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REVIEW ON UFASOMES AND VESICULAR DRUG DELIVERY SYSTEM

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ABSTRACT

A number of novel drug delivery systems have emerged emcompassing various administration, to achieve controlled and targeted delivery. Number of vesicular drug delivery systems likes liposomes, niosomes, tansferosomes and ufasome. Unsaturated fatty acid vesicles (ufasomes) are suspensions of closed lipid bilayers that are composed of fatty acids, and their ionized species (soap) which are restricted to narrow pH range from 7 to 9. Recent innovations can provide opportunity to formulate ufasomes with tailorable features such as extension of pH range, insensitivity toward divalent cations, and enhancement of stability. This article describes method of ufasome preparation, key issues in ufasome manufacturing and recent innovations in ufasomes, dynamicity, stability, and microscopic characterization of ufasomes. Ufasomes are relatively less costly than liposomes. There prepared by sonication retain less solute per unit weight of fatty acid. These can good capacity of entrapped glucose than liposome.

Keywords: Vesicular Drug Delivery System, Fatty Acid Vesicles, Soap Vesicles, Ufasome, Liposomes

INTRODUCTION

Vesicular structures is one such system, which can be expected to prolong the duration of the drug in systemic circulation, and reduce the toxicity by selective up taking. Biologic origin of these vesicles was first reported in 1965 by Bingham, and was given the name Bingham bodies. Consequently, a number of vesicular delivery systems such as liposomes, niosomes, pharmacosomes etc, were developed. Now a day vesicle as a carrier system in immunology, membrane biology and diagnostic technique and most recently in genetic Engineering. It provides an efficient method for delivery to the site of infection, leading to reduce of drug toxicity with no adverse effects. They can incorporate both by hydrophilic and lipophilic drugs have become

the vehicle of choice in drug delivery and lipid vesicles were found to be of value. [1, 2, 3, 4]

Vesicular drug delivery reduces the cost of therapy by improved bioavailability of medication, especially in case of poorly soluble drugs. Vesicular drug delivery systems delay drug elimination of rapidly metabolizable drugs, and function as sustained release systems. [5] This system solves the problems of drug insolubility, instability, and rapid degradation. The new vesicular delivery system consisting of unilamellar or multilamellar vesicles called niosomes was introduced. Encapsulation of the drug in have specific advantages while avoiding demerits associated with conventional dosage forms because these particles can act as drug reservoirs. These carriers play an increasingly important role in drug delivery because by slowing drug release rate, it is possible to reduce the toxicity of drug. In general vesicles made of natural or synthetic phospholipids are called liposomes. Different types of pharmaceutical carriers are present (figure 1). They are particulate, polymeric, macromolecular, and cellular carrier. [5, 6]

ADVANTAGE NIOSOMES OVER OTHER VESICULAR SYSTEMS

a) The vesicle suspension is water based vehicle. This offers high patient compliance in comparison with oily dosage forms.

b) 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.

c) The characteristics of the vesicle formulation are variable and controllable. Altering vesicle composition, size, lamellarity, tapped volume, surface charge and concentration can control the vesicle characteristics.

d) The vesicles may act as a depot, releasing the drug in a controlled manner.

In Vesicular delivery system provide an efficient method for delivery of drug directly to the site of infection, leading to reduction of drug toxicity with no adverse effect vesicular drug delivery reduce the cost of therapy by improve bioavaibility of medication especially in case of poorly soluble drugs. They can incorporate both hydrophilic & lipophilic drug. Microemulsions and externally triggered (e. g. temperature, pH, or magnetic sensitive) carriers load drugs passively, which may lead to low drug loading efficiency and drug leakage in preparation, preservation and transport in vivo. [7, 8]

1. 2 ADVANTAGES VESICULAR SYSTEM

a. Prolong the existence of the drug in systemic circulation, and perhaps, reduces the toxicity.

