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REVIEW ARTICLE

ADVANCED AND ROBUST TECHNIQUES OF DRUG DELIVERY: A CRITICAL REVIEW

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Abstract

Drug delivery plays an important role on its efficacy. Some drugs have an optimum concentration range within which maximum benefit is derived and concentration above (or) below the range can be toxic or produce no therapeutic effect. On the other hand, the very slow progress in the efficacy of the treatment of severe diseases, has suggested a growing need for a multidisciplinary approach to the delivery of therapeutics to targets in tissues. The main goal for developing such delivery systems is to minimize drug degradation and loss, to prevent harmful side-effects and to increase drug bioavailability and the fraction of the drug accumulated in the required zone. Targeting is the ability to direct the drug loaded system to the site of interest. Two major mechanisms can be distinguished for addressing the desired sites for drug release; (a) active targeting and (b) passive targeting. Drug carrier systems such as micellar solutions, vesicle and liquid crystal dispersions, as well as nanoparticle dispersions consisting of small particles of 10–400 nm diameter show great promise as drug delivery systems.

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Introduction

The aim of Novel Drug Delivery System is to provide a therapeutic amount of drug to the appropriate site in the body to accomplish promptly and then maintain the desired drug concentration. The drug- delivery system should deliver drug at a rate control by the necessity of the body over a specified term of treatment[1]. Novel drug delivery system is a novel approach to drug delivery that addresses the limitations of the traditional drug delivery systems[2]. Novel drug delivery systems present an opportunity for formulation scientists to overcome many challenges associated with antihypertensive drug therapy, antiretroviral drug therapy, chemotherapy and many more drug therapies, thereby improving the management of patients with hypertension, HIV, cancer etc[3,4,5].

On the other hand, very slow progress in the treatment of severe diseases has suggested a need for a multidisciplinary approach to delivery of therapeutics to targeted tissues, new ideas on controlling the pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, bio-recognition and efficacy of drugs were generated from the above. These new strategies, often called novel drug delivery systems (NDDS), are based on interdisciplinary approaches that combine polymer science, pharmaceutics, bioconjugate chemistry and molecular biology[6]. Novel drug delivery systems are based on physical and on biochemical mechanisms. Physical

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mechanisms also referred as controlled drug delivery systems includes osmosis, diffusion, erosion, dissolution, electro transport. While biochemical mechanisms include monoclonal antibodies, gene therapy, and vector systems, polymer drug adducts and liposomes[7].

Type of New Drug Carrier Systems

There has been a focus on the microenvironment of the cells and their interaction with these carriers[8]. As a result, these new technologies have prompted the old concept of the magic bullet proposed by Paul Ehrlich's vision[9]. Some of the drug carrier systems and their advantages are mentioned as follows:

a) Liposomes

Phospholipid vesicles (liposomes) were first described decades ago by Bangham et al. It has been shown that phospholipids spontaneously form closed structures when they are hydrated in aqueous solutions. On the basis of the ability of liposomes to interact with cells and/or blood components, at least two types of liposomes currently can be designed including: (i) non-interactive sterically stabilized (long-circulating) liposomes (LCL) and; (ii) highly interactive cationic liposomes[10]. Use of liposome-encapsulated enzymes for delivery into cells was first reported in 1971. At the same time, a specific receptor on hepatocytes was demonstrated to mediate clearance of β -galactose-terminated glycoproteins from circulation. Grafting specific ligands to the liposome surface facilitates a fusion of the liposome with target cells by endocytosis, thus releasing material to be delivered. In cancer chemotherapy, the toxicity of anticancer drugs is of major concern. Liposomes could be used to deliver such drugs and minimize their toxic effects on healthy cells. Targeted delivery to cancer cells could be achieved by coating monoclonal antibodies (MAbs) raised against tumor-cell specific antigens[11].

