [N(1)-octenoylFU (1), N(1)-lauroylFU (2), and N(1)-retinoylFU (3)], have been prepared and are potentially effective drugs against postsurgical proliferative vitreoretinopathy\textsuperscript{72}. Prodrug 1 was found to be readily soluble in silicone oil. The most promising prodrug was found to be compound 3 that slowly releases two active drugs (FU and retinoic acid) with a t (1/2 release) of 5.8 days\textsuperscript{73}.

2’ and 7 Polyol carbonates of paclitaxel were synthesized and screened as potential paclitaxel prodrugs. Paclitaxel is released from 7-(2’, 3’-dihydroxypropylcarbonato) paclitaxel (Protaxel) at rates inversely proportional to pH, by an intramolecular cyclization. Compared to paclitaxel, maximum tolerated i.v. or i.p. doses of Protaxel are about 2.5 to 3-fold higher; its efficacy is substantially higher in human cancer line xenografts in athymic mice, especially in prostate PC-3, breast MDA-MB 468 and ovary OVCAR-1\textsuperscript{75}.

Microspheres

Polymeric microspheres and polypeptides can be used as carriers for delivering drugs by a variety of routes\textsuperscript{76}. Phagocytic cells of reticuloendothelial system provide a physiological means of achieving cell and tissue specificity in drug delivery that has enormous potential\textsuperscript{77}. Albumin microspheres provide a potentially useful means of delivering drugs to endocytic cells because they are physically and chemically stable and rapidly removed from vascular system by phagocytosis. So, phagocytizable human albumin microspheres of mercaptopurine were prepared\textsuperscript{78,79}. A microencapsulation procedure was used to prepare biodegradable BCNU-loaded microspheres to be used as intracerebral implants. Local delivery system allowed high drug concentrations at the site of a resected brain tumor and adjacent tissues without significant toxicity\textsuperscript{80}. Cheung et al\textsuperscript{82} suggests that i.t. delivery of anticancer drugs by polymeric microspheres is an effective way of improving

Fig. 5 — ADEPT approach to drug targeting
therapeutic index for cancer chemotherapy of selected solid tumors under special conditions.

**Liposomes**

Liposomes are formed by the self-assembly of phospholipids molecules in an aqueous environment. Amphiphilic phospholipids molecules form a closed bilayer sphere in an attempt to shield their hydrophobic groups from aqueous environment while still maintaining contact with aqueous phase via hydrophilic head group. The resulting closed sphere may encapsulate aqueous soluble drugs within the central aqueous compartment or lipid soluble drugs within bilayer membrane. Unfortunately, liposomes are rapidly taken up by liver macrophages. This problem was overcome by coating surface of liposomes with liposome surface ligands, such as monosialoganglioside or polyoxyethylene, which are called stealth liposomes (Stealth liposomes of about 100 nm in size passively target solid tumors by extravasation into their intracellular space upon i.v. administration) (Fig. 6). Besides this, incorporation of cholesterol, polyvinylpyrrolidone polyacrylamide lipids, glucuronic acid lipids or the high phase transition temperature phospholipid distearoyl phosphatidyl choline into liposomes have also been found effective in extending their circulation in blood. Non-stealth liposomes prepared from high phase transition temperature phospholipids also prolong circulation times and accumulate within tumour tissue despite high levels of liver uptake. In patients, liposomal doxorubicin accumulates within Kaposi’s sarcoma lesions and produces a good therapeutic response. Liposomal doxorubicin is now licensed, as Caelyx, for the treatment of Kaposi’s sarcoma. This formulation is currently in clinical trials for ovarian cancer.

Open-ring form of the drug is a poor inhibitor of topo I, and a much less potent antitumor agent than camptothecin lactone. However, insolubility of camptothecin lactone makes it difficult to devise a suitable formulation for further clinical testing. So, successful incorporation of camptothecin into a liposome-based drug delivery system composed of DPPC:Sph:CHOL:PI (2.4:6.6:1.0:0.05 M) was accomplished, and this complex had considerable potential for treatment of human neoplastic diseases, especially lymph node metastases. Either lipid liposomes are less toxic to MethA cells than free compounds; liposomal alkylphosphocholines are more toxic toward KB and M22 cells than corresponding free lipids. A lyophilized liposome-based paclitaxel formulation is sterile, stable and easy-to-use due to its less toxic properties.

Combination of paclitaxel and doxorubicin or epirubicin is highly active against metastatic breast cancer, but may produce congestive heart failure.