If Selective uptake can be achieved due to the delivery of drug directly to the site of infection.

b. Improves the bioavailability especially in the case of poorly soluble drugs.

c. Both hydrophilic and lipophilic drugs can be incorporated.

d. Delays elimination of rapidly metabolizable drugs and thus function as sustained release Systems. [9]

e. Liposomes as a potential delivery system for the oral administration of insulin, have been extensively studied

f. It was observed by many scientists, that the liposomes had protective effects against proteolytic digestive enzymes like pepsin and pancreatin **and** they can increase the intestinal uptake of macromolecules and hence are capable of enhancing insulin uptake**.**

g. Liposomes with a specifically modified design, i. e. long-circulating and especially actively targeting liposomes, stand a better chance in becoming truly tumoritropic carriers of photosensitizers, and can hence be used successfully in photodynamic therapy.

h. Liposomal drug delivery system is advantageous in the fulfillment of the aspects related to protection of the drug, controlled release of the active moiety along with the targeted delivery, and cellular uptake via endocytosis. [9]

These vesicular systems are accompanied with some problems like drug carriers and externally triggered (eg. , temperature, pH, or magnetic sensitive) carriers load drugs passively, which may lead to low drug loading efficiency and drug leakage in preparation, preservation and transport in vivo. Vesicular drug delivery systems delay drug elimination of rapidly metabolizable drugs, and function as sustained release systems. [1, 4]

This system solves the problems of drug insolubility, instability, and rapid degradation Among various approaches investigated to overcome the skin barrier associated penetration, vesicular system are gaining importance recently of drug molecules. [5] vesicular carriers like liposomes, niosomes, pharmacosomes and discomes improved the pharmacokinetic and pharmacodynamic properties of various types of drug molecules. Vesicles are colloidal particles in which a concentric bilayer made-up of amphiphilic molecules surrounds an aqueous compartment. They are a useful vehicle for drug delivery of both hydrophobic drugs, which associate with the lipid bilayer and hydrophilic drugs, which are encapsulated in the interior aqueous compartment. [10] These vesicular delivery systems attracted considerable attention in topical/transdermal drug delivery for many reasons: niosomes can act as enhancers for the penetration through the skin of guest molecules, are biodegradable, effective in the modulation of drug release properties, and in most cases non-toxic. 6 Their effectiveness is strongly dependent on their physico-chemical properties, such as composition, size, charge and lamellarity. The differrent type of pharmaceutical artificial vesicles feature an aqueous compartment separated from an aqueous surrounding by a closed membrane that is almost impermeable for hydrophilic

substances. Like cell membranes, vesicle membranes consist *of* amphiphilic phospholipids that link a hydrophilic head and a lipophilic tail. [6, 7]

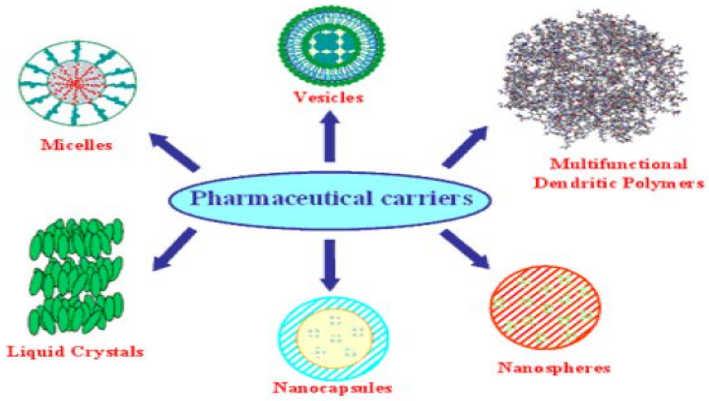

Figure 1. Pharmaceutical carriers [4]

