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A REVIEW ON TARGETED DRUG DELIVERY SYSTEM

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ABSTRACT

Recently, targeted drug delivery systems (TDDSs) have been extensively studied as a promising therapeutic for tumour therapy. In this review, we investigate the typical targeting mechanisms of TDDSs, covering both passively and actively targeting DDSs for tumour therapy. We highlight the popular active targeting strategies for different sites of action, including tumour cyto membrane or various organelles. Finally, we present some recent representative TDDSs that are under testing in preclinical/clinical trials and have shown excellent clinical potential as the alternate treatment strategy for tumour therapy. Although TDDSs are proving to be promising therapeutic nano platforms for tumour therapy, extended investigations should be considered in the landscape for highly efficient tumour therapy with good biosafety.

Keywords: Targeted Drug Delivery System, Liposomes, Nanoparticles, Drug Targeting.

INTRODUCTION

Target means specific organ or a cell or group of cells, which in chronic or acute condition need treatment. Targeted drug delivery is a kind of smart drug delivery system which is miraculous in delivering the drug to a patient. This conventional drug delivery system is done by the absorption of the drug across a biological membrane, whereas the targeted release system is that drug is released in a dosage form. Targeted drug delivery is a system of specifying the drug moiety directly into its targeted body area (organ, cellular, and subcellular level of specific tissue) to overcome the a specific toxic effect of conventional drug delivery, thereby reducing the amount of drug required for therapeutic efficacy. Targeted drug delivery system is a special form of drug delivery system where the medicament is selectively targeted or delivered only to its site of action or absorption and not to the non-target organs or tissues or cells.Targeted drug delivery system is based on a method that delivers a certain amount of a therapeutic agent for a prolonged period of time to a targeted diseased area within the body. This helps maintain the required plasma and tissue drug levels in the body, therefore avoiding any damage to the healthy tissue via the drug.

Drug targeting: A Targeted drug delivery system is preferred in the following situations

