ISSN- 2230-7346
Journal of Global Trends in Pharmaceutical Sciences

A REVIEW ON LIPOSOMAL DELIVERY SYSTEM

Faiz Mohammed Khan*, P Naga Haritha, K. Venu Madhav, M. Kiranmai

Department of Pharmaceutics,
St. Paul's College of Pharmacy, Turkayamjal, Hyderabad.

*****Corresponding Author E-mail: **faizmohammedkhan330@gmail.com**

ARTICLE INFO

Key words:
Liposomes, drug delivery system, phospholipid vesicles, membrane permeability.

Access this article online
Website:
https://www.jgtps.com/
Quick Response Code:

ABSTRACT

Liposomes are defined as closed bilayer phospholipid vesicles that act as drug carrier and have been successfully translated into real time clinical applications. Since the first development in 1965, liposomes have witnessed many technical advances in recent years. Various clinical studies have demonstrated the superiority of liposomal formulation over conventional delivery system and remarkable development with significant clinical applications enhancing the therapeutic index of various drugs by alter their biodistribution profile, increases the solubility, membrane permeation target delivery, controlled release. The liposomes are prepared by different methods and they vary from 30nm to several microns in size. Liposomes exhibit broad and potential application in different fields such as anticancer, anti-inflammatory, antifungal with their specific characteristics, nontoxic, fully biocompatible, high stability, optical properties and easy membrane permeability. In this review paper an attempt has been made to elaborate the types, drug delivery technology, preparation method, application and evaluation parameter of liposomes and their contribution in drug delivery system.

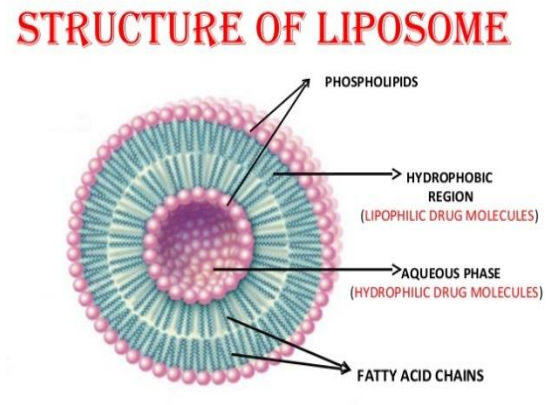
INTRODUCTION

Nanomedicine, a field of nanotechnology has various applications in human medicine such as, Targeted Drug Delivery, Controlled Release, Permeability Enhancement, increasing efficiency and solubility of drug along with reducing the toxicological effects. The fate of Drug molecules against biopharmaceutical properties such as ADME can be improved through nanotechnology. Numerous nanocarrier have been developed for transport of therapeutic to the targeted tissue. Significant advancements are done for preparation and characterization of nanoparticle to achieve increase stability and bioavailability of encapsulated drug contents. Liposomes being biocompatible and biodegradable along with their low Toxicity is efficient delivery material for therapeutic agents. Liposomes are closed microscopic spherical vesicles that are composed of phospholipids and sterols. Being amphipathic in nature liposomes can encapsulate lipophilic, amphipathic, hydrophilic drug substances into their inner aqueous phase. Generally a free drug achieves therapeutic level for shorter duration when reaches the systemic circulation, but the drug loaded in liposome achieve therapeutic activity for longer duration because of altered metabolism and excretion. Liposomes may vary in size from 30nm to several microns. Various preparation methods are developed for synthesis of liposomes. liposomes encapsulated a large number of drugs that

have low solubility and low membrane permeability and thereby increase the therapeutic activity (antiviral, antitumor etc.) of the drug molecule. In the present study, the formulation of liposomes using various approaches and their characterization done by transmission electron microscopy, free fracture electron microscopy, dynamic light scattering, laser light scattering, photon correlation spectroscopy, UV visible spectroscopy is discussed. This paper presents a review on types of liposomes present, preparation methods, evaluation parameters and finally characterization techniques and applications are discussed.

LIPOSOMES

Liposomes are nanosized vesicular structure consisting of an aqueous core surrounded with phospholipid layers. Generally, liposomes can also be defined as microscopic vesicles in which an aqueous volume is entirely enclosed by a membrane composed of lipid bilayer. The name liposome is derived from two Greek words "lipase" meaning fat and "soma" meaning body. They were first discovered by Dr Alec D Bingham (British hematologist) in 1961, at Abraham institute, Cambridge. The particle sizes of liposomes differ from 30nm to several microns based on type of preparation method followed. These are usually phospholipids that are amphipathic in nature i.e. they have a hydrophilic head group and hydrophobic tails. The head group consists of glycerol molecule attached to a phosphate group that is modified by an alcohol, the nonpolar tail is made up of two fatty acid chains insoluble in water.



The lipids in plasma membrane are phospholipids such as phosphatidylcholine, phosphatidylserines phosphatidylethanolamine, incorporated with sterol such as cholesterol. Cholesterol acts as a fluidity buffer and influences the membrane permeability. The incorporation of cholesterol increases the separation between the head group. Liposomes are promising tools for targeted drug delivery and have advantage of being biocompatible and biodegradable and ability to protect the encapsulated drug from unfavorable conditions.