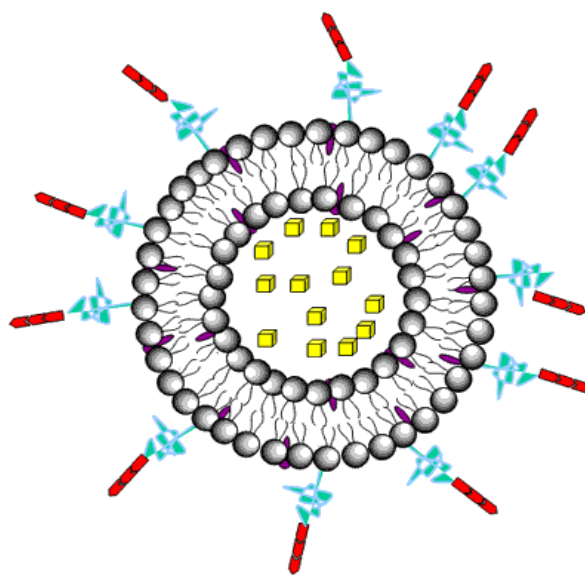


Fig 1:- Drug encapsulation in liposomes[12].

Because of the small size of the phospholipid molecule and microspheres, they can pass through the epidermis and act as a carrier for the enclosed substances. It is postulated that when they reach the outside of a living cell membrane in the dermis they may become accepted as part of the membrane, being of the same composition[13].

Advantages

Advantages of using liposomes in NDDS are as follows:

1. Provides selective passive targeting to tumor tissues (Liposomal doxorubicin).
2. Increased efficacy and therapeutic index.
3. Increased stability via encapsulation.
4. Reduction in toxicity of the encapsulated agents.
5. Site avoidance effect.
6. Improved pharmacokinetic effects (reduced elimination, increased circulation life times).
7. Flexibility to couple with site specific ligands to achieve active targeting[14].

b) Niosomes

In niosomes, the vesicles forming amphiphile is a non-ionic surfactant such as Span – 60 which is usually stabilized by addition of cholesterol and small amount of anionic surfactant such as dicetyl phosphate[15].

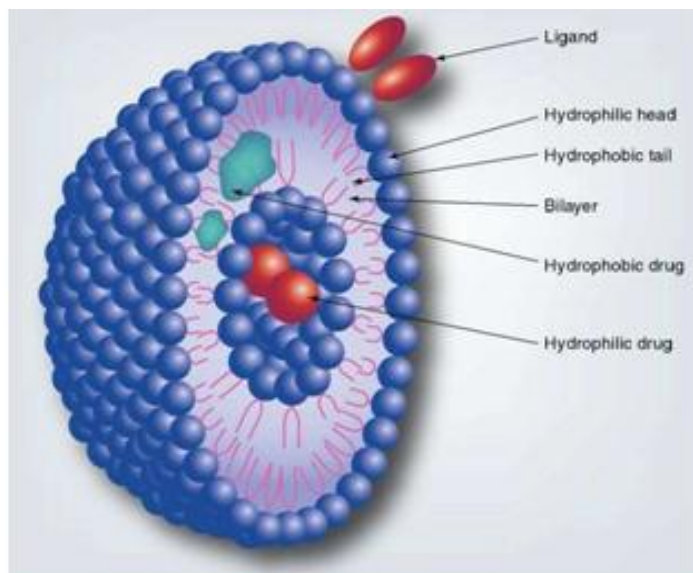


Fig 2:- Structure of Niosome[16].

Niosomes containing anti-cancer drugs, if suitably designed, will be expected to accumulate within tumors in a similar manner to liposomes. The niosomal encapsulation of Methotrexate and Doxorubicin increases drug delivery to the tumor and tumoricidal activity of the drug[17]. Niosomes and liposomes are equiactive in drug delivery potential and both increase drug efficacy as compared with that of free drug. Niosomes are preferred over liposomes because the former exhibit high chemical stability and economy[18].

Advantages

Advantages of using niosomes in NDDS are as follows:

1. They improve the therapeutic performance of the drug molecules by delayed clearance from the circulation, protecting the drug from biological environment and restricting effects to target cells.
2. They are osmotically active and stable, as well as they increase the stability of entrapped drug.
3. Handling and storage of surfactants requires no special conditions.
4. They improve oral bioavailability of poorly absorbed drugs and enhance skin penetration of drugs.
5. They can be made to reach the site of action by oral, parenteral as well as topical routes.
6. They possess an infrastructure consisting of hydrophilic, amphiphilic and lipophilic moieties together and as a result can accommodate drug molecules with a wide range of solubilities.
7. The vesicles may act as a depot, releasing the drug in a controlled manner[19].

c) Hydrogels

Hydrogels are three-dimensional, hydrophilic, polymeric networks capable of imbibing large amount of water or biological fluid. The networks are composed of homopolymers or copolymers, and are insoluble due to presence of chemical or physical cross-linkages. Several terms have been coined for hydrogels, such as 'intelligent gels' or 'smart hydrogels'[20]. Hydrogels are 'smart' or 'intelligent' in the sense that they can perceive the prevailing stimuli and respond by exhibiting changes in their physical or chemical behaviour, resulting in the release of entrapped drug in a controlled manner[21].

