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Novel Approaches in vesicular drug delivery systems

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ABSTRACT

Vesicular drug delivery system is one of the most promising particulate Drug carrier systems in the large family of pharmaceutical nanocarriers. Drug carriers are substances that serve as mechanisms to improve the delivery and effectiveness of drugs to the target sites of pharmacological actions. The application of vesicular system in drug delivery has changed the definitions of diagnosis and treatment in different aspects of biomedical field. Vesicular system is used as vehicle for wide variety of drugs, vaccines, enzymes, and genetic materials and now for some nutritional supplements as well. This review will focus on need for development of Vesicular system as there are some major drawbacks in present conventional dosage forms and Liposomal dosage form and its different modified forms, which are the most successful vesicular system.

Keywords: vasicular, novel, drug, delivery

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INTRODUCTION

The main reasons for development of vesicular system are major draw backs in traditional drug delivery system such as oral dosage forms of tablets, capsules and intravascular injections.

The main drawback of traditional system is, the drug is released from the dosage forms at the site of application, not at the site of action. Moreover, after absorption, the drug is distributed throughout the body through systemic blood circulation. Because of this, in most therapeutic drugs, only a small portion of the medication reaches the diseased part of the body. Hence, more doses and more frequency of administration are required to achieve the desired amount of drug at the diseased part of the body that may be particular organ or cell. As we can say overall, we can say, traditional dosage forms gives very less beneficial effects and more side effects.

The clinical utility of most traditional dosage form is limited either by the inability to deliver therapeutic concentration of drug to the target site or by severe and harmful toxic effects on normal organs and tissues. Hence in order to overcome this problem, we need controlled and targeted administration of therapeutic drug.

Targeted release system

It helps to avoid any damage to the healthy tissues via drug. The advantages of targeted release system are reduction in the frequency of the dosages taken by the patient, having a more uniform effect of drug, reduction of drug side effects and reduced fluctuation in circulating drug levels [1].

However, there are few significant challenges in targeting drugs.

They are drugs may undergo breakdown before they reach their target tissues and drugs may have poor pharmacokinetics or distribution or may unintentionally damage healthy tissues.

In this context, targeting plays a major role in pharmacological effectiveness of drug. The site of targeting is mainly depends on the nature of diseases. It may be first order targeting, i.e. compartmental targeting to the organs like liver, lung and heart or second order targeting i.e. targeting to the particular type of cells in the organ or third order targeting i.e. targeting to intra cellular components.

The two main objectives of making targeted and non-immediate release delivery system are spatial placement and temporal delivery of a drug [2].

Spatial placement relates to targeting of a drug to a specific organ or tissue, while temporal delivery refers to controlling the rate of drug delivery to the target tissue. These objectives can be fulfilled only by the selection of suitable carrier.

To bring out the 100 % pharmacological activity without any side effects of drug from the dosage form, we need proper carrier for each drug to attain specific order of targeting.

However, Selection of Suitable carrier is important. Because the carrier should carry the drug in the blood circulation without any interactions, damage or leakage until it reaches the target site. So selection of suitable carrier based on the physiochemical properties of drug is very important process.

An ideal drug carrier must be non-toxic, biocompatible, non-immunogenic, biodegradable and avoid recognition by the host defense mechanism and also able to cross anatomical barriers, Recognized specifically and selectively by the target cells and it should be stable in plasma & other biofluids.

Vesicular System

There are many vesicular system are under investigation. Among several promising vesicular Carrier systems, liposomes represent an advanced technology especially in the treatment of chronic diseases. Currently there are about 13 liposome-based drugs approved for clinical use and more are in various stages of clinical trials.

Liposomes consist of one or more concentric lipid bilayers which enclose an internal aqueous volume [3]. FDA considers liposomal drugs to be the products in which an active drug is encapsulated in or complexes with lipids and have capacity to alter the biodistribution of drugs and its pharmacokinetic behavior of drug in the body through delayed clearance and longer intravascular circulation time. Liposomes are micro particulate carriers of manmade cells, which form spontaneously when certain lipids are hydrated in aqueous media. The particle size of liposomes ranges from 20nm to 10 μ m in diameter. The two main ingredients are phospholipids and cholesterol. The phospholipids which form the lipid bilayers along with cholesterol which is often included in the liposome formulation to give further rigidity to the bilayer that may improve in-vitro and in-vivo stability of liposomes.