Liposome Technologies for Drug Delivery

Stealth Liposome Technology

It involves the attachment of strands of polymer to the drug molecule or system improves the efficacy of therapeutic agents. The polymer used in this technique polyethylene glycol and the process used is PEGylation. It is attained by incubation of reactive derivative of PEG with target moiety.

Non Pegylated Technology

It is a unique drug delivery system that offers benefits of pegylated liposomes while eliminating the side effects associated with pegylated liposome phospholipids from natural as synthetic sources and can further be designed to include reactive lipids or outer surface to allow conjugation of molecules such as antibodies peptides and proteins.

Depofoam Technology

A novel technology of liposomal formulation consisting of multivesicular liposomes. These liposomes are made up of multiple non concentric aqueous chambers and surrounded by lipoidal membrane network. The technique is used to develop extended release formulation of liposomes.

Conventional Liposome Technology

The first ever generation of liposomes where formulated by conventional technology, it involves the use of natural phospholipids or lipids such as 1,2-distearoryl -sn-glycero3-phosphatidylcholine for liposome preparation, this technique encountered instability, short blood circulation half life and many other challenges.

Classification of Liposomes

Based On Structural Parameters: They are classified into four types based on the no of bilayers

Unilamellar vesicles: These are spherical made up of single bilayer entrapping an aqueous solution. They are further divided into three categories depending on size

a. SUV: size varying from 20 – 40 nanometers
b. MUV: size varying from 40 -80 nanometers.
c. LUV: size varying from 100-1000nanometers.

Oligolamellar Vesicles; These are made up of 2-5 concentric lamellae, surrounding a large internal volume.

Multilamellar Vesicles: these are liposomes containing several bilayers that are formed by extrusion methods or by sonicating the lipid solution.

The liposomes are also classified on the basis of their method of preparation, composition and applications.

Based on Preparation and Composition

Liposomes being biocompatible with various drugs and readily encapsulate drugs with low solubility and low membrane permeability, various methods are for preparing liposomes of various size. To increase the bioactive molecular delivery of drug to the cytoplasm new liposomes are being developed. In order to achieve targeted delivery of drugs, fusogenic, cationic and immunoliposomes are prepared. thus a need of classification of liposomes based on their composition, application and preparation methods, have emerged.

Method of liposome preparation

Active loading: compounds with ionizable groups are introduced after the formation of vesicles

Passive loading: the entrapped agents are loaded during or before the liposome manufacturing process.

Passive loading technique: involves three techniques based on different principles

Mechanical /physical dispersion; involves 4 basic methods that are

Hand shaking method: it is the most widely used mechanical dispersion method involving five steps

Step -1: chloroform, methanol solvent cause dissolution of lipid mixture and charge components

Steps-2: the solvent is evaluated y either hand shaking or by rotatory evaporator for the formation of film.

Step-3: the film is further dried by attaching the hand of lyophilizer.

Step-4: Dispersion of the casted film takes place in aqueous medium.

Step-5: Multilamellar vesicles are formed upon hydration due to swelling of the lipid and peeling off of walls of the flask.

b) Non shaking method: Unlike hand shaking method agitation is provided from a steam of nitrogen rather than the rotatory movement.

Step-1: The lipid film is exposed to water saturated solution for (15-20mins)

Step -2: 10-20ml of bulk fluid i.e. sucrose (0.2m) in distilled water is added after hydration which causes swelling of the lipid.

Step-3: Flush the flask with nitrogen, allow to stand for 2 hours at 37*C after sealing it. Swell the contents of the flask gently to yield a milky suspension.

c) Freeze drying method:

Principle: The lipids can be dispersed by another method i.e. a finely divided while adding the aqueous solution which is by freeze drying of liquid which dissolved in an aqueous solution. one of the most ideal solvent is tertiary butanol after expansion of the dry cupid from a foam type structure 'MLV's can be obtain by face transition temperature by adding water or saline with rapid mixing.

2) Solvent Dispersion Methods

Principle: The method involves dissolution of lipids in an organic solvent. It is then brought into contact with materials to be entrapped within the liposomes in an aqueous phase.

Ethanol injections: It is mainly employed as an alternative for the preparation of the SUVs without sonification. By using a fine needle, ethanol solution is injected into an excess of saline or other aqueous medium. A high proportion of SUVs obtained i.e.:-

25 nm. This process causes less degradation of sensitive lipids and is extremely simple.

Ether injections: involves injecting the immiscible organic solution through a narrow needle slowly into aqueous phase. The procedure is similar to the ethanol injection method and carried out at a temperature suitable for solvent evaporation. The method can be used for treating sensitive lipids.

Rapid solvent exchange vesicles (RSEVs): Organic solution of lipids is subjected to pass through the orifice of blue tipped syringe under vacuum into a tube loaded with an aqueous buffer. The tube is mounted on vortexer. The bulk solvent is made to be vaporized within seconds before coming in contact with aqueous environment.

Other methods include: Reverse phase evaporation vesicles

Stable pleura lamellar vesicles (SPLV's)

3) Detergent Removal Method

Principle: This method involves application of detergents to bring phospholipids into contact with aqueous phase. They screen the hydrophobic portions of the molecule forming micelles. By increasing the micelles concentration, the size of the micelles gets reduced until saturation is obtained with detergent. The point when the free molecule concentration equals to the CMC, formation of simple detergent takes place. Removal of detergent from preformed mixed micelles containing phospholipid leads to spontaneous formation of unilamellar vesicles.

