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NANOPARTICLES DRUG DELIVERY SYSTEM USING LIPOSOMES FOR CANCER TREATMENT

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ABSTRACT

The first closed bilayer phospholipid systems, called liposomes, were described in 1961 and soon were proposed as drug delivery systems. Nanoparticles particles in the size range 1–100 nm are emerging as a class of therapeutics for cancer. Nanoparticles composed of biodegradable polymers show assurance in fulfilling the stringent requirements placed on these delivery systems, such as ability to be transferred into an aerosol, stability against forces generated during aerosolization, biocompatibility, targeting of specific sites or cell populations in the lung, release of the drug in a predetermined manner, and degradation within an acceptable period of time. Their use offers improved pharmacokinetic properties, controlled and sustained release of drugs and, more importantly, lower systemic toxicity. A number of liposomes (lipidic nanoparticles) are on the market, and many more are in the pipeline. Lipidic nanoparticles are the first nano medicine delivery system to make the transition from concept to clinical application, and they are now an established technology platform with considerable clinical acceptance. We can look forward to many more clinical products in the future.

KEYWORDS: Transmucosal, Phagocytic cells, Anthracycline drug, Interstitial space.

INTRODUCTION

The application of nanotechnology in cancer, also known as Cancer Nanotechnology, is an emerging field of research involving collaborations between various disciplines, including biology, chemistry, engineering, and medicine. Nanoparticles have promising applications in diagnostic, therapeutic and drug delivery systems for cancer, as they can enter the tissues at the molecular level; these particles have given platforms for cancer therapy and diagnostics. Nanoparticles provide a new mode for cancer drug delivery as a carrier for entry through fenestrations in tumour vasculature, allowing direct cell access. The modified nanoparticles allow binding to cancer cell membranes, microenvironment, or cytoplasmic or nuclear receptor sites. This initiates the delivery of high drug concentrations to the targeted cancer cell with reduced toxicity of normal tissues. Over the past several decades, the development and application of engineered nanoparticles to more effectively treat cancer have witnessed significant advancement.[1] The field has gained a strong support over the years because of its potential as a solution for improving cancer therapy. Its main goal is to develop novel technologies for more advanced cancer detection, diagnosis, and treatment Development of new drug molecule is expensive and time-consuming. Improving safety efficacy ratio of "old" drugs has been attempted using different methods such as individualizing drug therapy, dose titration, and therapeutic drug monitoring,[2-4] Since the internet has made literature searches relatively straightforward, there has been a tendency to overlook the early scientific literature and to forget, or fail to cite, the important contributions of the early pioneers in the liposome field. We have made a special effort in this paper to find those early references and give credit to the liposome pioneers and put their contributions into context. It is our intent to focus on the early work in the liposome field, especially work done with small molecule therapeutics, and we apologize to our many colleagues whose more recent work we have not been able to cite due to space limitations.

Some examples of CRTs are transdermal and transmucosal controlled release delivery systems, ml6 nasal and buccal aerosol sprays, drug-impregnated lozenges, encapsulated cells, oral soft gels, iontophoretic devices to administer drugs through the skin, and a variety of programmable, implanted drug-delivery

devices. There are a number of factors stimulating interest in the development of these new devices, concepts, and techniques. Conventional drug administration methods, while widely utilized, have many problems that may be potentially overcome by these methods. Equally important, these advances may appear attractive relative to the costs of new drug development. Rising research and development costs, alternative investment opportunities for drug firms, fewer firms conducting pharmaceutical research, and erosion of effective patent life have resulted in a decline in the introduction of new chemical entities since the late 1950s. Bringing a new drug through discovery, clinical testing, development, and regulatory approval is currently estimated to take a decade and cost well over $ 120 million. Novel drug delivery systems may account for as much as 40% of US marketed drug products by 2000.[5-7] Nanoparticles applied as drug delivery systems are submicron sized particles (3-200 nm), devices, or systems that can be made using a variety of materials including polymers (polymeric nanoparticles, micelles, or dendrimers), lipids (liposomes), viruses (viral nanoparticles), and even organo metallic compound.