Over the past few decades, liposomes have received widespread attention as a carrier system for therapeutically active compounds, due to their unique characteristics such as capability to incorporate hydrophilic and hydrophobic drugs, good biocompatibility, low toxicity, lack of immune system activation, and targeted delivery of bioactive compounds to the site of action. Although they were first described in 1960's only at the beginning of 1990's did the first therapeutic liposomes appear on the market. Liposomes are the leading drug delivery systems for the systemic (intravenous) administration of drugs. There are now liposomal formulations of conventional drugs that have received clinical approval and many others in clinical trials that bring benefits of reduced toxicity and enhanced efficacy for the treatment of cancer and other life-threatening diseases [4].

Also, Liposomes can be formulated as a suspension, as an aerosol, or in a semisolid form such as gel, cream and lotion, as a dry vesicular powder (proliposome) for reconstitution and

they can be administered through most routes of administration including ocular, pulmonary, nasal, oral, intramuscular, subcutaneous, topical and intravenous.

Liposomes are biphasic a feature that renders them the ability to act as carriers for both lipophilic and hydrophilic drugs. Lipophilic drugs are generally entrapped almost completely in the lipid bilayers of liposomes and Hydrophilic drugs may either be entrapped inside the aqueous cores of liposomes or be located in the external water phase. Liposomes have been proved as suitable vehicles for selective drug delivery and controlled drug release. Liposomes help to avoid the problems in Therapeutic index, metabolism, pharmacokinetics, solubility, stability of many drugs [5].

Clinical Application of Liposomes

Regarding the clinical applications, liposome drug delivery systems have played a significant role in reformulation of potent drugs to improve their therapeutics in the treatment of various diseases such as cancer, tumor, infectious diseases, liver diseases, lung diseases and systemic inflammatory diseases.

In-vivo Release of Drug from the Liposomes

There are several mechanisms involved in the drug release from liposomes. The major mechanisms are passive diffusion, fusion, adsorption and vesicle erosion.

In passive diffusion, the encapsulated drug molecules penetrate a series of bilayers in a gradient to reach the extravascular layer, then to the circulating blood plasma. The permeability of drug from liposome is altered by the addition of cholesterol.

In another mechanism of adsorption, the liposomes are adsorbed on the cell surface either as a result of physical attractive forces or as a result of binding by specific receptors to ligands on the vesicle membrane [6].

In fusion, close approach of liposomes and cell membrane can lead to fusion of the two, resulting in complete mixing of liposomal contents in to the cytoplasm. Fusion between liposome and bacterial cell also takes place in order to get anti-bacterial activity of drugs.

In the next mechanisms of vesicle rupture or erosion, phospholipases and lipoproteins present in blood plasma can attack and compromise vesicle integrity, gradually exposing the drug entrapped in the interbilayer spaces.

In the endocytosis, the liposome is engulfed by phagocytic cells and the lysozyme present in the cytoplasm degrades or digests the membrane structure of liposomes, there by releasing the entrapped material in to the medium.

Hence, the predominant mechanism behind the intracellular delivery of drugs by liposomes may mainly depend on their composition and size. On the basis of their size and number of bilayers, liposomes can also be classified in to three categories. They are multilamellar vesicles, large unilamellar vesicles and small unilamellar vesicles [7].

There are many Factors controlling the fate of liposomes in-vivo after intravenous administration [8]. The major factors are Size and type of the liposomes, Charge of the bilayer, Rigidity of the bilayer and Route of administration.

Liposomes-based technology has progressed from the first generation 'conventional vesicles' to stealth liposomes, targeted liposomes and gene-based liposomes. There are four kinds of liposomes, each with its own advantages and disadvantages. All of them consist of lipid bilayer that encapsulates a payload of therapeutic molecules. All of them bypass the digestive tract, thus increasing the bioavailability of their payloads, which remain biologically inert until the cell membrane ruptures. When and where that occurs and why and how it occurs is what makes the difference. It depends on many different physical and chemical properties of the liposome and on the physiological environment in which they find themselves.

Conventional liposome formulations

Regarding the Conventional liposome formulations, they are mainly comprised of natural Phospholipids [9].