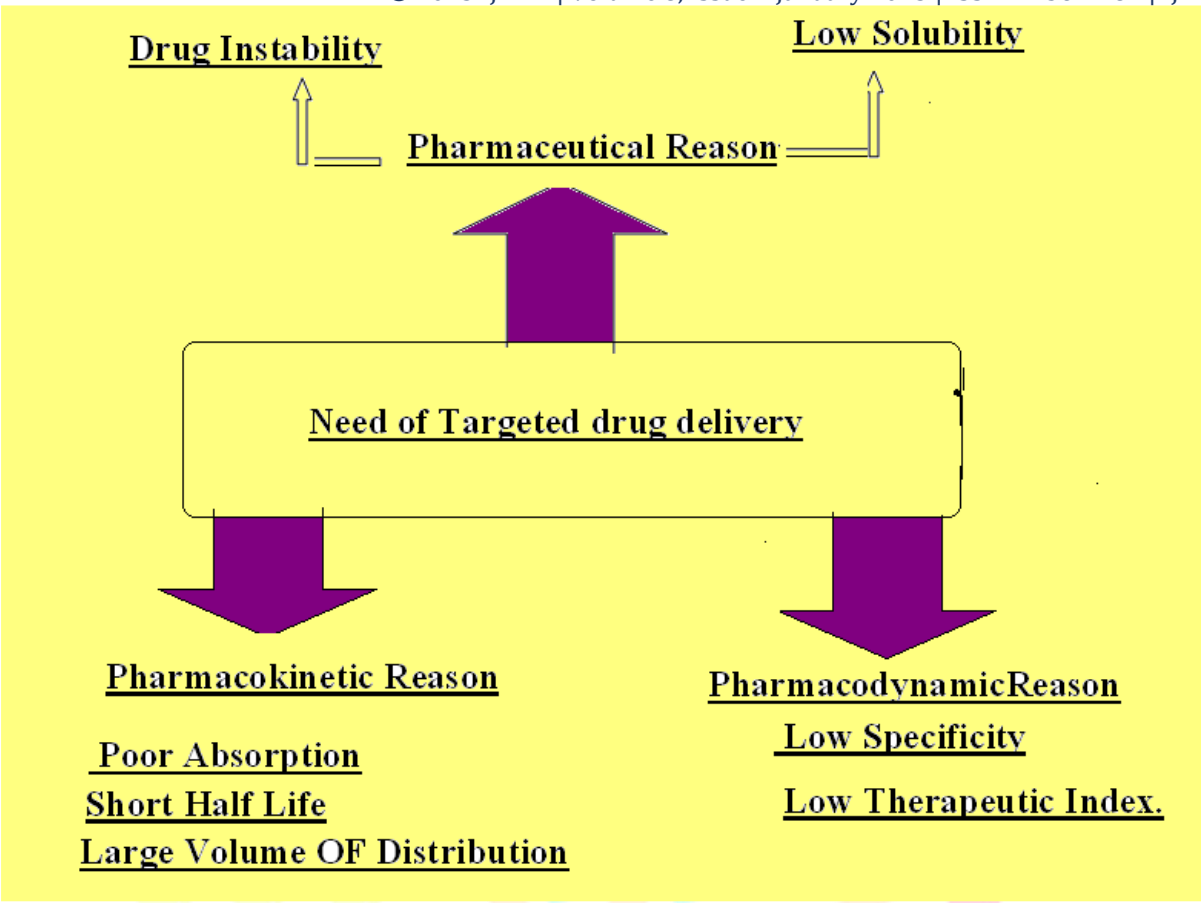

Fig: 1 Targeted Drug Delivery System

DRUG TARGETING DELIVERED TO

- To the capillary bed of the active sites.
- To the specific type of cell (or) even an intracellular region. Ex: Tumour cells but not to normal cells.
- To a specific organ (or) tissues by complexion with the carrier that recognizes the target.
- This improves efficacy and reduce side effects

REASON FOR DRUG TARGETING

- In the treatment or prevention or diseases.
- Pharmaceutical drug instability in conventional dosage form solubility, biopharmaceutical low absorption, high membrane bounding, biological instability, pharmacokinetic / pharmaco dynamic short half-life, large volume of distribution, low specificity, clinical, low therapeutic index

PROPERTIES OF IDEAL TARGETED DRUG DELIVERY

- It should be nontoxic, biocompatible, biodegradable, and physicochemical stable
- *invivo* and *invitro.*
- Restrict drug distribution to target cells or tissue or organ or should have uniform capillary distribution.
- Controllable and predictable rate of drug release.
- Drug release should not affect the drug distribution.
- Therapeutic amount of drug release.
- Minimal drug leakage during transit

- Carrier used must be biodegradable or readily eliminated from the body without any problem and no carrier should induce modulation of diseased state.
- The preparation of drug delivery system should be easy or reasonably simple, reproductive and cost effective.

ADVANTAGES OF TDDS

1) Avoids chemically hostile GI environment (drug degradation in acidic and basic environments is prevented).
2) No GI distress and the factors like Gastric emptying, intestinal motility, transit time, do not effect this route as in oral route.
3) Avoidance of significant pre systemic metabolism (degradation in GIT or by the liver) and therefore need lower doses.
4) Allows effective use of drugs with short biological half-life.
5) Allow administration of drugs with narrow therapeutic window because drug levels are maintained within the therapeutic window for prolonged periods of time.
6) Reduced inter and intra patient variability.
7) Enhance therapeutic efficacy, reduced fluctuations (rapid blood level spikes-low and high) due to optimization of blood concentration –time profile.
8) Reduction of dosing frequency and enhancement of patient compliance.
9) Provides controlled plasma levels of very potent drugs.
10) Can provide adequate absorption of certain drugs.
11) Avoids the risk and inconveniences of parenteral therapy (Painless method of drug administration).
12) Drug input can be promptly interrupted simply by removal of the patch when toxicity occurs.
13) Provides suitability of self-medication.

DISADVANTAGES OF TDDS

1. Drug that require high blood levels cannot be administered
2. Drug or drug formulation may cause skin irritation or sensitization
3. Uncomfortable to wear
4. May not be economical.
5. Rapid clearance of targeted systems.
6. Immune reactions against intravenous administered carrier systems.
7. Insufficient localization of targeted systems into tumour cells.
8. Diffusion and redistribution of released drugs.