The detergent and all transition of micelle to the concentration of bilayer film can be removed by any one of three methods

1) Column chromatography
2) Use of Bio heads
3) Dialysis

Dialysis: Detergents are used to solubilize lipids at CMC(critical micellar concentration). The micelles combine to form LUVS. The detergents are now removed by dialysis with the help of commercial devices such as Lipo Preparation.

Gel permeation chromatography: Depletion of detergent is done by size special chromatography. The liposomes percolate through the inter bead space rather than penetrating into pores of beads packed in a column. Pre treatment is done to obtain the remaining amount of amphiphillic lipids that get adsorb on the swollen polysaccharide. The pre treatment is done by pre saturation of gel filtration column.

Active or remote loading methods

Procedure: Apply potential difference across the liposomal membranes and using pH meter, load drug molecules into preformed liposomes.

Loading of amphipathic molecules can be derived from the difference in concentration of proton across the liposomal membrane.

Advantages of liposomes:

1) Liposomes increased the stability of the encapsulated drug
2) Useful in passive targeting to cancer cells.
3) Liposomes encapsulated drug show high efficacy and therapeutic property.
4) Drugs with high toxicity can be encapsulated in liposomes there by reducing toxicological effect.
5) Drugs with low solubility and low permeability can be loaded in liposomal formulation and thereby increasing membrane permeation.
6) Improved pharmacological effect (reduced drug elimination, increased systemic circulation lifetime.

Disadvantages of Liposomes:

1) Liposomes production cost is relatively high
2) Encapsulation of drug sometimes leads to leakage and fusion between drug & molecule.
3) Liposomes are subjected to undergo reaction like oxidation and hydrolysis. Liposomes are show short half-life & low solubility.