Advantages

Advantages of using hydrogels in NDDS are as follows:

1. Sustained and prolonged action in comparison to conventional drug delivery systems
2. Decreased dose of administration.
3. Decreased side-effects.
4. Improved drug utilization.

5. Improved patient compliance.
6. Drug targeting to specific site like colon.
7. Protection of mucosa from irritating drugs.
8. Drug loss is prevented by extensive first pass metabolism.
9. Lower daily cost to patient due to fewer dosage units are required by the patient in therapy.
10. Drug adapts to suit circadian rhythms of body functions or diseases[22].

d) Nanoparticles

Nanoparticles are defined as particulate dispersions or solid particles with a size in the range of 10-1000nm. The drug dissolved, entrapped, encapsulated or attached to a nanoparticles matrix. Depending upon to the method of preparation, nanoparticles, nanospheres or nanocapsules can be obtained[23].

In recent years, biodegradable polymeric nanoparticles have attracted considerable attention as potential drug delivery devices in view of their applications in the controlled release of drugs, in targeting particular organs/tissues, as carriers of DNA in gene therapy, and in their ability to deliver proteins, peptides and genes through the peroral route[24,25].

Advantages

Advantages of using nanoparticles in NDDS are as follows:

1. Nanoparticulate system delivers the formulation directly to the site of action.
2. Increased efficacy and therapeutic index.
3. Increased stability via encapsulation.
4. Improved pharmacokinetic effect.
5. Producing with various sizes, compound surface properties[26].

e) Phytosomes

Phytosomes are herbal products that are better absorbed, utilized and as a result produce better results than conventional extracts. The bioavailability of some orally administered botanical extracts is erratic and poor gastrointestinal adsorption. Bioavailability of these botanical extracts can be modified or improved using suitable delivery systems which can enhance the rate and extent of solubilization into aqueous intestinal fluids and the ability to cross bio-membrane[27].

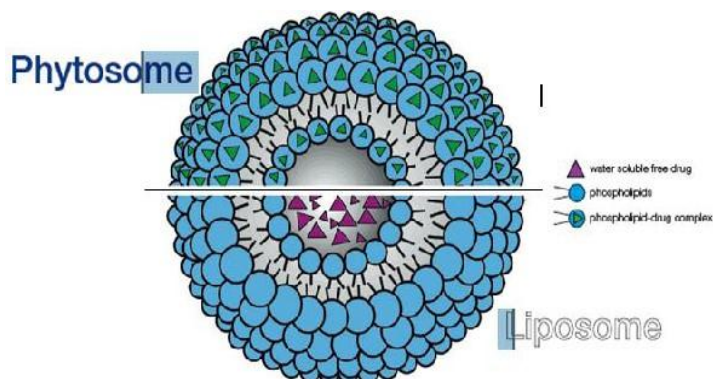


Fig. 3:- Difference between Phytosome and Liposome[28].

They have improved pharmacokinetic and pharmacological parameters in the treatment of crohn's disease, pharmaceutical products and in cosmetics[29].

Advantages

Advantages of using phytosomes in NDDS are as follows:

1. Increased bioavailability due to phospholipid complex.
2. Improved absorption in GIT.
3. Increased bioavailability causes improved therapeutic effect.
4. Less dose requirement due to high bioavailability.

5. Higher stability.
6. High lipophilicity causes high penetrability, henceforth used in cosmetics over liposomes.
7. Greater clinical benefits.
8. Phosphatidylcholine acts as liver protective other than a carrier[30].

f) Dendrimers

The term "dendrimer" is derived from the Greek words dendron, meaning tree and meros, meaning part. Dendrimers were introduced in 1980's by Donald A. Tomalia. In a dendrimer, the branches are interlinked polymerized chains of molecules, each of which generates new chains, all of which converge to a single focal point or core. Dendrimers are repeatedly branched roughly spherical large molecules and possess well defined chemical structures[31].