STRATEGIES OF DRUG TARGETING

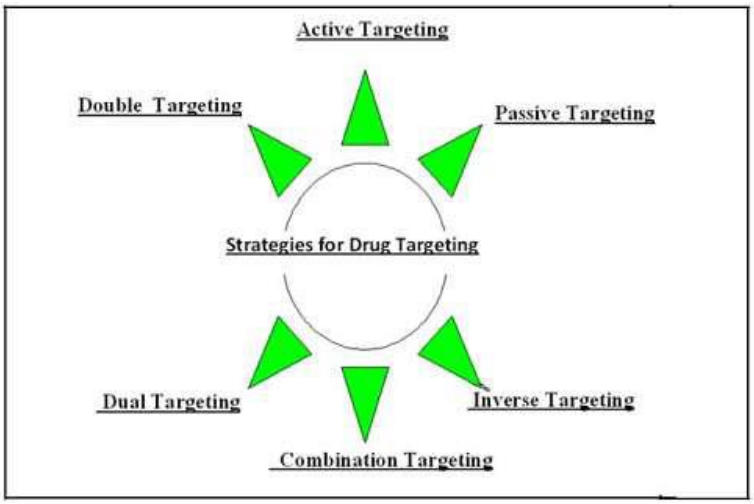

Fig: 2 Strategies of Drug Targeting

1. PASSIVE TARGETING

It refers to the accumulation of drug or drug carrier system at a specific site such as anti-cancerous drug whose explanation may be attributed to physicochemical or pharmacological factors of the disease. Hence, in case of cancer treatment the size and surface properties of drug delivery nanoparticles must be controlled specifically to avoid uptake by the reticulo-endothelial system (RES) to maximize circulation times and targeting ability. The bottom line is called passive targeting as misnomer which is simple drug delivery system via blood circulation. Drug release or drug actions are limited to selective sites within the body such as a tumour but not the liver. Other examples include targeting of antimalarial drugs for treatment of leishmaniasis, brucellosis, candidiasis .

2. ACTIVE TARGETING

Active targeting means a specific ligand–receptor type interaction for intracellular localization which occurs only after blood circulation and extravasations. This active targeting approach can be further classified into three different levels of targeting which are:

a) First order targeting refers to restricted distribution of the drug carrier systems to the capillary bed of a predetermined target site, organ or tissue e.g. compartmental targeting in lymphatics, peritoneal cavity, plural cavity, cerebral ventricles and eyes, joints.

b) Second order targeting refers to selective delivery of drugs to specific cell types such as tumour cells and not to the normal cells e.g. selective drug delivery to kupffer cells in the liver.

c) Third order targeting refers to drug delivery specifically to the intracellular site of targeted cells e.g. receptor based ligand mediated entry of a drug complex into a cell by endocytosis .