UFASOMES

INTRODUCTION

Fatty acid vesicles always contain two types of amphiphiles, the nonionized neutral form and the ionized form (the negatively charged soap). The ratio of nonionized neutral form and the ionized form is critical for the vesicle stability. Fatty acid vesicles are actually mixed "fatty acid/soap vesicles," but for the sake of simplicity, we just call them fatty acid vesicles. The formation of fatty acid vesicles was first reported by Gebicki and Hicks in 1973 and the vesicles formed were initially named "ufasomes," "unsaturated fatty acid liposomes. [10, 11]

Fatty acid vesicles are colloidal suspensions of closed lipid bilayers that are composed of fatty acids and their ionized species (soap). They are observed in a small region within the fatty acid-soap-water ternary phase diagram above the chain melting temperature (Tm) of the corresponding fatty acid-soap mixture. However, even natural phospholipids are chemically heterogeneous, and pure synthetic phospholipids are not yet available in reasonable quantities. The advantage of ufasomes over liposomes is the ready availability of fatty acids. [13]

METHODS

Only unoxidized materials are preferred for preparation of ufasome commonly using vortex mixer

In this method, Stock solutions containing 10% of oleic and linoleic acids in chloroform are prepared and stored at 20°C. For typical preparations, 0.02 ml of the stock solution is evaporated in a test tube on a water pump and finally dried with a stream of nitrogen. The fatty acid film is then broken up completely in 0. 2 ml of 0.1 M *tris*-hydroxymethyl aminomethane buffer, pH 8-9, by vigorous shaking on vortex mixer. to get

resultant suspension of ufasomes are stable for at 20hr. In sometimes preparation of ufasomes by using ultrasonic generator with titanium microtip also used. [14]

SELECTION OF FATTY ACID

In fact, most of the studies were confined to the C-18 acids because they showed the greatest promise in early trials. Only oleic acid (cis-9 octadecenoic acid) and linoleic acid (cis, cis-9, 12-octadecadienoic acid) formed membranes which all perfable in preparation ufasome. In generally Charging of membrane with small amount of oleic acid, linoleic acid and also stearic acid which do not improve the preparation. Stability tests showed that oleic acid remained uncontaminated by peroxides for at least 6 weeks while linoleic acid developed significant peroxide after 2-3 weeks. [15, 16]

ADDITION OF CHOLESTEROL

Cholesterol serves a unique purpose of modulating membrane fluidity, elasticity, and permeability in vesicle prepared from lipid. It literally fills in the gaps created by imperfect packing of other lipid species. There is a rapid decrease in the ability to hold solute by vesicle in the presence of higher proportions of cholesterol. There is a rapid decrease in the ability to hold solute by vesicle in the presence of higher proportions of cholesterol. Also, there is no enhancement of membrane impermeability at any cholesterol concentration. It was concluded from their results that leakage of glucose from vesicles containing 17% of incorporated cholesterol was higher than leakage from cholesterol free oleic and linoleic acid ufasomes. [14, 17]

PH AND SELECTION OF BUFFER

In generally Ph range 7-9 of formulation of fatty acid vesicles where approximately half of the carboxylic groups are ionized. Below their Ph range 7 that fatty acid called unsaturated fatty acid. Micelles are the dominant aggregation species at higher pH (higher ratio of ionized to protonated molecules), whereas oil droplets form in the low pH region. It is also better to understand fatty acid vesicle systems at concentrations just above the concentration at which vesicle formation is observed, often called "critical vesiculation concentration," CVC. At the critical vesiculation concentration, monomers and nonvesicular aggregates assemble into a bilayer structure and form colloidal suspensions of vesicles. [15, 18] The widely accepted buffer for ufasome preparation is *tris*-hydroxymethyl aminomethane. Selection of buffer is largely dependent on the type of solute to be incorporated, i. e. , in the case of glucose entrapment in vesicle; ufasomes prepared in bicarbonate did not hold glucose, while the borate preparations could not be tested for retention because of formation of glucose-buffer complex. [16]

ELECTROLYTE

Most electrolytes inhibit formation of ufasomes. However, once the spheres are stabilized in appropriate buffer. They can expose to solution of buffer phosphates and still retained to occlude gulose. [17]

PEROXIDATION

Introduction of a bulky hydrophilic group by peroxidation would distort the hydrophobic membrane interior, allowing an easier passage of water-soluble molecules. Mostly effecting on ufasome membranes and to produce disturb on normal bilayer of fatty acid molecules.