Nanoparticles As Anticancer Agents

Contemporary cancer therapy, particularly with respect to drug delivery, has begun an evolution from the traditional methodology. Part of this change is based on the need to increase the therapeutic index of chemotherapy drugs. Although cancer cells are inherently more vulnerable than normal cells to the effect of chemotherapy agents, the drugs are nonselective and can cause injury to normal tissues. Indeed, it is toxicity of normal cells that constrains dose and frequency both important factors in the persistence of cancer cells after completion of chemotherapy treatment. Attempts are now focused on efforts to kill cancer cells by more specific targeting while sparing normal cells. To achieve these goals, the focus is the development of novel carriers for both existing and new drugs and defining better therapeutic targets relative to the molecular changes in the cancer cells, their vasculature, and the related stroma.

Nanoscaled systems for systemic cancer therapy and their latest stage of development. We have included PEG-containing proteins and PEG-conjugated small molecules, which, as single molecules in solution, can be defined as nanoscale therapeutics or as nanoparticles if they have some degree of polymer-polymer interaction to give assembled entities with more than one polymer chain contained within. liposomes (~100 nm and larger) carrying chemotherapeutic small-molecule drugs have been approved for cancer since the mid-1990s, and are mainly used to solubilize drugs, leading to biodistributions that favour higher uptake by the tumour than the free drug. However, liposomes do not provide control for the time of drug release, and in most cases do not achieve effective intracellular delivery of the drug molecules, therefore limiting their potential to be useful against multidrug resistant cancers.

Nanoparticles In Clinical Use

Despite extensive research and development, only a few drug delivery nanoparticles currently are FDA approved and available for cancer treatment. Liposomal anticancer drugs were the first to be approved for therapy in cancer. Two commercial liposomal formulations are available in the United States. These are pegylated liposomal doxorubicin (Doxil in the U.S. and Caelyx outside the U.S.) and liposomal daunorubicin (Dauno Xome). A third liposomal formulation approved in Europe is non pegylated liposomal doxorubicin (Myocet). Adding to this formulary, an albumin-bound paclitaxel nanoparticle Abraxane was recently approved by the FDA for the treatment of breast cancer. The remaining parts of this discussion will focus on those nanoparticles approved and marketed for clinical oncology use.

Advantages of Nanoparticles

1. Entry into tissues at the molecular level.
2. Increased drug localization and cellular uptake.
3. Cancer diagnosis and treatment applications.
4. Feasibility to programme nanoparticles for recognizing cancerous cells.
5. Selective and accurate drug delivery, and avoiding interaction with healthy cells.
6. Direct and selective targeting of the drug to cancerous cells (both active and passive targeting).
7. Larger surface area with modifable optical, electronic, magnetic and biologic properties vis-à vis macroparticles.
8. Assisting therapeutic agents to pass through biologic barriers, mediate molecular interactions and identify molecular changes.

Mechanism of Targeting

Nanoparticles target tumour cells in two ways: active and passive.

Passive Targeting

This term refers to the accumulation of the drug in areas around the tumour with leaky vasculature; it also known as the enhanced permeation and retention (EPR) effect. Nanoparticles that satisfy the size and surface characteristics requirements described above for escaping reticuloendothelial system capture have the ability to circulate for longer times in the bloodstream and a greater chance of reaching the targeted tumor tissues. Fast-growing, hyperproliferative cancer cells show a high metabolic rate, and the supply of oxygen and nutrients is usually not sufficient for them to maintain this. Therefore, tumor cells use glycolysis to obtain extra energy, resulting in an acidic environment.[8] The pH-sensitive liposomes are designed to be stable at a physiologic pH of 7.4 but degraded to release active drug in target tissues in which the pH is less than physiologic values, such as in the acidic environment of tumour cells.