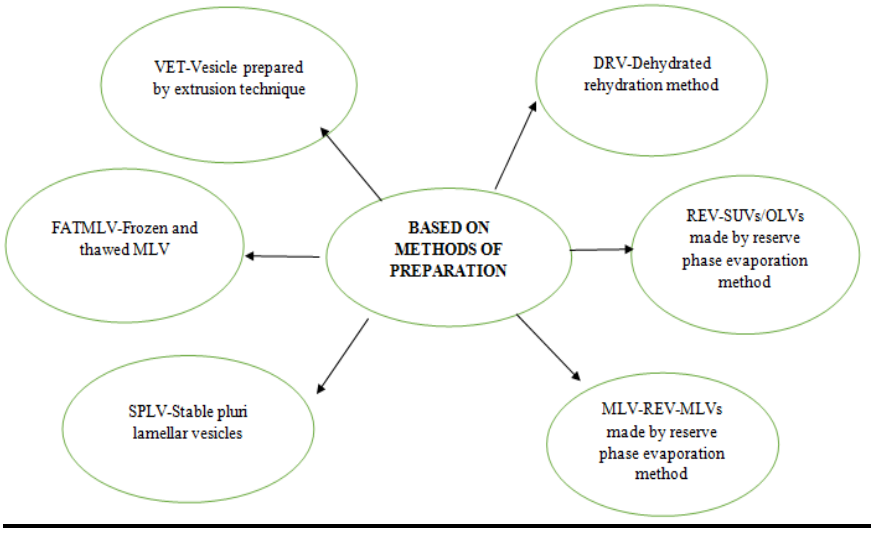


Fig1:Liposomes based on the methods of preparation

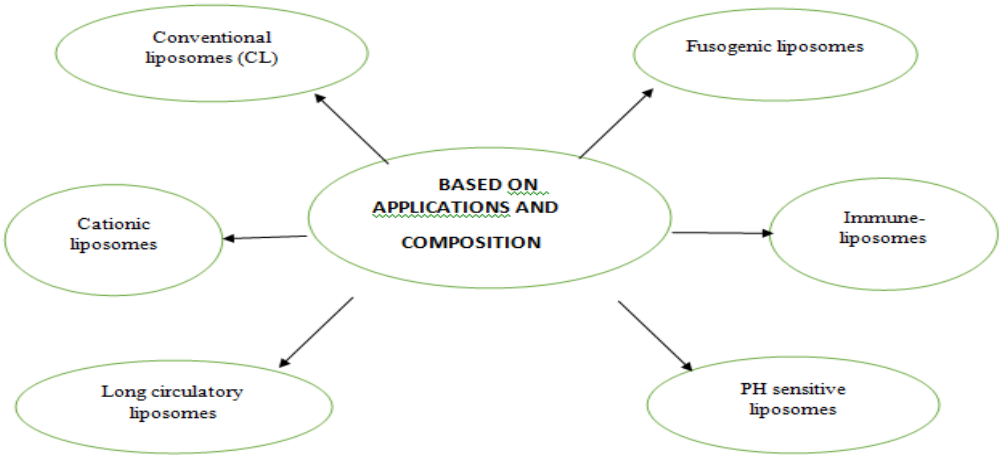


Figure 2: liposomes based on applications and composition

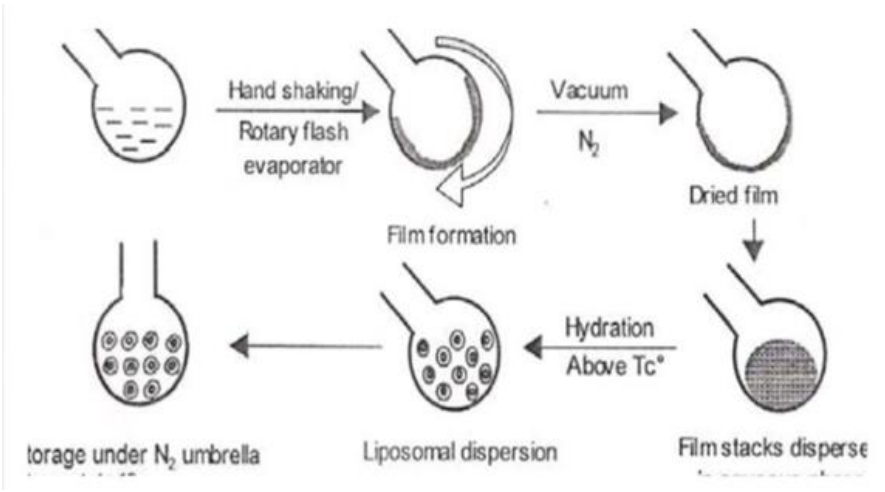
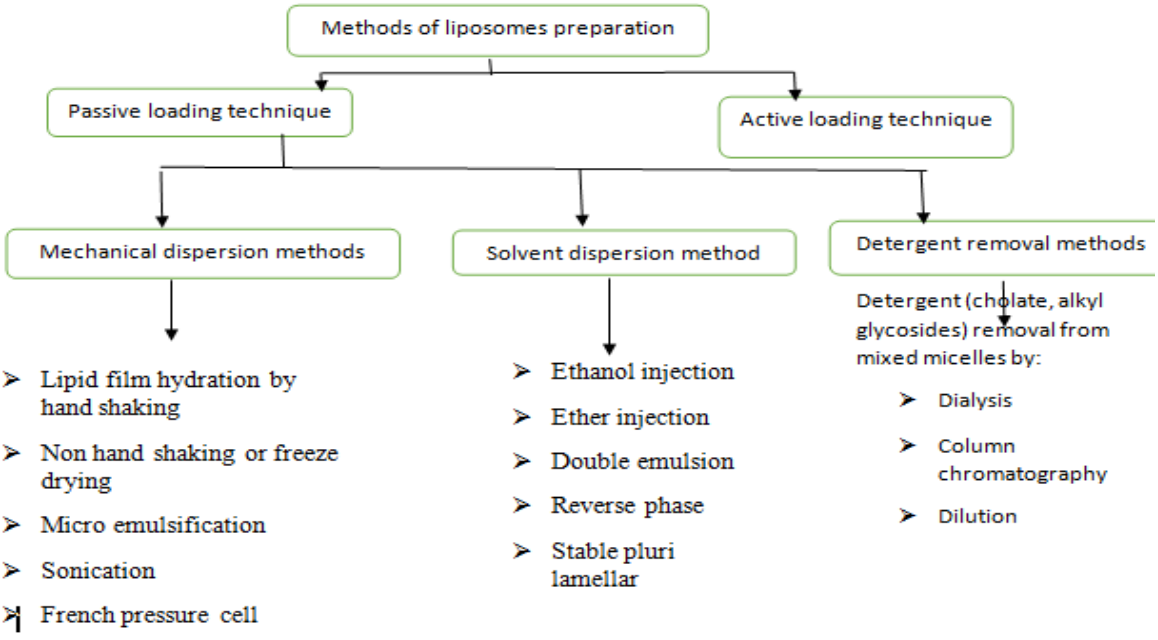