Method of preparation can widely affect the extent of peroxidation of fatty acid. No peroxidation occurred during the short periods required for hand vortexing. Under the more violent ultrasonic resuspension, linoleic acid oxidized at 0.1% per minute in air-saturated buffers when exposed to 30-W irradiations. Since 3 min was the longest exposure used, this method did not produce extensive oxidation of even oxidation sensitive linoleic acid. It is interesting to note that the enzyme was unable to induce leakage from oleic acid ufasomes. It means lipoxygenase fails to peroxidase monoenoic fatty acids. [17, 19]

Lipid peroxidation (LPO) involves both enzymatic and nonenzymatic catalytic mechanism. Transition metal ions are important components of nonenzymatic lipid peroxidation relatively few metals that undergo a change in valency involving a single electron transfer can catalyze a rapid rate of peroxidation in unsaturated lipids. Nonvariable valence state metals such as calcium, magnesium, and zinc which cannot take part in redox-coupled homolysis have also been shown to influence lipid peroxidation. It was shown that at low concentrations (~10 -6 -10 -5), Ca 2+ stimulated LPO in lipid by its ability to interact with negatively charged groups of lipid (phosphate groups of lecithin, carboxyl groups of linolenic acid), thereby displacing the bound Fe 2+ ions so increasing the concentration of free Fe 2+ ions, which participate directly in LPO catalysis. Incidentally, not only Ca 2+ ions may have such a biphasic action on LPO; other cations with high charge density are also capable of releasing Fe 2+ ions bound with negatively charged groups of lipids and of interacting with superoxide free radicals. It was found that in the absence of Ca 2+ ions, addition of La 3+ ions to linolenic acid ufasomes in a concentration corresponding to that of the Fe 2+ ions stimulated LPO. An effect of inhibition of peroxidation of linolenic acid was observed on the combined action of equimolar concentrations of Ca 2+ and La 3+. [19, 20]

New type of fatty acids in ufasome preparation

Cis - 4, 7, 10, 13, 16, 19-docosahexaenoic acid (DHA) was reported to self-assemble into vesicles between pH 8. 5 and 9. [17]

NOVEL APPROACHES OF PH RANGE [20, 21, 23]

The pH range suitable for the formation of fatty acid vesicles is generally narrow.

a)Addition of amphiphilic additives such as linear alcohols or a surfactant with a sulfate for example, mixtures of decanoic acid and decanoate form vesicles between pH 6. 4 and pH 7.8, but the pH for vesicle formation can be lowered to at least 4. 3 by adding sodium

dodecylbenzenesulfonate (SDBS).

b) Synthetically modify the size of the hydrophilic head group of fatty acids: enhanced stability of vesicles at lower pH was reported by using a fatty acid with an oligo (ethylene oxide) unit intercalated between the hydrocarbon chain and the carboxylate head group. The very bulky polar group has two effects, a lowering of the phase.

INSENSITIVITY TOWARD DIVALENT CATION

Cryogenic transmission electron microscopy studies of the ternary monoolein-sodium oleate-water system have also shown that uni- and multilamellar vesicles formed from mixtures of mono-olein and sodium oleate and the vesicles remained stable for a prolonged period of time (over 1 year). [21]

ENHANCEMENT OF STABILITY BY CROSSLINKING FATTY ACID MOLECULES BY CHEMICAL BONDS

One example is the formation of vesicles from anionic gemini surfactants with the carboxylic head group. Example both monomeric and polymerized SAU were reported to self-assemble into vesicular aggregates and vesicles from polymeric SAU were stable at elevated temperatures. [19, 22]