Active Targeting

This term refers to specific interactions between the drug/drug carrier and target cells, usually through specific ligand receptor interactions or antibody-antigen recognition, for intracellular localization of the drug. The EPR effect, a unique characteristic of tumour cells, enables targeted delivery of anticancer agents. Passive targeting is based primarily on size; the nanoparticle surface may be modified with several ligands that would interact with specific receptors over-expressed on the surface of the tumour cells, thus imparting specificity for active targeting. A drug delivery system comprising a binary conjugate (i.e., polymer-drug conjugate) that depends only on passive targeting mechanisms inevitably faces intrinsic limitations to its specificity. One approach suggested to overcome these limitations is the inclusion of a targeting ligand or antibody in polymer-drug conjugates.[9] Initially, direct conjugation of an antibody to a drug was attempted. However, in clinical trials conducted thus far, such early antibody-drug conjugates have failed to show superiority as a targeted delivery tool for the treatment of cancer.[10] One of the reasons for this is that the number of drug molecules that can be loaded on the antibody while preserving its immune recognition is limited.

Type of Nanoparticles Used As Drug Delivery Systems

Nanoparticles applied as drug delivery systems are submicron-sized particles (3-200 nm), devices, or systems that can be made using a variety of materials including polymers (polymeric nanoparticles, micelles, or dendrimers), lipids (liposomes), viruses (viral nanoparticles), and even organometallic compound.

Liposomes

Liposomes are self-assembling closed colloidal structures composed of lipid bilayers and have a spherical shape in which an outer lipid bilayer surrounds a central aqueous space. Liposomes were first produced in England in 1961 by Alec D. Bangham. One end of each molecule is water soluble, while the opposite end is water insoluble. Water-soluble medications added to the water were trapped inside the aggregation of the hydrophobic ends; fat-soluble medications were incorporated into the phospholipid layer as in [**Figure 1**]. Liposomes are self-assembling closed colloidal structures composed of lipid bilayers and have a spherical shape in which an outer lipid bilayer surrounds a central aqueous space. In some cases liposomes attach to cellular membranes and appear to fuse with them, releasing their or drugs into the cell. In the case of phagocytic cells, the liposomes are taken up, the phospholipid walls are acted upon by organelles called lysosomes, and the medication is released. Liposomal delivery systems are still largely experimental; the precise mechanisms of their action in the body are under study, as are ways in which to target them to specific diseased tissues. Liposomes generally reach their site of action by extravasation into the interstitial space from the bloodstream. Intravenously administered liposomes are rapidly cleared by the reticuloendothelial system (RES) after surface coating with protein (opsonization). Additionally, electrostatic, hydrophobic, and van der Waals forces can disintegrate liposomes. Liposomal vesicles release drug at the cell membrane and can access tumor cells at high concentrations compared to their distribution in normal tissues. This strategy of passive targeting reduces toxic side effects to normal tissue, while enhancing the therapeutic index of the delivered drug. Liposomes can target specific tissues through both active and passive targeting strategies. This is because liposomes can easily be manipulated by adding additional molecules to the outer surface of the lipid bilayer. Because liposomes are of the order of 400 nmin size, they are rapidly cleared by the MPS system. Reducing opsonization of liposomes by PEGylation therefore reduces clearance by the MPS, increasing the circulation half-life.

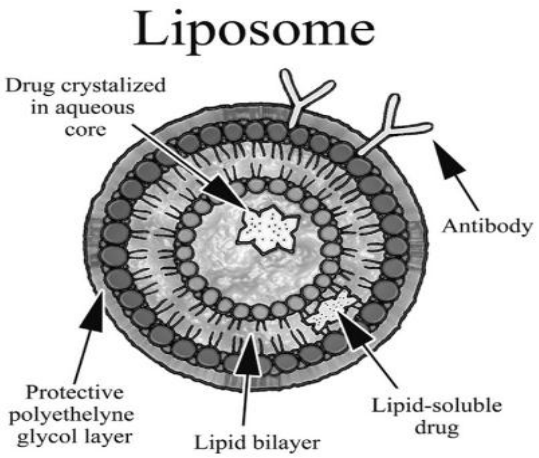

Figure 1: Liposomes.[10]

