Journal of Formulation Science & Bioavailability

Rishpa, J Formul Sci Bioavailab 2017, 1:1

Review Article OMICS International

A Review on Cipla Liposomes (Dsoxorubicin and Amphotericin B)

Rishpa K*

St. Peters Institute of Pharmaceutical Sciences, Vidhyanagar, Warangal, Telangana

Abstract

The Cipla has developed strategies in technologies such as sustained release and combination products, and also in made better improvements to enhance drug delivery system capabilities. Liposomal technology is new technique used by us to improve the delivery of drugs. These delivery system gives opportunity to target drugs on their respective sites may improve the pharmacological effect and also pharmacokinetics of the drug. Cipla has introduced the new liposomal formulations for anti-cancer drug (Doxorubicin) and anti-fungal drug (Amphotericin-B). Doxorubicin is an anticancer drug and it is a chemotherapy medication. Cipla laboratories had introduced these liposomal doxorubicin drugs for targeting tumours. Doxorubicin is in pegylated form reduces cytotoxicity and improve the efficacy of the drug. Conventional Amphotericin drugs causes cytotoxicity, reduce the efficacy these liposomes formulation may improve the efficacy of the drug and acts as anti-fungal drug. Phosome Amphotericin B is a polyene antifungal which alters cell membrane permeability by binding and forms the suspectable fungal membrane.

Keywords: Pharmacokinetics; Cytotoxicity; Doxorubicin; Polyene; Amphotericin

Introduction

Liposomes are spherical structures with one or more phospholipid bilayer in which aqueous solution is enclosed with lipid bilayer. Liposomes are good at drug delivery system because of their hydrophilic and hydrophobic characters. Bilayer components maintain the 'rigidity' or 'fluidity' and the charge of the bilayer. For an explanation, unsaturated phosphatidylcholine species from natural sources give good permeable and less stable bilayers, whereas the saturated phospholipids with long acyl form a rigid, and impermeable bilayer structure. Cholesterol cannot form itself a bilayer structure it acts as fluidity buffer, it binds with the hydroxyl group towards aqueous surface and aliphatic to the centre of the bilayer (Figure 1) [1-5].

Classification of Liposomes

Based on the structure

- Multilamellar vesicles (MLV)
- Unilamellar vesicles(ULV)
- Oligo unilamellar vesicles

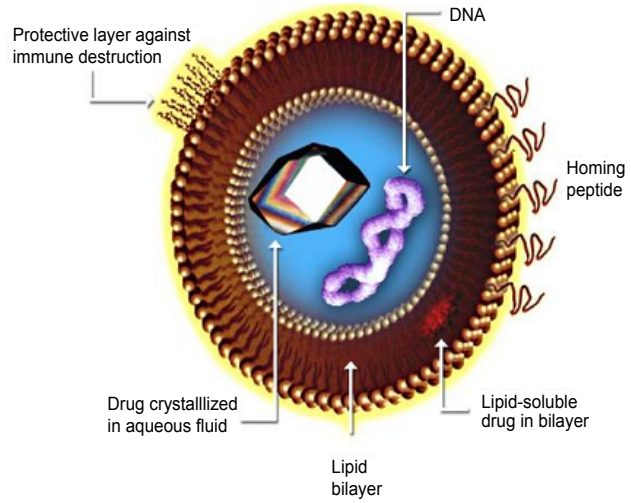

Figure 1: Interior structure of liposome.

- Small unilamellar
- Large unilamellar vesicles
- Gaint unilamellar vesicles
- Multi vesicular vesicles.

Salient features of liposomes

- Biologically inert and biodegradable and weakly immunogenic
- Passive targeting to REC by pegylation possibility to avoid RES by pegylation
- Increased plasma circulation and increased half life
- Active targeting reduced toxicity and increased efficacy.

Methods of Liposomal Preparation

Liquids and hydrophobic drugs in organic solvent are adjusted to rotary evapouration and then lipid films are formed and hydrophillic drugs are adjusted to water solution and then hydration is undergone, finally it forms into multilamellar vescicles LUV and SUVS by undergoing sonication, extrusion, homogenization, microfluidization, centrigugation, dialysis, ultrafiltration, column chromatography, purification finally liposome are formed. In the preparation liposomes involves the following steps:

1. At first drying down the lipids from organic solvent.
2. Dispersing the lipid in aqueous media.
3. Purifying the resultant liposome.
4. Analyzing the final product.