MIXTURE OF FATTY ACID / SOAP VESICLE

Mixtures of tetradecyltrimethylammonium hydroxide (TTAOH) and fatty acids were investigated as a model system of mixed vesicles. Unilamellar and multilamellar vesicles were reported to form, if approximately the same concentration of TTAOH and fatty acid were mixed. [24, 23]

DYNAMIC NATURE OF UFASOMES

Dynamic features that place fatty acid vesicles in between conventional vesicles formed from double-chain amphiphiles and micelles formed from single-chain surfactants. The formation kinetics of micelles and vesicles from a saturated fatty acid/soap monomer solution was compared by dialyzing the fatty acid/soap monomers through a cellulose acetate membrane. An equilibrium state was readily obtained in the case of the micellar system (micelles formed in the diffusate chamber and the fatty acid/soap concentrations in both chambers became the same). In the case of vesicles, however, the attainment of an equilibrium state was severely hindered (the concentration in the diffusate increased very slowly after the solution was saturated with monomers). Vesicles are generally composed of a much greater number of amphiphiles than micelles. A convenient way of fatty acid vesicle preparation is the addition of an alkaline soap solution to a buffer solution of intermediate pH. For example, a concentrated solution of sodium oleate micelles is added to a buffered solution at pH 8.5, and oleic acid/sodium oleate vesicles form spontaneously as a result of a partial protonation of the oleate molecules, caused by the drop in pH from about 10.5 to 8. 5. Vesicles thus formed are polydisperse in size and lamellarity. [21, 26, 29, 30]

MICROSCOPIC STUDIES

The arrangement of biological membrane components such as fatty acid, phospholipid

was derived from the electron microscopy of sectioned vesicular structures. As attempts to study the ufasome structure by electron microscopy of negatively stained specimens showed that they did not survive the preparatory steps. All attempts to stain ufasomes with neutralized potassium phosphotungstate for electron microscopy failed to produce specimens with any internal structure. [31]

FREEZE FRACTURING AND EACHING

First of all, ufasome suspension is equilibrated with 17% glycerol for 10 min before freezing. The ufasome suspensions are then rapidly frozen on to copper helmets with Freon and then stored in liquid nitrogen. Fracturing is carried out in a Balzers microtome at 110°C and at 2×10 -6 Torr pressure. For etching, the temperature is increased to 100°C for 1 min. After cutting, a film of platinum and carbon is deposited on the fracture face to a thickness of 3 nm at an angle of 45°. The most successful technique used to clean replica is to float them off the metal helmet on to water, to which methanol is gradually added, until the solution is 80% alcohol. It took 30 min to remove all traces of fatty acid. The replicas are then examined in a Hitachi HS8 electron microscope. [28, 29, 32]

COMPARISION OF UFASOME AND LIPOSOME [1, 10, 31, 33, 34]

Method of preparation

Virtually identical techniques can be used for either type of vesicle. The one interesting difference is that intensive sonication of fatty acid dispersions does not lead to uniformly-sized particles. Instead, there is some evidence to suggest that oleic and linoleic acids can be forced into the solution to produce a clear supersaturated system that becomes turbid after standing for a few minutes. Ufasomes prepared by sonication retain less solute per unit weight of fatty acid.

Ph Sensitively

Compared to liposomes, ufasomes are much more sensitive to pH and ionic strength of medium. While the phospholipid vesicles tolerate the range of conditions, fatty acid membranes fail to form, except at slightly alkaline pH and at low ionic strengths.

Light scattering property

Comparison of the light scattering properties of ufasomes and liposomes shows that the phospholipid vesicles are stronger scatterers per mole of material. It is not easy to make an exact comparison; roughly, a 10 -3 molar liposome suspension has absorbance of 0. 7, while a similar preparation of ufasomes reads about 0.2.

Cross-sectional area

Reasonable cross-sectional areas at 10-20 dyne cm -1 are 0.8 nm 2 for lecithin and 0.4 for oleic and linoleic acids. It appears likely; therefore, a mole of lecithin forms a membrane twice as large as that formed from a mole of either of these acids.