Since conventional liposomes are made-up of phospholipids only, they have encountered one major challenge, i.e., low blood circulation half-life due to their fast removal from blood circulation by components of the RES through phagocytic action. The removal of liposomes is carried out by the mononuclear phagocyte system (MPS), in particular the resident macrophages of the liver (Kupffer cells), spleen, lung and bone marrow. The bulk of the injected liposomes accumulate in the liver and spleen. That phagocytosis of liposomes was due to the size of the liposome formulation. Larger size or multilamellar liposomes with a size range of 500–5000 nm were the first to be eliminated from the systemic circulation. Nanosized liposomes or small unilamellar vesicles with a size range of 20–50 nm were only developed later. In order to overcome this problem, stealth liposomes technology was developed. This strategy was developed to overcome most of the challenges encountered by conventional liposome technology such as the inability to evade interception by the immune system, toxicity due to charged liposomes, and low blood circulation half-life.

Stealth liposome

Stealth liposome strategy was achieved simply by modifying the surface of the liposome membrane, through pegylation [10]. Pegylation means, Coating of the liposomal surface with polyethylene glycol would suppress the uptake of the drug by the reticuloendothelial system, thereby prolonging the biological half life of drug in the plasma. It is specifically employed to increase the hydrophilicity of the liposome surface via a cross-linked lipid mainly by using

Polyethylene glycol. So that prominent results were achieved from this model such as reduction of macrophage uptake and long circulation time.

PEGylated liposomal doxorubicin (DOXIL/Caelyx) is the only example of stealth liposome technology to be approved by both the USA Food and Drug Administration (FDA) and Europe Federation.

Although prominent results were achieved from this model such as reduction of macrophage uptake, long circulation, and low toxicity. Passive targeting is still a major disadvantage since liposomes can deliver active molecules not only to abnormal cells but also to sensitive normal cells. Since liposome can deliver active molecules not only to abnormal cells but also to sensitive normal cells. In order to overcome this problem targeted liposome based system was suggested.

Targeted liposomes :

Targeted liposomes can be categorized as either immunoliposomes or ligand-targeted liposomes [11].

The two main strategies in developing targeted liposomes are the attachment of a monoclonal antibody (mAb) (i.e., immunoliposomes) or the attachment of a tissue-specific ligand to the surface of the liposomes. Immunoliposomes have specific antibodies or antibody fragments on their surface to enhance binding to target site. Targeted delivery to cancer cells can be achieved by coating monoclonal antibodies raised against tumor-cell specific antigens either aberrantly expressed tumor associated antigens or over expressed antigens. To utilize cell surface molecules as tumor recognition targets for immunoliposomal therapy, a variety of monoclonal antibodies against selected cell surface molecules have been developed. The preparation of tumor –specific antibodies remains the most critical requirement in the development and clinical application of immunoliposomal drug targeted to tumors.

It has been postulated that ligands can be conjugated on to pegylated liposomes via different types of coupling methods, such as covalent and noncovalent binding.

Attachment of a tissue-specific ligand to the surface of the liposomes can increase specificity and reduce undesired transfection. Peptides, protein and antibodies are used as ligands. So far used tumor-specific ligands are folate, transferrin or carbohydrates coupled to conventional or stealth liposomes to attain a specific tumor targeting.

Targeted ligands can further increase the rate of liposomal drug accumulation in the ideal tissues/cells via over expressed receptors, and antigen. Cationic liposomes are widely used in gene therapy as a safe alternative to highly immunogenic viral vectors.

CONCLUSION

To summarize we can say, various approaches are being undertaken to enhance the bioavailability and tissue targeting ability. Among them conventional liposomes will be useful for enhance the pharmacological activity at the target site especially in Reticuloendothelial system, and pegylated or stealth liposomal products can give more retention time and effective targeting in RES and non-RES also. Immunoliposomal product will be useful for enhance the pharmacological activity at the tumor site and specific cancer cells. Commercial introduction of the various liposomal formulations represents a milestone in the history of liposomal drug delivery. Many more liposome-based drug formulations can be expected in the near future. With the recent development in the field, several companies are already actively engaged in expansion and evaluation of liposome products for anticancer, antifungal therapy and for prophylaxis.

The future of drug therapeutics may not only lie in the development of new chemical entities but also in the modification of the existing drug molecules using suitable carriers to eliminate toxicity and improve activity with the principle of new lives for old drugs.

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