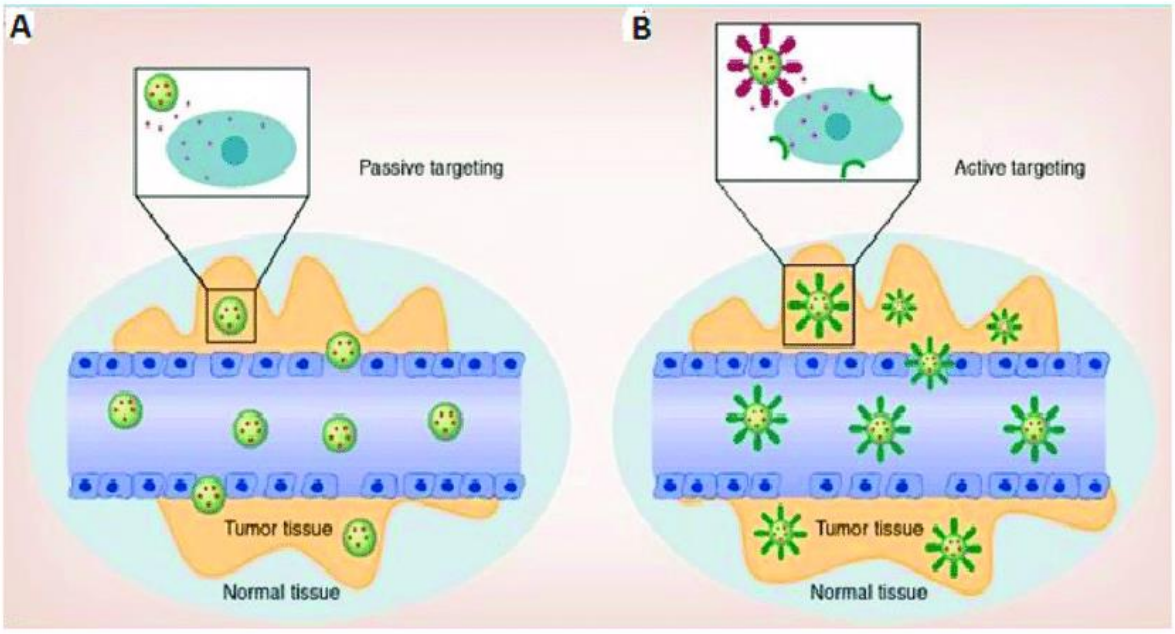

Fig: 3 Targeted Drug Delivery System

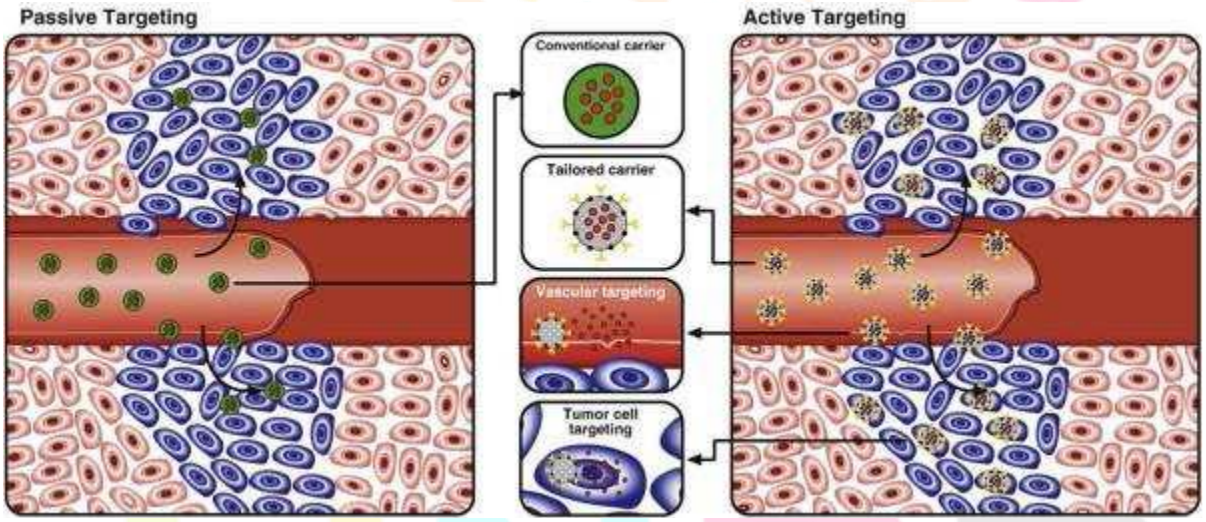

Fig: 4 Active & Passive Targeting

3. Inverse Targeting

In this type of targeting attempts are made to avoid passive uptake of colloidal carrier by RES and hence the process is referred to as inverse targeting. To achieve inverse targeting, RES normal function is suppressed by pre injecting large amount of blank colloidal carriers or macromolecules like dextran sulphate. This approach leads to saturation of RES and suppression of defense mechanism. This type of targeting is a effective approach to target drug(s) to non-RES organs.

4. Dual Targeting: In this targeting approach carrier molecule itself have their own therapeutic activity and thus increase the therapeutic effect of drug. For example, a carrier molecule having its own antiviral activity can be loaded with antiviral drug and the net synergistic effect of drug conjugate was observed.

5. Double Targeting: When temporal and spatial methodologies are combined to target carrier system, then targeting may be called double targeting. Spatial placement relates to targeting drugs to specific organs tissues, cells or even subs cellular compartment whereas temporal delivery refers to controlling the rate of drug delivery to target site.

TARGETED DRUG DELIVERY SYSTEM USING LIPOSOMES

INTRODUCTION

Liposomes are microscopic vesicles composed of one or more lipid bilayers arranged in concentric fashion enclosing an equal number of aqueous compartments [5]. The name liposome is derived from two Greek words: 'Lipos' meaning fat and 'Soma' meaning body. A liposome can be formed at a variety of sizes as uni-lamellar or multi-lamellar construction, and its name relates to its structural building blocks, phospholipids, and not to its size. A liposome does not necessarily have lipophobic contents, such as water, although it usually does. Liposomes are artificially prepared vesicles made of lipid bilayer. Liposomes can be filled with drugs, and used to deliver drugs for cancer and other diseases. Liposomes can be prepared by disrupting biological membranes, for example by sonication. Liposomes are micro particulate or colloidal carriers, usually 0.05- 5.0 µm in diameter which form spontaneously when certain lipids are hydrated in aqueous media.

MECHANISM OF LIPOSOMES

1. Liposome attaches to cellular membrane and appears to fuse with them, releasing their content into the cell.
2. They are taken up by the cell and their phospholipids are incorporated into the cell membrane by which the drug trapped inside is released
3. In case of phagocyte cell, the Liposomes are taken up, the phospholipid walls are acted upon by organelles called lysosomes and the active pharmaceutical ingredients are released.