Figure 3: Diagrammatic Representation of hand shaking method



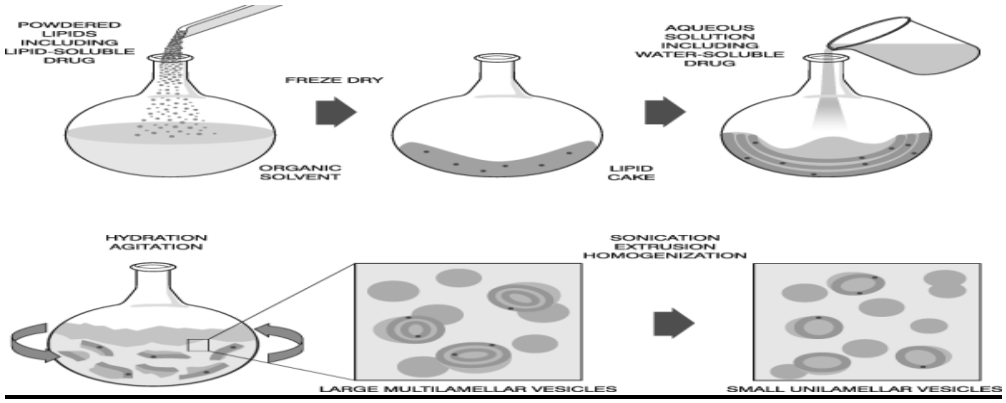


Figure 4: Diagrammatic representation of freeze dry method

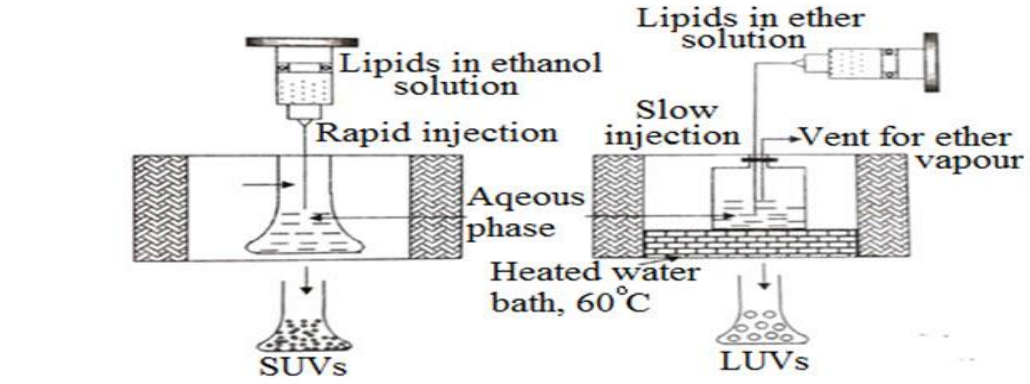


Figure 5: Diagrammatic representation ether/ethanol method

.

Applications of liposomes:

Liposomes are considered as ideal vehicle for the targeting drug molecule. The benefits of the drugs encapsulation in Liposomes which can be applied in various dosage forms such as colloidal solution, semi-solids forms creams & gels. Application in medicine and pharmacology can be divided into various aspects.

Liposomes As Drug Delivery Vehicles:

Drug delivery in controlled &sustained release (SR) can be obtained. Solubility of drugs is enhanced, pharmacokinetic & biodistribution can be altered.

Liposomes act as delivery vehicles for various enzyme & aid in enzyme replacement therapy and Lysosomal disorder.

Liposomes in tumour therapy:

Liposomes helps in targeted drug delivery and act as carrier for small cytotoxic molecule and gene and thus useful in cytokinesis.

Liposomes in immunology:

Liposomes used as artificial blood surrogates & acts as carriers for radiopharmaceuticals, they also show applications in cosmetics and dermatology Liposomes in enzymes Immobilization & bioreactor technology.

Liposomes In Parasitic Disease And Infections: Treatment of leishmaniasis antifungal therapy (Amphotericin B).

Liposomes encapsulation can be considered for administration of very potent and toxic antibiotics via parental route and in antiviral therapies (for drugs like ribavirin, paclitaxel, acyclovir).

Evaluation Parameter of Liposomes

Particle Size and Zeta Potential: It is the most important parameter foe characterization of liposomes. particle size, size distribution are measured by various methods such as photon correlation spectroscopy, UV visible spectroscopy. It has been found that the drug release highly effected by particle size, smaller particle offer large surface areas resulting in fast drug release but diffusion is slower inside the larger particles. The particle size and the zeta potential are measured using zetasizer (nano ZS, Malvern instruments)

Surface morphology: Evaluation of morphology of vesicles was performed by transmission electron microscopy. 10microL of sample solution was placed on lacey carbon coated copper grids. A very fine film of sample is obtained on the grid after blotting with a filter paper. The sample then loaded into 626cryospecimen holder. The images of sample were obtained using FEI titan halo80-300. The TEM was operated at 100Kv voltage.

Entrapment Efficiency And Drug Loading: Determination of entrapment efficiency can be done by comparing the amount of drug entrapped against amount of drug added. It can also be defined as ratio of concentration of drug and concentration of phospholipids. Entrapment efficiency%= {Drug entrapped in liposome /Total drug add initially} x100. Drug loading%= {Drug entrapped in liposome/Total lipids add initially} x100

Surface Charge:

Surface charge of liposome is done by free flow electrophoresis. It is used to examine the activity of active substances, lipid composition on the surface of the liposomes.

***In vitro* cytotoxicity:**It is performed using various calorimetric assays such as MTT assay, LDH {lactate dehydrogenase assay} and fluorometric assays such as ATP assay. Different chemicals have different cytotoxic mechanism such as destruction of cell membranes, irreversible receptor binding, protein synthesis prevention etc.

***In vitro* Drug Release:** It is performed by diffusion cell /dialysis tubing, membrane diffusion method. it is performed while maintaining sink conditions. The release of drug is determined using the following equation

%Drug release= Qt/Qi x100

Where Qt is the amount of drug present, Qi is the amount of drug added initially.

PH Measurement: The determination of pH for different formulation is done by a digital PH meter. The pH measurement of all formulation is done in triplicate and average values are calculated.

Stability studies: evaluated for optimized formulation storage at 4*C for 60 days. The percent entrapped for drug content is determined as a function of time. Stability of orthisiphon stamineus liposomes were studied at different pH (1.6, 5.5, 7.4) in gastrointestinal tract after mixing with PBS. The results obtained indicate that the liposomes at pH are unstable and can undergo agglomeration. The agglomeration is any how reversible by redispersing the solution in PBS (phosphate buffer solution).