***Corresonding author:** Rishpa k, St. Peters Institute of Pharmaceutical Sciences, Vidhyanagar, Warangal, Telangana, India, Tel: 7330252833; E-mail: koppularishpa@gmail.com

Received April 24, 2017; **Accepted** May 04, 2017; **Published** May 05, 2017

Citation: Rishpa K (2017) A Review on Cipla Liposomes (Dsoxorubicin and Amphotericin B). J Formul Sci Bioavailab 1: 109.

These preparation methods involves Passive loading technique and Active loading techniques

In passive loading techniques undergo three more steps:

Mechanical dispersion method

This method involves lipid film hydration by hand shaking, non-hand shaking or freeze drying, it involves sonication, French pressure cell: extrusion, Freeze-thawed liposomes [6-10].

Solvent dispersion method

a) Ether injection (solvent vaporization): A solution of lipids dissolved in diethyl ether or ether-methanol mixture is gradually injected to an aqueous solution of the material to be encapsulated at 55°C to 65°C or under reduced pressure. The consequent removal of ether under vacuum leads to the creation of liposomes. The main disadvantages of the technique are that the population is heterogeneous (70 to 200 nm) and the exposure of compounds to be encapsulated to organic solvents at high temperature.

b) Ethanol injection: A lipid solution of ethanol is rapidly injected to a huge excess of buffer. The MLVs are at once formed. The disadvantages of the method are that the population is heterogeneous (30 to 110 nm), liposomes are very dilute, the removal all ethanol is difficult because it forms into azeotrope with water, and the probability of the various biologically active macromolecules to inactivate in the presence of even low amounts of ethanol is high.

c) Reverse phase evaporation method: This method provided a progress in liposome technology, since it allowed for the first time the preparation of liposomes with a high aqueous space-to-lipid ratio and a capability to entrap a large percentage of the aqueous material presented. Reverse-phase evaporation is based on the creation of inverted micelles. These inverted micelles are shaped upon sonication of a mixture of a buffered aqueous phase, which contains the water-soluble molecules to be encapsulated into the liposomes and an organic phase in which the amphiphilic molecules are solubilized. The slow elimination of the organic solvent leads to the conversion of these inverted micelles into viscous state and gel form. At a critical point in this process, the gel state collapses, and some of the inverted micelles were disturbed. The excess of phospholipids in the environment donates to the formation of a complete bilayer around the residual micelles, which results in the creation of liposomes. Liposomes made by reverse phase evaporation method can be made from numerous lipid formulations and have aqueous volume-to-lipid ratios that are four times higher than hand-shaken liposomes or multi lamellar liposomes [11-16].

Detergent removal method (removal of non-encapsulated material)

a) Dialysis: The detergents at their critical micelle concentrations (CMC) have been used to solubilize lipids. As the detergent is detached, the micelles become increasingly better-off in phospholipid and lastly combine to form LUVs. The detergents were removed by dialysis. A commercial device called LipoPrep (Diachema AG, Switzerland), which is a version of dialysis system, is obtainable for the elimination of detergents. The dialysis can be performed in dialysis bags engrossed in large detergent free buffers (equilibrium dialysis).

b) Detergent (cholate, alkyl glycoside, Triton X-100) removal of mixed micelles (absorption): Detergent absorption is attained by shaking mixed micelle solution with beaded organic polystyrene adsorbers such as XAD-2 beads (SERVA Electrophoresis GmbH, Heidelberg, Germany) and Bio-beads SM2 (Bio-RadLaboratories, Inc., Hercules, USA). The great benefit of using detergent adsorbers is that they can eliminate detergents with a very low CMC, which are not entirely depleted.

c) Gel-permeation chromatography: In this method, the detergent is depleted by size special chromatography. Sephadex G-50, Sephadex G-l 00 (Sigma-Aldrich, MO, USA), Sepharose 2B-6B, and Sephacryl S200-S1000 (General Electric Company, Tehran, Iran) can be used for gel filtration. The liposomes do not penetrate into the pores of the beads packed in a column. They percolate through the inter-bead spaces. At slow flow rates, the separation of liposomes from detergent monomers is very good. The swollen polysaccharide beads adsorb substantial amounts of amphiphilic lipids; therefore, pre-treatment is necessary. The pre-treatment is done by pre-saturation of the gel filtration column by lipids using empty liposome suspensions.

d) Dilution: Upon dilution of aqueous mixed micellar solution of detergent and phospholipids with buffer, the micellar size and the polydispersity increase fundamentally, and as the system is diluted beyond the mixed micellar phase boundary, a spontaneous transition from polydispersed micelles to vesicles occurs.