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Fig. 6 — Stealth liposomes encapsulate a drug (red) in a phospholipid bilayer (blue and white) [A polyethylene glycol coating (green) allows liposomes to evade immune system, increasing half-life of drug in body]
Liposome-encapsulated doxorubicin\textsuperscript{108}, a new formulation of doxorubicin, had no dose-limiting cardiac toxicity. Combination of weekly paclitaxel and liposomal doxorubicin every 2 weeks was found highly effective in previously treated patients\textsuperscript{109}. A phase I pharmacokinetics and dose-finding study and a phase II study of combination of pegylated liposomal doxorubicin HCl and paclitaxel demonstrated activity in recurrent or metastatic head and neck cancer\textsuperscript{110}. Mitomycin C in combination with infusional 5-fluorouracil is a well-tolerated active combination therapy for advanced gastric cancer. Its safety and good tolerability as established in phase I trial was confirmed\textsuperscript{111}. A liposomal formulation of vincristine\textsuperscript{113-115} (VCR-Lip), compared with vincristine in aqueous solution (VCR-Conv), revealed that VCR-Lip is an effective vincristine delivery system with superior antitumor activity\textsuperscript{116}.

Liposomes designed to combat cancer chemotherapy associated multidrug resistance\textsuperscript{117} are also being developed. Liposomal formulations of FU lipid analogue\textsuperscript{118}, a porphyrin for use in combination with laser light irradiation\textsuperscript{119}, bleomycin\textsuperscript{120} and mitozantrone\textsuperscript{121} are also reported.

Nanoparticles

Nanomedicines consisting of nanoparticles (Fig. 7) are able to deliver drugs to the tissue and/or intracellular compartment under infection. These nanocarriers are able to protect associated drug against degradation and facilitate its transport across critical and specific barriers. Nanocarriers have been made of synthetic biodegradable polymers, lipids and polysaccharides. A number of nanotechnologies have been developed that enable the association of a variety of drugs to these nanocarriers\textsuperscript{122}. Cisplatin is one of the most widely used agents in the treatment of solid tumors, but liposomal formulations of cisplatin have been hampered by the low water solubility and low lipophilicity of cisplatin. So nanocapsules, which are small aggregates of cisplatin covered by a single lipid bilayer, had improved solubility and lipophilicity\textsuperscript{123}.

A novel nanoparticle/liposome construct containing camptothecin CPT-11 (irinotecan) exhibited active antitumor activity with low toxicity\textsuperscript{124}. Bovine seminal ribonuclease (BS-RNase) shows antitumoral, aspermatogenic, antiembryonic, immunosuppressive and antiviral properties. BS-RNase with nanoparticles as carriers holds promise as an antitumoral agent\textsuperscript{125}.

Solid lipid nanoparticles (SLNs), having high adaptability, superior handling properties, and low toxicity\textsuperscript{126-128}, can be a generic carrier system for anticancer drugs. A formulation of doxorubicin HCl has been prepared by using SLNs\textsuperscript{129}. Cholesteryl butyrate solid lipid nanoparticles (chol-but SLN) were prepared as pro-drug to deliver butyric acid. Chol-but SLN affects proliferation pattern of both myeloid and lymphoid cells to an extent greater than natural butyrate\textsuperscript{130}. Idarubicin-loaded solid lipid nanoparticles (IDA-SLN) acted as a prolonged release system for the drug\textsuperscript{131}. Intravenously delivered non-stealth and stealth SLN carrying
doxorubicin has also been prepared as drug delivery systems. Hyaluronic, has been used for targeting of mitomycin C and doxorubicin, mediated by tHA-LIP.

**Immunotoxins**

GrB based immunotoxins have emerged as a new class of immunotoxins with low immunogenicity and their directed delivery has a significant potential for cancer treatment. These rationally designed therapeutics offer a dual hope of maximizing antitumor efficacy and minimizing toxicity in normal tissue.

**Conclusions**

Cosolvents, emulsions and multiple emulsions can enhance aqueous solubility by virtue of their ability to alter polarity of the combined solvent. Precipitation inhibitors decrease precipitation of drugs and cyclodextrins increase solubility by incorporating lipophilic drugs in their lipophilic interior. Cell adhesion and intracellular release of drugs is achieved by using various non-biodegradable and biodegradable polymer drug carrier systems. Proteins and amino acid conjugate of drugs use specific carrier or receptors. Dendrimers can be used to enhance both solubility and target delivery of the drugs. Prodrugs with enzyme cause their hydrolysis in the target cell increasing the solubility of the drugs. Liposomes and stealth liposomes are used to incorporate lipophilic and hydrophilic drugs and provide long-term delivery of these anticancer drugs. Nanomedicines are another set of delivery devices, which increase both solubility and lipophilicity of anticancer drug substances. Solubility and adverse impact of the drug in human cells is of utmost concern. There is alarming need to revolutionize existing anticancer drug carrier systems by developing human cell environment friendly drugs and their effective delivery for sustaining long life of healthy and recovered cells.

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