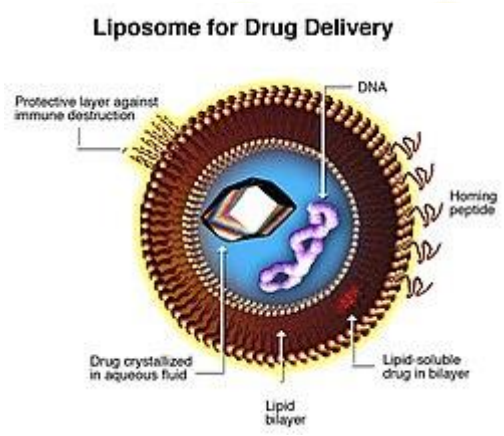

Fig: 5 Liposomal Drug Delivery

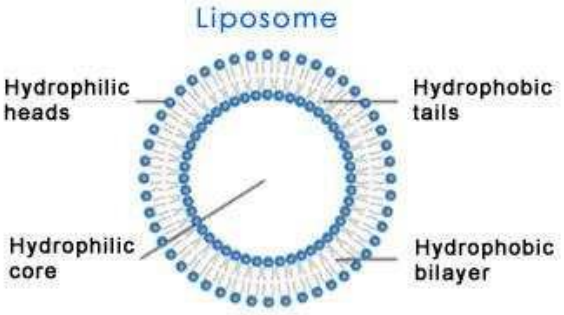

Fig: 6 Liposome

Advantages of Liposomes

1. Liposomes are biocompatible, completely biodegradable, non-toxic and immunogenic.
2. Suitable for delivery of hydrophobic, amphipathic and hydrophilic drug.
3. Protect the encapsulated drug from the external environment.
4. Reduce toxicity and increased stability as therapeutic activity of chemotherapeutic agents can be improved through liposome encapsulation.
5. Reduce exposure of sensitive tissue to toxic drugs.

Disadvantages of Liposomes

1) Production cost is high.
2) Leakage and fusion of encapsulated drug or molecules.
3) Short half-life.

CLASSIFICATION OF LIPOSOMES

1. BASED ON COMPOSITION AND MODE OF DRUG DELIVERY

a) Conventional liposomes

These types of liposomes are composed of neutral or negatively charged phospholipids and cholesterol. It is useful for E.E.S targeting; rapid and saturable uptake by R.E.S; short circulation half life, dose dependent pharmacokinetics.

b) pH sensitive liposomes

These types of liposomes are composed of phospholipids such as phosphatidyl ethanolamine, dioleoyl phosphatidyl ethanolamine. These are subjected to coated pit endocytosis at low pH, fuse with cell or endosomes membrane and release their contents in cytoplasm; suitable for intracellular delivery of weak base and macromolecules. Bio distribution and pharmacokinetics are similar to conventional liposomes.

c) Cationic Liposomes

These types of liposomes are composed of cationic lipids. These are mainly suitable for delivery of negatively charged macromolecules (DNA, RNA); ease of formation, structurally unstable; toxic at high dose, mainly restricted to local administration

d) Temperature or heat sensitive liposomes

These types of liposomes are composed of dipalmitoyl phosphotidyl choline. These are vesicles showed maximum release at 41°C, the phase transition temperature of dipalmitoyl phosphotidyl choline. Liposomes release the entrapped content at the target cell surface upon a brief heating to the phase transition temperature of the liposome membrane.

e) Immuno liposomes

These are conventional or stealth liposomes with attached antibody or recognition sequence.

These are subjected to receptor mediated endocytosis. It has cell specific binding (targeting) and can release contents extra cellularly near the target tissue and drugs diffuse through plasma membrane to produce their effects.

f) Long circulating or stealth liposomes

These types of liposomes are composed of neutral high transition temperature lipid, cholesterol and 5-10% of PEG-DSPE. These are subjected to hydrophilic surface coating, low opsonisation and thus low rate of uptake by R.E.S. So, it has long circulating half-life (40 hrs) and dose independent Pharmacokinetics.

g) Magnetic Liposomes

These types of liposomes are composed of phosphotidyl choline, cholesterol and small amount of a linear chain aldehyde and colloidal particles of magnetic iron oxide. These are liposomes that indigenously contain binding sites for attaching other molecules like antibodies on their exterior surface. These can be made use by an external vibrating magnetic field on their deliberate, on site, rapture and immediate release of their components.