Remote loading technique or Active loading techniques

Drug loading can be attained either passively (i.e., the drug is encapsulated during liposome formation) or actively (i.e., after liposome formation). Hydrophobic drugs, for example amphotericin B taxol or annamycin, can be directly combined into liposomes during vesicle formation, and the amount of uptake and retention is governed by drug-lipid interactions. Trapping effectiveness of 100% is often achievable, but this is dependent on the solubility of the drug in the liposome membrane. Passive encapsulation of water-soluble drugs depends on the ability of liposomes to trap aqueous buffer containing a dissolved drug during vesicle formation. Trapping effectiveness (generally <30%) is limited by the trapped volume delimited in the liposomes and drug solubility. On the other hand, water-soluble drugs that have protonizable amine functions can be actively entrapped by employing pH gradients, which can result in trapping effectiveness approaching 100%.

Preparation of Amphotericin B and Doxorubicin

The amphotericin B liposomes were prepared by indiculation method, liposomes forms into uni-lamellar by high pressure homogenization and sonication, finally amphotericin B is centered in the liposome in which water soluble materials are entrapped by using aqueous solution or hydrating fluid and lipid soluble materials are solubilized in the organic solvent and evaporated to a dry drug containing lipid film.

Pegylated doxorubicin (oncodox-peg): These were formulated by remote loading doxorubicin into plain pegylated liposomes containing an ammonium sulphate gradient. During the creation of liposomes the doxorubicin complexes bind to one another form a long inflexible band of doxorubicin sulphate aggregate inside the liposome. Liposome in this application is formulated with surface bound polyethylene glycol known as pegylation. However creating true liposomes is expensive and involves several complex processes.

Mechanism of action

Amphotericin B is an active ingredient in the Ambisome, it acts by binding to the sterol components of the fungi cell membrane, thus it forms trans-membrane channels leading to alterations in cell

membrane so, that monovalent ions leak out of the cell and cell leads to death, these ambisome makes the fungi susceptible and kills the cells (Figure 2).

Mechanism of pegylated doxorubicin (oncodox-peg)

The Doxorubicin acts on cancer cells and this pegylated doxorubicin avoid cell toxicity. Pegylated liposomes avoid detection by mono nuclear phagocyte system and ensure that the drug longer blood circulation time. Due to its controlled size liposomes could penetrate vasculature of tumor cell but not the healthy cells it enhance permeation and retention time over time. The liposomes accumulate in the tumor tissue and the encapsulate doxorubicin HCL becomes available to act on the tumor cell. These pegylated doxorubicin are biologically inert and biodegradable and weakly immunogenic; passive targeting to RECby pegylation possibility to avoid RES by pegylation; increased plasma circulation and increased half-life; active targeting reduced toxicity and increased efficacy (Figure 3).

Applications of Liposomes

Liposomes in medicine and pharmacology, delivery of new biotechnology products, parasitic diseases and infections, anticancer therapy, first-line treatment of AIDS-related, there are major pharmaceutical uses as systemic lymphoma, the effect of liposome encapsulation showed enhanced efficacy due to the continued release effect, i.e., longer presence of therapeutic concentrations in the circulation, reduced toxicity, better tolerability of administration.

Conclusion

Cytotoxic drugs are toxic to cells and prevents the replication and growth (cardiotoxicity, bone marrow toxicity and nephrotoxicity) such drugs used in conventional formulation could lead to adverse side effects and they also harm healthy human tissue, so, targeted drug delivery systems enable high efficacy with minimal side effects.

Figure 2: Mechanism of action of phosome (Amphotericin b) on fungal parasites.

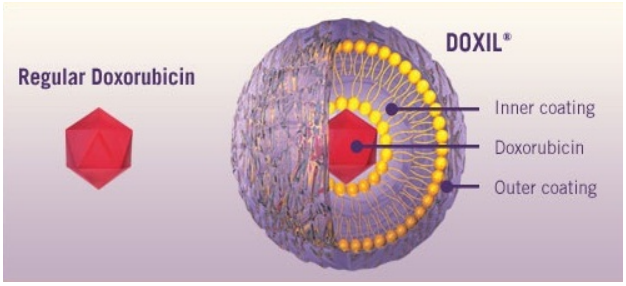

Figure 3: Regular and pegylated liposomes.