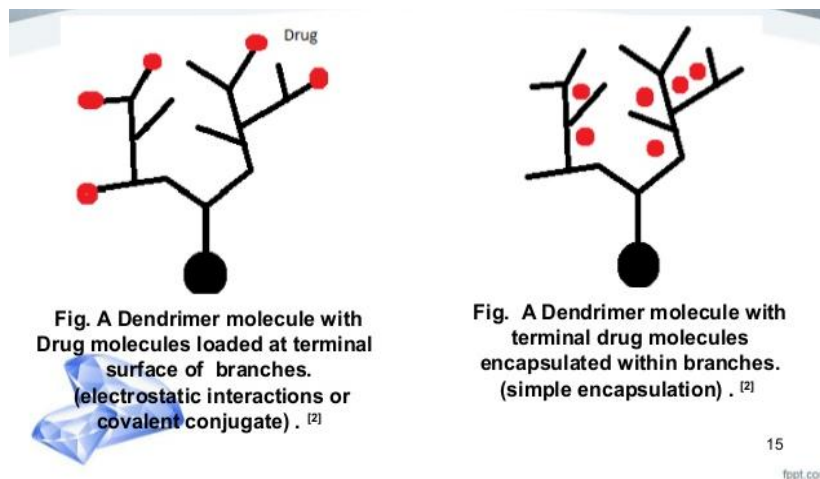


Fig.4:- Dendrimer in Drug Delivery[32].

Dendrimer have the 3-D highly branched structure, thus availability of many functional groups at the surface. The drug may bind to the interior of dendrimer and thus encapsulating the drug within the dendritic structure or the drug may bind to the surface via functional group i.e. covalent bonding. Hence providing targeted as well as controlled delivery of drugs[33].

Advantages

Advantages of using dendrimers in NDDS are as follows:

1. Provide medication to the affected part inside a patient's body directly.
2. Reduce systemic toxicity.
3. Controlled and sustained release of drugs can also be obtained.
4. Drugs can be easily made to remain within layers of skin and not penetrate in systemic circulation.
5. Bypassing the gastric medium and hence the eschewing the variation due to effect of gastric secretions.
6. Increase in therapeutic efficacy, decrease in side effects.
7. Relatively high drug loading[34].

g) Drug Loaded Erythrocytes

Carrier erythrocytes are prepared by collecting blood sample from the organism of interest and separating erythrocytes from plasma. By using various physical and chemical methods the cells are broken and the drug is entrapped into the erythrocytes, finally they are resealed and the resultant carriers are then called "resealed erythrocytes". Surface modification with glutaraldehyde, antibodies, carbohydrates like sialic acid and biotinylation of loaded erythrocytes (biotinylated erythrocytes) is possible to improve their target specificity and to increase their circulation half-life[35].

Advantages

Advantages of using drug loaded erythrocytes in NDDS are as follows:

1. Biocompatible, particularly when autologous cells are used hence no possibility of triggered immune response.

2. Biodegradability with no generation of toxic products.
3. Considerable uniform size and shape of carrier.
4. Relatively inert intracellular environment can be encapsulated in a small volume of cells.
5. Isolation is easy and large amount of drug can be loaded.
6. Prevention of degradation of the loaded drug from inactivation by endogenous chemical.
7. Entrapment of wide variety of chemicals can be possible.
8. Entrapment of drug can be possible without chemical modification of the substance to be entrapped.
9. Possible to maintain steady-state plasma concentration, decrease fluctuation in concentration.
10. Protection of the organism against toxic effect of drug.
11. Ideal zero-order drug release kinetic.
12. Prolong the systemic activity of drug by residing for a longer time in the body[36].

Techniques

a) Microencapsulation

Microencapsulation has been important to the development of new therapeutics and has been used to produce microspheres containing both hydrophilic and hydrophobic drugs entrapped within biocompatible polymers. The purpose of using these carriers is to obtain a controlled release thus maintaining therapeutic drug levels over a specified time period while reducing systemic absorption[37].

Advantages

Advantages of using microencapsulation technique in NDDS are as follows:

1. Reliable means to deliver the drug to the target site with specificity, if modified, and to maintain the desired concentration at the site of interest without untoward effects.
2. Solid biodegradable microspheres have the potential throughout the particle matrix for the controlled release of drug.
3. Microspheres received much attention not only for prolonged release, but also for targeting of anticancer drugs to the tumour[38].
4. The size, surface charge and surface hydrophilicity of microspheres have been found to be important in determining the fate of particles in vivo.
5. Studies on the macrophage uptake of microspheres have demonstrated their potential in targeting drugs to pathogens residing intra-cellularly[39].

b) Molecular Imprinting Technology

Controlled release systems based on molecular imprinting involves the deposition of monomers around a template molecule, to form a mould stabilized by a highly cross-linked network with selective recognition to the template. This is followed by the subsequent removal of the imprint molecule, and resulting in an organic polymer with a predetermined arrangement of ligands tailored as binding pockets for the original imprint molecule or something closely related[40].