Characterization techniques for liposomes

Liposomes characterization is essential for assuring the specificity of functionality and reproducibility. The important parameters such as size distribution provide useful information about quality of preparations and aid in physical stability determination methods (for example microscopy or nanoparticles tracking analysis) and are used for visualization of liposomes, aids in determination of lamellarity.

Other methods which are easy, fast and automated such as dynamic light scattering or field flow fractionation, flow cytometry, are performed and measurements are obtained by experimental data.

Transmission electron microscopy:

A microscopic technique which in a beam of electron is transmitted through a specimen. The interaction of electron that passes through specimens form an image. The image obtained is focused on to a fluorescent screen or to be detected by sensor. TEMs provide high resolution than light microscopes owing to de Broglie wavelength of electrons. Several TEM methods can be used to apply TEM evaluation of morphology.

Negative staining an easier way in which liposomes are embedded in electron dense4material. Cationic negative stain is used that bind to phosphate group and poorly penetrating the lipid bilayer. It allows indicative evaluation of internal structure of liposome without discriminative fine details.

Dynamic Light Scattering:

DLS measures the intensity of light scattered by dispersed particles. It is based on Brownian motion of particles, stating that when particles are dispersed in liquid medium they are constantly colliding with each other and solvent molecules and move in every direction. These collision results in transfer of certain amount of energy that have greater effect on smaller particles. A beam of light is incident on the solution. Now the intensity of light tends to fluctuate with time, DLS measure this intensity at an specific angle 90* at 460 nm, and the . A intensity versus time profile is plotted and the fluctuations are measured. The maximum are dependent on wavelength of incident light. A correlation is obtained from the profile, and the maximum are observed 50nm and 120 nm or wavelengths 250nm and 600nm. at DLS is considered a simple method to calculate the particle size distribution for nanoparticles.

Flourescence microscopy:

Size measurement and lamellarity of fluorescently labelled liposome is achieved by this technique. The technology involves the use of fluorescent probe called N-(7-Nitro benz-2-Oxa-1,3-diazol-4-yl)-1,2dihexade canoyl -sn-glycero-phosphoethanolamine. It quenches the outer surface of liposomes fluorescence microscopy provide advantages such as high sensitivity and convenience. Certain limitations are faced that this method requires the immobilization of sample to glass surface increasing the risk of shape alteration, fusion of liposomes.

Atomic force microscopy

Investigate surface properties, size distribution, morphology and stability of liposomes. The method is based on interaction between sample and tip of cantilever, able to measure liposomes with great resolution 0.1nm. it is found that liposomal rigidity affects the drug delivery, which is characterized by stability profile, drug release, systemic circulation time. Advantages of Atomic Force microscopy are high resolution, non-invasive method, quick and reliable, large particles are identified in suspension.

MTT assay:

It is most commonly used colorimetric assay for evaluation of cytotoxicity or cell viability. The principle

involved is measuring the activity of mitochondrial enzymes such as succinate dehydrogenase. In this assay MTT is reduced to a purple formazan by NADH and quantified by light absorbance at specific wavelength. MTT formazan is insoluble in water results in formation of purple needle shaped crystals in the cells. Thus for prevention of crystals an organic solvent such as isopropanol is used for solubilization. The assay is based conversion of tetrazolium salt into colored formazan by mitochondrial activity. The amount of formazan produced indicates the viable cell number. It is rapid sensitive, specific and very competitive to other toxicological tests and thus suitable for toxicological assessments.

LDH (lactate dehydrogenase assay):

It is a calorimetric assay for analyzing cellular cytotoxicity. It can be used with different cell culture, an indicative for chemical and cell mediated cytotoxicity. The quantitative determination of lactate dehydrogenase enzyme (i.e. released from damaged cells) can be done. Reduction in cell viability results in increase of leakiness of plasma membrane and therefore, LDH enzyme starts releasing in cell culture. This release is measured with a coupled enzymatic reaction in which a red colored formazon is formed due to conversion of tetrazolium salt by diaphorase. The resulted red formazon is absorbed maximum at 492nm and can be quantitatively measured at 490nm. The assay is simple, reliable, and speed. The release of LDH into culture medium is an indicator of cell deaths.

Conclusion:

Liposomes are the most preferable carrier, due to their diverse properties, biocompatibility and application. They are reported as best carrier of drugs in human therapy ranging from conventional drugs to hormones, peptides immunoglobin and genes. liposomes can be formulated in various size, composition and lamellarity. The therapeutic activity of various drugs is enhanced by encapsulating in liposomes, mainly by alteration in pharmacokinetics and pharmacodynamic property. Liposomes are characterized by Transmission electron microscopy (TEM), fluorescence microscopy, UV visible spectroscopy, Atomic force Microscopy (AFM), LDH assay, MTT assays.

The application of liposomes as carriers in drug delivery is promising and will undergo tremendous growth in future in clinical therapy.