2. BASED ON SIZE AND NUMBER OF LAMELLAE

a) Multi Lamellar Vesicles (M.L.V.) Multi lamellar vesicles have more than one bilayer; moderate aqueous volume to lipid ratio 4: 1mole lipid. Greater encapsulation of lipophilic drug, mechanically stable upon long term storage, rapidly cleared by R.E.S, useful for targeting the cells of R.E.S, simplest to prepare by thin film hydration of lipids in presence of an organic solvent.

- Oligo lamellar vesicles or Paucilamellar vesicles: Intermediate between L.U.V. & M.L.V.
- Multi vesicular liposomes: Separate compartments are present in a single M.L.V.
- Stable Pluri lamellar vesicles: Have unique physical and biological properties due to osmotic compression.

b) Large Unilamellar Vesicles (L.U.V.)

Large unilamellar vesicles have single bilayer, high aqueous volume to lipid ratio (7: 1 mole lipid), useful for hydrophilic drugs, high capture of macro molecules; rapidly cleared by R. E. S. Prepared by detergent dialysis, ether injection, reverse phase evaporation or active loading methods.

c) Small Unilamellar Vesicles (S.U.V.)

Single bilayer, homogeneous in size, thermodynamically unstable, susceptible to aggregation and fusion at low or no charge, limited capture of macro molecules, low aqueous volume to lipid ratio(0.2 : 1.5 : 1 mole lipid) prepared by reducing the size of M.L.V. or L.U.V. using probe sonicator or gas extruder or by active loading or solvent injection technique.

METHOD USED IN THE PREPARATION OF LIPOSOME

The preparation of all types of vesicular systems requires the input of energy. Generally all the methods of liposome preparation involve three basic stages

1. Drying down of mixture of lipids from an organic solvent.
2. Dispersion of lipids in aqueous media.
3. Separation and purification of resultant liposomes