Opsonization presents such a problem to the development of therapeutically useful liposomes that nearly all research reported in the literature involves PEG-coated or PEGylated liposomes. Liposomal formulations of anticancer drugs have already been approved for human use. Doxil1 is a liposomal formulation of the anthracycline drug doxorubicin used to treat cancer in AIDS-related Kaposi sarcoma and multiple myeloma.[11] Its advantages over free doxorubicin are greater efficacy and lower cardiotoxicity. One of the most interesting developments in this field is the potential of liposomes to combat the increasing problem of multidrug resistance (MDR) acquired by cancers, which drastically reduces chemotherapeutic efficacy.

Proposed mechanisms underlying MDR at the cellular level include

1. Increased metabolism of drugs due to increased enzyme expression, especially of glutathione S-transferase.
2. Drug transporters and efflux proteins.[12]

3. Point mutations in proteins that are therapeutic or drug targets.

Recently investigated the effect of PEG liposomal doxorubicin (Doxil1) in a male mouse tumour model inoculated with either colon cancer (C26) cells or their doxorubicin-resistant (MDR) subclone, which overexpresses P-gp efflux pumps.[13] The results showed that PEG liposomal doxorubicin had anti-tumour effects on both doxorubicin-resistant and non-doxorubicin-resistant C26 cells. With increasing incidence of resistance to chemotherapy, the use of liposomes offers effective treatment without the need for the costly discovery of new chemotherapeutic drugs because current drugs can be reformulated.

Types Of Liposomes

Liposomes can be classified by different factors. They can be classified by the method of their preparation, the number of bilayers present within the liposome vesicle, or the vesicle size.

However, the most commonly known classes of liposomes are multilamellar vesicles (MLVs) and unilamellar vesicles (ULVs), which can be further classified into large unilamellar vesicles (LUVs) and small unilamellar vesicles (SUVs). These liposome types are discussed in further detail below.

1. Multilamellar Vesicles

The simplest and the most popular method for the preparation of MLVs is thin film hydration. In this method, MLVs can be formed spontaneously by adding an excess volume of aqueous buffer to a thin film of dry lipids at a temperature above the phase transition temperature (PTT) of lipids. For thin film hydration, the desired drug to be encapsulated within MLVs can either be included in the aqueous hydration buffer for hydrophilic drugs or in the lipid film for lipophilic drugs [14]. Although it is easy to prepare MLVs using thin film hydration, such a method provides relatively poor drug encapsulation efficiency (5–15%).[14] In the preparation of MLVs using thin film hydration, a thin film of lipids is preferred because this enhances the encapsulation efficiency of drug. The time allowed for the hydration of lipid film with aqueous or drug solution also influences the amount of drug trapped within liposomal vesicles.

2. Large Unilamellar Vesicles[15]

LUVs are liposomal vesicles consisting of a single phospholipid bilayer and are considered to be of a size greater than 100 nm. However, the size range of LUVs is debatable, because some investigators previously described unilamellar vesicles in a size range of 50–100 nm as LUVs. Unlike MLVs, LUVs have the ability to hold a larger volume of solution within their cavity. In the reverse-phase evaporation technique, a waterin-oil (w/o) emulsion is formed between water and phospholipids in an excess of organic solvent by mechanical means or by sonication. When the organic solvent is removed from the mixture under vacuum, phospholipid droplets containing water are formed. These droplets come together to form a gel-like matrix, which transforms into a smooth paste of LUV suspension once the organic solvent is completely removed. The reverse phase evaporation technique has been reported to allow a drug encapsulation efficiency of up to 60–65% to be achieved. In the detergent removal technique, the detergent can be removed by different methods, such as dialysis, column chromatography, or adsorption using Bio-Beads. In this technique, the detergent is allowed to flow through a dialysis cell from a phosphor lipid detergent mixture, resulting in a homogeneous population of single bilayer liposome vesicles ranging in size between 50 and 100 nm in diameter. This allowed the detergent to bind to Bio-Beads selectively and rapidly, separating phospholipid vesicles from the detergent. However, a nonionic detergent must be used in this method.