Advantages

Advantages of using molecular imprinting technology in NDDS are as follows:

Molecular imprinted polymers (MIPs) possess two of the most important features of biological receptors- the ability to recognize and bind specific target molecules. In comparison to their biological counterparts other than possessing antibody-like molecular selectivity the major advantages of using molecular imprinted polymers are:

1. They can be stored in the dry state at ambient temperature for several years and can be regenerated and reused many times without loss of their molecular memory.
2. Polymers can be imprinted with substances against which natural antibodies are difficult to raise. Therefore, artificial receptors prepared by molecular imprinting can provide an attractive alternative or complement to natural antibodies and receptors in many applications[41].
3. Because of the three dimensional polymeric structure they exhibit high physical resistance against external degrading factors and are stable against mechanical stress, high temperature and pressure, resistant against treatment with acids, bases or metal ions and are stable in a wide range of solvents[42].

c) Iontophoresis

Iontophoresis, derived from the Greek word “ionto” meaning ‘ion’ and “phoresis” meaning ‘to bear’ involves enhancing the permeation of a topically applied therapeutic agent by the application of a low level electric current

either directly to the skin or indirectly via the dosage form[43,44,45,46]. There are three major enhancing mechanisms for drug reflux through the skin, which include: Iontophoresis(also known as electro repulsion, electro migration or Nernst-Planck effect), electro-osmotic flow and current induced increase in skin permeation, also known as damage effect[47].

Advantages

Advantages of using iontophoresis in NDDS are as follows:

1. It is a non-invasive.
2. It eliminates problems like toxicity problems, adverse reaction formulation problems associated with presence of chemical enhancers in pharmaceuticals.
3. It may permit lower quantities of drug compared to use in TDDS, and this may lead to fewer side effects.
4. Eliminate the chance of over or under dosing by continuous delivery of drug programmed at the required therapeutic rate.
5. Permit a rapid termination of the modification, simply by stopping drug input from the iontophoretic delivery system.
6. Self-administration is possible[48,49,50,51].

d) Phonophoresis

It involves transport of drug through the skin by ultra sound or ultra sonophoresis[52]. Drug mix with coupling agent (usually with gel, cream or ointment) that causes ultrasonic energy transfer from the system to the skin. Lipid present in stratum corneum get ruptured which allows the medicament to permeate via biological barrier[53].

Advantages

Advantages of using phonophoresis in NDDS are as follows:

1. Non-invasive technique.
2. Easy to use.
3. May cause fewer systemic side effects than their oral counterparts.
4. Custom made to meet your individual needs[54].

Administration Routes

The choice of a delivery route is driven by patient acceptability, the properties of the drug (such as its solubility), access to a disease location, or effectiveness in dealing with the specific disease. The most important drug delivery route is the peroral route. An increasing numbers of drugs are protein- and peptide-based. They offer the greatest potential for more effective therapeutics, but they do not easily cross mucosal surfaces and biological membranes; they are easily denatured or degraded, prone to rapid clearance in the liver and other body tissues and require precise dosing. At present, protein drugs are usually administered by injection[55,56].

Conclusion:-

Novel drug delivery system plays an important role in the field of pharmacy, and provides desired therapeutic effect with much lesser chances of toxicity. As seen, the effort to produce these new drug carrier systems is clearly high. Undoubtedly, those carriers provide the hope to treat and diagnose several diseases. Several technologies have advanced into clinical studies and are nowadays market products that have been shown favorable results. It was also shown in this review that these recent drug carriers are a promising set of technologies that already penetrated the cancer area and they likely have a strong impact in this field in the future. In fact, the rationale development of anticancer carriers will provide new ways of treatment, circumventing current limitations for conventional dosage forms. However, there are some issues that need to be understood in order to ensure their safety and effectiveness. Nevertheless, in the future, new entities will become available and responsive and “clever” polymers will offer new perspectives for the treatment of diseases.

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