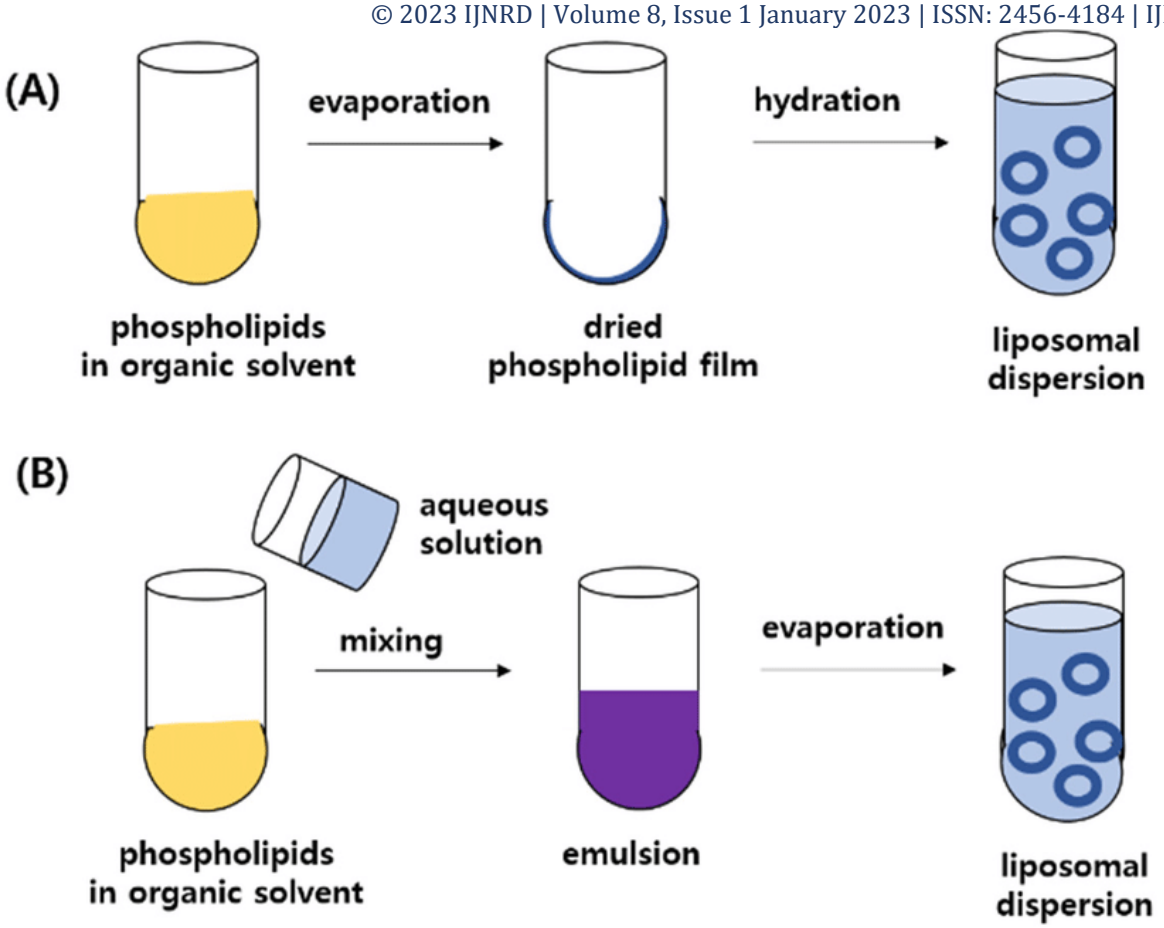

Fig: 7 Preparation of Liposome

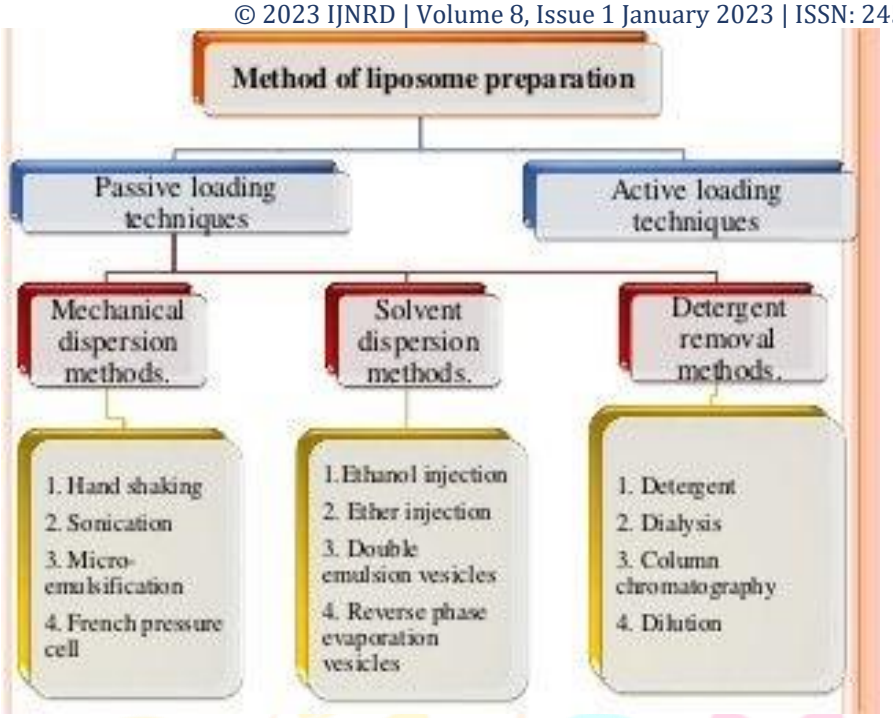

Fig: 8 Flow Chart for Preparation of Liposome

APPLICATIONS OF LIPOSOMES

Liposomes have great pharmaceutical applications in oral and transdermal drug delivery systems. Reduction in the toxic effect and enhancement of the effectiveness of drugs are achieved by this drug delivery system. The targeting of liposome to the site of action takes place by the attachment of amino acid fragment that target specific receptors cell. Several modes of drug delivery application have been proposed for the liposomal drug delivery system, few of them are as follows:

1. Enhancement of solubilisation (Amphotericin-B, Paclitaxel)
2. Protection of sensitive drug molecules (Cytosine arabinosa, DNA, RNA, Ribozymes)
3. Enhancement of intracellular uptake (Anticancer, antiviral and antimicrobial drugs)
4. Alteration in pharmacokinetics and bio-distribution (prolonged or SR drugs with short circulatory half life)

A. Liposome for Respiratory Drug Delivery System

Liposome is widely used in several types of respiratory disorders. Liposomal aerosols can be formulated to achieve sustained release, prevent local irritation, reduced toxicity and improved stability. Whilst preparing liposomes for lung delivery, composition, size, charge, drug/lipid ratio and drug delivery method should be considered. The liquid or dry form is taken for the inhalation during nebulisation. Drug powder liposome is produced by milling or by spray drying.