3. Small Unilamellar Vesicles.[16,17,18]

SUVs are usually found with diameters ranging between 25 and 50 nm. They can be prepared from MLVs or LUVs using sonication or extrusion under high pressure. In the preparation of SUVs using sonication, the MLVs or LUVs suspension is sonicated under nitrogen or argon gas to reduce the size of the vesicles to the SUV size range. Both types of sonication, namely a bath or a probe sonicator, can be used to generate SUVs. However, bath sonication offers advantages over probe sonication, because the preparation of SUVs can be performed aseptically with sealed containers and the temperature can be controlled throughout the preparation. The characterization of SUVs generated by sonication has previously demonstrated that this method is able to synthesize liposomes with sizes ranging between 25 and 50 nm.

This technique allows for the reproducible production of SUVs. However, the temperature of the preparation cannot be accurately controlled using this technique, resulting in temperature fluxes during preparation that can affect phospholipid packing within the liposome. In addition, SUVs can also be prepared directly by the solvent injection method using diethyl ether or ethanol. In general, using this method, lipids dissolved in an organic solvent are injected into an excess amount of aqueous solution or water by a syringe-type infusion pump, forming SUVs spontaneously. The organic solvent is then removed from the preparation completely. This method has been reported to produce SUVs with sizes between 50 and 200 nm. Similar to other liposome preparations, it is almost impossible to completely remove organic solvents from the preparations when using this technique.

Liposomal And Targeted Drug Delivery System

Drug delivery systems can in principle provide enhanced efficacy and/or reduced toxicity for anticancer agents. Long circulating macromolecular carriers such as

liposomes can exploit the 'enhanced permeability and retention' effect for preferential extravasation from tumor vessels.[19] Liposomal anthracyclines have achieved highly efficient drug encapsulation, resulting in significant anticancer activity with reduced cardiotoxicity, and include versions with greatly prolonged circulation such as liposomal daunorubicin and pegylated liposomal doxorubicin. Pegylated liposomal doxorubucin has shown substantial efficacy in breast cancer treatment both as monotherapy and in combination with other chemotherapeutics. Additional liposome constructs are being developed for the delivery of other drugs.

The next generation of delivery systems will include true molecular targeting; immunoliposomes and other ligand-directed constructs represent an integration of biological components capable of tumor recognition with delivery technologies.[20] As discussed, currently approved liposomal drug delivery systems provide stable formulation, provide improved pharmacokinetics, and a degree of 'passive' or 'physiological' targeting to tumor tissue.[21] However, these carriers do not directly target tumor cells. The design modifications that protect liposomes from undesirable interactions with plasma proteins and cell membranes, and which contrast them with reactive carriers such as cationic liposomes, also prevent interactions with tumor cells. Instead, after extravasation into tumor tissue, liposomes remain within tumor stroma as a drug-loaded depot. Liposomes eventually become subject to enzymatic degradation and/or phagocytic attack, leading to release of drug for subsequent diffusion to tumor cells. The next generation of drug carriers under development features direct molecular targeting of cancer cells via antibody-mediated or other ligand-mediated interactions. Immunoliposomes, in which mAb fragments are conjugated to liposomes, represent a strategy for molecularly targeted drug delivery. Anti-HER2 immunoliposomes have been developed with either Fab' or scFv fragments linked to long-circulating liposomes. In preclinical studies, anti-HER2 immunoliposomes bound efficiently to and internalized in HER2-overexpressing cells, resulting in efficient intracellular delivery of encapsulated agents. Anti-HER2 immunoliposomes loaded with doxorubicin displayed potent and selective anticancer activity against HER2-overexpressing tumors, including significantly superior efficacy versus all other treatments tested (free doxorubicin, liposomal doxorubicin, free mAb [trastuzumab], and combinations of trastuzumab plus doxorubicin or liposomal doxorubicin). Anti-HER2 immunoliposomes are currently undergoing scale up for clinical studies. The immunoliposome approach offers a number of theoretical advantages as compared with other antibody-based strategies. Anti-HER2 immunoliposome delivery of doxorubicin may circumvent the prohibitive cardiotoxicity associated with combined trastuzumab plus doxorubicin treatment. Anti-HER2 immunoliposomes can be constructed using scFv that, unlike trastuzumab, lack antiproliferative activity, are incapable of antibody-dependent cellular cytotoxicity, and require threshold levels of HER2 expression for delivery. In contrast to drug immunoconjugates, which consist of a small number of drugs (typically <10 drugs per mAb) directly coupled via linkers to selected residues on the mAb, immunoliposomes exploit the exponentially greater capacity of drug-loaded liposomes (up to 104 drugs per liposome). Immunoliposomes also appear to be nonimmunogenic and capable of long circulation even with repeated administration.[22]