Solute entrapment capacity

Ufasomes and liposomes have a similar capacity to entrap glucose. Liposomes made up from lecithin with added cholesterol and dicetyl phosphate held about 1200 nM

glucose per µM lipid. When lecithin is replaced by sphingomyelin, this amount was nearly doubled.

Cost

Conventional fatty acids are inexpensive, certainly cheaper than purified diacylglycero-phospholipids. Ufasomes are relatively less costly than liposomes.

Intestinal absorption

In rats, orally delivered insulin, encapsulated into liposomes, proved to exert a considerably smaller hypoglycaemic response than i. p. delivered free or encapsulated insulin as reported by Patel and Ryman. Entrapment into egg phosphatidylcholine-cholesterol liposomes strongly reduced carboxyfluorescein absorption from the rat everted jejunum and only marginally increased absorption of fluorescein isothiocyanate-conjugated dextran.

CONCLUSION

Unsaturated fatty acid vesicles (ufasomes) are suspensions of closed lipid bilayers that are composed of fatty acids, and their ionized species (soap) which are restricted to narrow pH range from 7 to 9. In ufasomes, fatty acid molecules are oriented in such a way that their hydrocarbon tails are directed toward the membrane interior and the carboxyl groups are in contact with water. Stable ufasome formulation critically depends on proper selection of fatty acid, amount of cholesterol, buffer, pH range, amount of lipoxygenase. Recent innovations can provide opportunity to formulate ufasomes with tailorable features such as extension of pH range, insensitivity toward divalent cations, and enhancement of stability. Recent innovations in ufasomes, dynamicity, stability, and microscopic characterization of ufasomes. Later part of this article deals with comparison of ufasomes with thoroughly studied liposomes.

REFERENCES

1. Annakula Deepthi, Rao Madhukar, Jukanti Raju, Bandari Suresh, and Reddy Prabhakar Reddy Veera: Provesicular drug delivery systems: An overview and appraisal. Scholars Research Library 2010; 2:135-146.
2. Keservani Raj K., Sharma Anil K., Ayaz MD. , Kesharwani Rajesh K.: Review Novel drug delivery system for the vesicular delivery of drug by the niosomes. International Journal of Research in Controlled Release 2011; 1:1-8.
3. Gupta Stuti , Singh Ravindra Pal , Lokwani Priyanka , Yadav Sudhir , Gupta Shivjee K. : Vesicular System As Targeted Drug Delivery System: An Overview. International Journal Of Pharmacy&Technology 2011; 3: 1021
4. Doijad Rajendra C., Bhambere Deepak S. , Manvi Fakirappa V. and Deshmukh Narendra V. : Formulation And Characterization Of Vesicular Drug Delivery System For Anti-Hiv Drug.

Journal of Global Pharma Technology 2009 ; 1: 94-100.