REFERENCES:

1. Fasili Z, Mehri F, Ebrahimi HA, Jamali Zh, Mohammad Khanlou E, Kahrizi F, Salimi A. Applying Nanoparticles in the Treatment of Viral Infections and Toxicological Considerations. Pharmaceutical and Biomedical Research. 2019; 5(4):1-20.
2. Subash Chandran M.P, Prasobh G.R, Jaghatha T, Aswathy B.S, Remya S.B (2019). "An Overview on Liposomal Drug Delivery System", International Journal of Pharmaceutical and Phytopharmacological Research, 9(2), pp.61-68.
3. Maluta S. Mufamadi,1 Viness Pillay,1 Yahya E. Choonara,1 Lisa C. Du Toit,1 Girish Modi,2Dinesh Naidoo,3 and Valence M. K. Ndesendo, "A Review on Composite Liposomal Technologies. Hindawi Publishing Corporation Journal of Drug Delivery Volume 2011, Article ID 939851, 19 pages, Doi:10.1155/2011/939851Specialized Drug Delivery
4. Claudia Zylberberg & Sandro Matosevic (2016) Pharmaceutical liposomal drug Delivery: a review of new delivery systems and a look at the regulatory landscape, Drug Delivery, 23:9, 3319-3329, DOI: 10.1080/10717544.2016.1177136.
5. Upendra Bulbake , Sindhu Doppalapudi , Nagavendra Kommineni and Wahid Khan Pharmaceutics 2017, 9, 12; doi:10.3390/pharmaceutics9020012
6. Kant Shashi*, Kumar Satinder, Prashar Bharat, A COMPLETE

REVIEW ON: LIPOSOMES Department of Pharmaceutical Sciences, IRJP 2012, 3 (7) ISSN 2230 –8407
7. Saraswathi Marripati, K. Umasankar1, P. Jayachandra Reddy, A Review On Liposomes Journal of Research in Pharmaceutical and Nano Sciences. 3(3), 2014, 159 – 169. ISSN: 2319 – 9563
8. Shende PK, Desai D, Yawalkar R, Mrinal P. Multidrug Liposomes of Glycolic Acid and Nutraceuticals for Cosmetic Application. Nov Appro Drug Des Dev. 2017; 2(5) : 555597
9. Yunes Panahi, Masoud Farshbaf, Majid Mohammadhosseini, Mozhdeh Mirahadi, Rovshan Khalilov, Siamak Saghfi & Abolfazl Akbarzadeh (2017) Recent advances on Liposomal nanoparticles: synthesis, characterization and biomedical applications, Artificial Cells, Nanomedicine, and Biotechnology, 45:4, 788-799, DOI: 10.1080/21691401.2017.1282496
10. Aisha et al.: Preparation and characterization of nano Liposomes of Orthosiphon stamineus ethanolic extract in soybean phospholipids. BMC BIOTECHNOLOGY 2014 14:23
11. Barbara Ruozi1, Daniela Belletti1, Andrea Tombesi 2, Giovanni Tosi1, Lucia Bondioli1 Flavio Forni1, Maria Angela Vandelli1, AFM, ESEM, TEM, and CLSM in liposomal Characterization: a comparative study, International Journal of Nanomedicine 2011:6, Dove press
12. D. H. Anjum Characterization of nanomaterials with Transmission electron microscopy 2016 IOP Conf. Ser.: Mater. Sci. Eng. 146 012001
13. Stefan Hupfeld, Ann Mari Holsæter, Merete Skar, Christer B. Franzen, And Martin Brandl∗ "Liposome Size Analysis by Dynamic/StaticLight Scattering upon Size Exclusion-/Field Flow-Fractionation" Journal of Nanoscience and Nanotechnology Vol.6, 1–7, 2006, DOI: 10.1166/jnn.2006.454 · Source: PubMed
14. Maria Kanasov´1,2• Karel Nesmeˇrek1Systematic review of liposomes' characterization methods. Monatsh Chem (2017) 148:1581–1593, DOI 10.1007/s00706-017-1994-9
15. Özlem Sultan Aslantürk, In Vitro Cytotoxicity and Cell Viability Assays: Principles, Advantages, and Disadvantages, http://dx.doi.org/10.5772/intechopen.71923
16. Ghule MM, Bhoyar GS (2018) Formulation and Evaluation of Modified Liposome for Transdermal Drug. J Develop Drugs 7: 186. Doi:10.4172/2329-6631.100018
17. Muhammad Wahab Amjad1* and Maria Abdul Ghafoor Raja1Development and Characterization of Liposome Enriched Ketoprofen Liposomal Hydrogels, Journal of Pharmaceutical Research International 27(1): 1-7, 2019; Article no.JPRI.48577
18. Xiaoyuan Ding1, Chenyang Yin1, Weiwei Zhang2, Yu Sun1, Zhenzhen Zhang1, Endong Yang1,Dongdong Sun1* and Weiyun Wang, Designing Aptamer-Gold Nanoparticle Loaded pH-Sensitive Liposomes Encapsulate Morin for Treating Cancer Nanoscale Research Letters (2020)15:68 https://doi.org/10.1186/s11671-020-03297-x
19. Vieri Piazzini 1ID , Elisa Landucci 2, Giulia Graverini 1, Domenico E.PellegriniGiampietro 2,Anna Rita Bilia 1 and Maria Camilla Bergonzi 1,*Stealth and Cationic Nanoliposomes as Drug Delivery Systems to Increase Andrographolide BBB Permeability, Pharmaceutics 2018, 10, 128; doi:10.3390/pharmaceutics10030128
20. Mahmoud Mokhtar Ibrahim, Anroop B. Nair,Bandar E. Aldhubiab and