Antibody-based targeting is also being developed in conjunction with polymer systems. Similarly, ligand-based targeting using growth factors, hormones, vitamins (e.g., folate), peptides or other specific ligands is being pursued in conjunction with both liposomes and polymers. Liposomes are concentric bilayered structures made of amphipathic phospholipids and depending on the number of bilayer, liposomes are classified as multilamellar (MLV), small unilamellar (SUVs), or large unilamellar (LUVs). They range in size from 0.025-10 μ in diameter. The size and morphology of liposomes are regulated by the method of preparation and composition. Liposomes are used for delivery of drugs, vaccines, and genes for a variety of disorders.

Liposomal Anthracyclines

The available liposomal formulations represent encapsulated anthracyclines doxorubicin in Doxil and Myocet and daunorubicin in DaunoXome. While anthracyclines are highly active cytotoxic drugs, they have significant toxicity associated with their use both acute and cumulative. High peak plasma concentrations of anthracycline are associated with risk for congestive cardiomyopathy as is the lifetime cumulative dose of the drugs. By liposomal encapsulation, the anthracycline pharmacokinetics are altered and cardiac risk is decreased, but not eliminated. Additionally, anthracycline toxicity to normal tissue, including alopecia and myelosuppression, are reduced by liposomal encapsulation.

CONCLUSIONS

In the future, nanoparticle technology and development for cancer chemotherapy delivery will continue to expand. Nanoparticles provide opportunities for designing and tuning properties that are not possible with other types of therapeutics, and as more clinical data become available the nanoparticle approach should improve further as the optimal properties are elucidated.[23] Liposomes and NPs are promising candidates for the development of drug delivery systems. Early experimental evidence, both clinically and preclinically, shows great potential for the widespread adoption of liposomes and NPs in cancer treatment. Their attractive properties include biocompatibility, low toxicity, lower clearance rates, the ability to target specific tissues and controlled release of drugs. They

offer numerous advantages over conventional chemotherapy using free drug treatment, as evidenced by the approval of Abraxane1 and Doxil.[24] Both of these nanomaterial-based formulations of existing drugs offer better pharmacokinetic properties and lower systemic toxicity of the chemotherapeutic drugs that they deliver. However, the full potential of these emerging technologies has not yet been fully realized. The toxicology of nanomaterials in humans still needs to be fully studied and evaluated. Studies so far have been small and limited to short-term exposure; few have looked at the wider impact. Investigation into so-called nanotoxicity should focus on long-term exposure in humans, animals and the environment. Further in vivo studies are needed to determine the efficacy of these new drug formulations, culminating in phase I trials.[25] The reproducibility of batches of drug formulations such as liposomes and NPs also needs to be refined. The next generation of liposomal drugs may be immunoliposomes, which selectively deliver the drug to the desired sites of action.[26] While oncology therapeutic drug delivery has been the focus of this discussion, nanoparticles have many more capabilities including uses in imaging and sensing, diagnosis, targeting, radiotherapy, and transport of genetic material.[27,28] Liposomes and NPs are just beginning to make an impact in chemotherapy owing to the dual drive to reduce the toxicity and side effects of existing treatments and increase efficacy by selective targeting of tumours.[29,30]

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