B. Liposome in Eye Disorders

Liposome has been used widely to treat disorders of eye. The disease of eye includes dryness, keratitis, corneal transplant rejection, endopthelmitis and proliferative vitro retinopathy. Retinal diseases are important cause of blindness. Liposome is used as vector for genetic transfection and monoclonal antibody directed vehicle. Applying of focal laser to heat induced release of liposomal drugs and dyes are the recent techniques

of the treatment of selective tumour and neo-vascular vessels occlusion, angiography, retinal and choroidal blood vessel stasis.

C. Liposome as Vaccine Adjuvant

Liposome has been established firmly as immune adjuvant that is potentiating both cell mediated and non-cell mediated immunity. Liposomal immuno-adjuvant acts by slow release of encapsulated antigen on intramuscular injection and also by passive accumulation within regional lymph node. The accumulation of liposome to lymphoid is done by the targeting of liposome with the help of phosphotidyl serine. Liposomal vaccine can be prepared by inoculating microbes, soluble antigen and cytokinesis of deoxyribonucleic acid with liposome.

CONCLUSION

Many problems which appeared during the development of drug targeting strategies for clinical application for different types of therapies have been identified, analyzed and solved. A specific area of which belongs in the treatment of cancer therapy. Several such preparations have entered the phases of clinical testing and/or have now been marketed. However, such strategies should be subjected to continuous evaluation in the light of advances in the understanding of the numerous processes occurring in response to administration of the carriers and/or the drugs. Liposomes have been realised as extremely useful carrier systems for targeted drug delivery. one of the unique drug delivery system; they can be use in controlling and targeting drug delivery. Now, in days the Liposomal topical formulations are more effectively and give the safe therapeutic efficacy. These are also used in the cosmetic and hair Technologies, diagnostic purpose and good carrier in gene delivery. Liposomes are giving a good and encouraging result in the anticancer therapy and human therapy. The major problem in the formulation of liposome is its stability problem. These problems can be overcome by employing modification in the preparation method and also by using some specialized carriers. Nowadays liposomes are used as carrier for wide variety of drugs.

REFERENCES

1) Prabhakar Vishvakrama and Saurabh Sharma. Liposomes: An Overview. International journal of Research in Pharmaceutical and Biomedical Sciences.2012; 3(3): 1074-1076.
2) Ravichandiran , Masilamani , Senthilnathan . Liposome- A Versatile Drug Delivery System . Der Pharmacia Sinica. 2011; 2(1): 19-30.
3) Bhargav, Madhuri,Ramesh, Anand manne, Ravi. Targeted Drug Delivery- A Review. World Journal of Pharmacy and Pharmaceutical Sciences.2013; 3(1):150-169.
4) Maheswaran, Brindha, Mullaicharam, Masilamani. Liposomal Drug Delivery Systems – A Review. International Journal of Pharmaceutical Sciences Review and Research.2013; 23(1): 295-301.
5) Kirti Rani, Saurabh Paliwal. A Review on Targeted Drug Delivery: its Entire Focus on Advanced Therapeutics and Diagnostics. Scholars Journal of Applied Medical Sciences.2014;2(1):328-331.
6) Elvis A. Martis, Rewa R. Badve, Mukta D. Degwekar, Nanotechnology Based Devices andApplications in Medicine: An Overview 2013; 3(1):69-70.

7) Kateřina Holá,Vladimir Šubr. Targeted Drug Delivery with Polymers and Magnetic Nanoparticles: Covalent and Noncovalent Approaches, Release Control, and Clinical Studies.ACS Publication site.2016; 2(1):5338–5431.

8) Prabhakar Vishvakrama and Saurabh Sharma.Liposomes: An Overview.International journal of Research in Pharmaceutical and Biomedical Sciences.2012; 3(3): 1074-1076.Tpo

9) Mohanraj, Chen, Nanoparticles – A Review, Topical Journal of Pharmaceutical Research. 2006; 5(1):561-564 International Journal of Pharmaceutical Sciences.

10) Book- Targeted & controlled drug delivery, Author- Vyas / Khar.

11) Rukhsana Yusaf wt al. Structural Components of liposomes and Characterization Tools. American Journal of Pharm Research,2014, 4(08).

12) Kataria Sahil1, Middha Akanksha1, Sandhu Premjeet1, Ajay Bilandi and Bhawana Kapoor, Microsphere: A Review, International Journal of research in Pharmacy and Chemistry 2011; 1(4):1186-1188.