Tamer M. Shehata, Hydrogels and Their Combination with Liposomes, Niosomes, or Transfersomes for Dermal and Transdermal Drug Delivery. 157 http://dx.doi.org/10.5772/intechopen.6815

21. Snehal K. Shukla 1, Nishant S. Kulkarni 1, Amanda Chan 2, Vineela Parvathaneni 1,Pamela Farrales 1, Aaron Muth 1 and Vivek Gupta 1Pharmaceutics 2019, 11, 559; doi:10.3390/pharmaceutics11110559
22. Heba F. Salem1, Sabry M. Tamam2, Sahar M. Lotayef1biodegradable Liposomes For Acyclovir-Gold Nanoparticles As An Efficient Carrierfor Enhanced Topical Delivery Int J Pharm Pharm Sci, Vol 9, Issue 8, 60-64
23. Ana Casadó1,2 M Lluïsa Sagristá1Margarita Mora1A novel microfluidic liposomal formulation For the delivery of the SN-38 camptothecin: Characterization and in vitro assessment of its Cytotoxic effect on two tumour cell lines, Dove press journal https://www.dovepress.com/ by 106.77.181.246
24. Ravi Theaj Prakash Upputuri, Abul Kalam Azad Mandal*Sustained Release of Green Tea Polyphenols from Liposomal Nanoparticles; Release Kinetics and Mathematical Modelling, Iranian J Biotech. 2017 October;15(4):e1322/ DOI:10.15171/ijb.1322
25. Ramkrishna Sen1 Sunit Kumar sahoo*1 Soumya Ranjan Satpathy2 Liposomes as drug deliver system: A brief review (2014) Int. J. Res. Pharm. Sci., 5(4), 309-321
26. Satyavathi K, Bhojaraju P, Srikranthi M, Sudhakar P (2015) Formulation and In-Vitro Evaluation of Liposomal Drug Delivery System of Cabazitaxel. J Pharm Drug Delivery Res 4:2.doi:http://dx.doi.org/10.4172/2325-9604.1000133
27. Akshay Singha Roy , Sudipta Das*, Arnab Samantha, International journal of Applied pharmaceutics , Vol 10, Issue 2, 2018, 52-56
28. Hanumanaik M, Patel SK and Sree KR: Solid Lipid Nanoparticles; A Review. International journal of Pharm Sci Res. 2013; 4(3); 928-940
29. Tiesong Zhang1*, Jing Ma1*, Chao Li2, Ken Lin1, Fan Lou1, Hongchao Jiang3,Yingqin Gao1, Yanli Yang4, Cheng Ming5 And Biao Ruan4 ONCOLOGY REPORTS 37: 1653-1661, 2017, DOI: 10.3892/or.2017.5365
30. Heba F. Salem1, Rasha M. Kharshoum1, Mohamed Mahmoud1*, Saleh A. Azim2, EL-Zeiny M. Ebeid2 (2017) http://dx.doi.org/10.4321/S2340-98942018000100001
31. Pillai G (2014) Nanomedicines for Cancer Therapy: An Update of FDA Approved drugs and Those under Various Stages of Development. SOJ Pharm Pharm Sci, 1(2), 13
32. Bethany Almeida 1,2, Okhil K. Nag 2, Katherine E. Rogers 2,3 and James B. Delehanty 2,*Recent Progress in Bioconjugation Strategies for Liposome Mediated Drug Delivery Molecules 2020, 25, 5672; doi:10.3390/molecules25235672
33. Marwa Mohamed , Amr S. Abu Lila , Taro Shimizu , Eman Alaaeldin , Amal Hussein, Hatem A. Sarhan , Janos Szebeni & Tatsuhiro Ishida (2019) PEGylated liposomes: Immunological responses, Science and Technology of Advanced Materials, 20:1, 710-72
34. Mi-Kyung Lee Liposomes for Enhanced Bioavailability of Water-Insoluble Drugs: In Vivo Evidence and Recent Approaches Department of Pharmaceutical Science 2020, 12, 264; doi:10.3390/pharmaceutics12030264
35. Wajed Khan*, Pethe. A.S.* and Talib Y.A.PREPARATION OF DRUG LOADED LIPOSOME

Journal of Global Biosciences Vol. 5(6), 2016 pp. 4221-4226, ISSN 2320-1355

36. Maluta S. Mufamadi,1 Viness Pillay,1 Yahya E. Choonara,1 Lisa C. Du Toit,1 Girish Modi,2 Dinesh Naidoo,3 and Valence M. K. Ndesendo1 A Review on Composite Liposomal Technologies for Specialized Drug Delivery Journal of Drug Delivery Volume 2011, Article ID 939851, 19 pages, Doi:10.1155/2011/939851
37. Katsumi Matsuzaki *, Osamu Murase, Ken'ichi Sugishita, Shuji Yoneyama, Ken'ya Akada, Mayu Ueha, Akemi Nakamura, Satoe Kobayashi "Optical characterization of liposomes by right angle light scattering And turbidity measurement", Biochimica et Biophysica Acta 1467 (2000) 219^226W,

.