This issues may be medicated by lowering the dose but by lowering the dose these are following causes compromised dosing; Narrow therapeutic window; Poor efficacy; so, liposomal formulation of pegylated doxorubicin (oncodox-peg) or Amphotericin B (Phosome) were formulated. The formulated liposomes reduced the cytotoxicity and sustained blood circulation causes improved efficacy of drug.

References

1. Aref NEM, Nasr M, Osman R (2017) Novel Heat-Stable Enterotoxin (STa) Immunogen Based on Cationic Nanoliposomes: Preparation, Characterization and Immunization. J Vaccines Vaccin 8: 354.
2. Kuwabara K, Ichihara H, Matsumoto Y (2011) Inhibitory Effects and Anti-Invasive Activities of Trehalose Liposomes on the Proliferation of Lung Carcinoma Cells. J Carcinog Mutagen: 8: 283.
3. Sharma S (2016) Strategies for Effective Oral Insulin Delivery with Protamine Coated Proliposomes Encased in Eudragit S100 Coated Capsule: A Review. Journal of Pharmacology and Toxicological Studies.
4. Dávila LCM, Márquez IAP (2016) Anti-leishmanial Vaccination with Parasite Antigens in Liposomes Relies on the Effective Induction of T cell Responses and Inhibits Parasite Metastasis in Mice. J Carcinog Mutagen 7.
5. Vaze OS (2016) Pharmaceutical Nanocarriers (Liposomes and Micelles) in Cancer Therapy. Journal of Nanomedicine & Nanotechnology. J Nanomed Nanotechnol 7.
6. Wang X, Lu W (2015) Active Targeting Liposomes: Promising Approach for Tumor-Targeted Therapy. J Bioequiv Availab 8: 013-014.
7. Ichihara H, Komizu Y, Ueoka R, Matsumoto Y (2015) Inhibitory Effects of Hybrid Liposomes on the Growth of Non-small Cell Lung Carcinoma Cells and Anti-invasive Activity by Ceramide Generation without any Drugs. J Carcinog Mutagen 6: 1-10.
8. Nunes SS, Barros ALB (2015) The Use of Coating Agents to Enhance Liposomes Blood Circulation Time. J Mol Pharm Org Process Res 3: 25-29.
9. Ichihara H, Yamasaki S, Hino M, Ueoka R, Matsumoto Y (2015) Hybrid Liposomes inhibit the Growth and Angiogenesis in Human Breast Cancer Model. J Carcinog Mutagen 6: 56-70.
10. Gortzi O, Athanasiadis V, Lalas S, Chinou I, Tsaknis J (2014) Study of Antioxidant and Antimicrobial Activity of Chios Mastic Gum Fractions (Neutral, Acidic) Before and After Encapsulation in Liposomes. J Food Process Technol 5: 1-5.
11. Mijan MC, Longo JPF, Melo LND, Simioni AR, Tedesco AC, et al. (2014) Vascular Shutdown and Pro-inflammatory Cytokine Expression in Breast Cancer Tumors after Photodynamic Therapy Mediated by Nano-sized Liposomes Containing Aluminium-Chloride-Phthalocyanine. J Nanomed Nanotechnol 5: 1-5.
12. Venturini M, Mazzitelli S, Micetic I, Benini C, Fabbri J, Mucelli SP, et al. (2014) Analysis of Operating Conditions Influencing the Morphology and In vitro Behaviour of Chitosan Coated Liposomes. J Nanomed Nanotechnol 5: 1-5.
13. Watarai S, Sasaki Y (2014) Evaluation of Stearylamine-Modified Liposomes for the Oral Vaccine Adjuvant. J Infect Dis Ther 2: 4-10.
14. Devi RSK (2012) Immunotherapy Monitoring Through Liposomes-An Altered Form of Bio-Sensing. J Allergy Ther 3: 1-5.
15. Vaghasia N, Federman N (2011) Liposomes for Targeting Cancer: One Step Closer to the Holy Grail of Cancer Therapeutics? J Nanomedine Biotherapeutic Discov 1: 1-5.
16. Afergan E, Najajreh Y, Gutman D, Epstein H, Elmalak O, et al. (2010) P-NMR and Differential Scanning Calorimetry Studies for Determining Vesicle Drug Physical State and Fraction in Alendronate Liposomes. Journal of Bioanalysis and Biomedicine 2: 1-5.

Citation: Rishpa K (2017) A Review on Cipla Liposomes (Dsoxorubicin and Amphotericin B). J Formul Sci Bioavailab 1: 109.