5. Prajapati SK1, Kumar S, Sahu VK, Prakash G.: Proniosomal Gel Of Flurbiprofen: Formulation And Evaluation. Journal of Drug Delivery & Therapeutics 2012 ; 2:
6. Gangwar Mayank, Singh Ranigi, Goel RK, Nath Gopal: Recent Advances In Various Emerging Vescicular Systems: An Overview. Asian Pacific Journal Of Tropical Biomedicine 2011;33: 848.
7. Keservani Raj K., Sharma Anil K. , Ayaz MD. , Kesharwani Rajesh K.: Review Novel drug delivery system for the vesicular delivery of drug by the niosomes. International Journal of Research in Controlled Release 2011; 1:1-8.
8. Patel Vishal, Agrawal Y K : Current Status And Advanced Approaches In Ocular Drug Delivery System. Journal of Global Trends in Pharmaceutical Sciences 2011; 2:131-148.
9. Kumarn Gannu P. , warrao Pogaku Rajesh : Nonionic surfactant vesicular systems for effectivedrug delivery—an overview. Acta Pharmaceutica Sinica B 2011; 1: 208-219.
10. Maik Hadorn, Peter Eggenberger Hotz : DNA-Mediated Self-Assembly of Artificial Vesicles. Plos One 2010 ; 5:
11. Fukuda H, Goto A, Yoshioka H, Goto R, Morigaki K, Walde P. Electron spin resonance study of the pH-induced transformation of micelles to vesicles in an aqueous oleic acid/oleate system. Langmuir 2001; 17:4223-4231.
12. Markvoort AJ, Pfleger N, Staffhorst R, Hilbers AJ, Vansanten RA, Killian AJ. Self-reproduction of fatty acid vesicles: A combined experimental and simulation study. Biophys J 2010; 99:1520-1528.
13. Namani T, Ishikawa T, Morigaki K, Walde P. Vesicles from docosahexaenoic acid. Colloids Surf B Biointerfaces 2007; 54:118-123.
14. Namani T, Walde P. From decanoate micelles to decanoic acid/ dodecylbenzenesulfonate vesicles. Langmuir 2005; 21:6210-6219.
15. Roy S, Dey J. spontaneously formed vesicles of sodium N-(11-acrylamidoundecanoyl)-glycinate and L-alaninate in water. Langmuir 2005; 21:10362-10329.
16. Nayak RR, Roy S, Dey J. Characterization of polymeric vesicles of poly (sodium 11-acrylamidoundecanoate) in water. Colloid Polym Sci 2006; 285:219-224.
17. Roy S, Dey J. Self-organization and microstructures of sodium 11-acrylamidoundecanoate in water. Langmuir 2003; 19:9625-9629.
18. Caschera F, Stano P, Luisi PL. Reactivity and fusion between cationic vesicles and fatty acid anionic vesicles. J Colloid Interface Sci 2010; 345:561-575.
19. Robenek H, Severs NJ. Recent advances in freeze-fracture electron microscopy: The replica immunolabeling technique. Biol Proced Online 2008; 10:9-19.

20. Barenholz Y. Liposome application: Problems and prospects. Curr Opin Colloid Interface Sci 2001; 6:66-77.

21. Takeuchi H, Yamamoto H, Hino T, Kawashima Y. Enteral absorption of insulin in rats from mucoadhesive chitosan coated liposomes. Pharma Res 1996; 13:896-901.

22. Vemuri S, Rhodes CT. Preparation and characterization of liposomes as therapeutic delivery systems: A review. Pharm Acta Helv 1995; 70:95-111.

23. Vandenbergh BA, Salomonsdevries I, Bouwstra JA. Interactions between liposomes and human stratum corneum studied by freeze-substitution electron microscopy. Int J Pharm 1998; 167:57-67.

24. Schreier H, Bouwstra J. Liposomes and niosomes as topical drug carriers: Dermal and transdermal drug delivery. J Control Release 1994; 30:1-15.

25. Aruoma OI, Halliwell B, Laughton MJ, Quinlan GL, Gutteridge JM. The mechanism of initiation of lipid peroxidation: Evidence against a requirement for an iron (II)-iron (III) complex. Biochem J. 1989; 258:617-620.

26. Quinlan GJ, Halliwell B, Moorhouse CP, Gutteridge JM. Action of lead (II) and aluminium (III) ions on iron-stimulated lipid peroxidation in liposomes, erythrocytes and rat liver microsomal fractions. Biochim Biophys Acta 1988; 962:196-200.

27. Scarpa M, Rigo A, Maiorino M, Ursini F, Gregolin C. Formation of a-tocopherol radical and recycling of a-tocopherol by ascorbate during peroxidation of phosphatidylcholine liposomes: An electron paramagnetic resonance study. Biochim Biophys Acta 1984; 28:215-219.

28. Oconnell MJ, Ward RJ, Baum H, Peters TJ. The role of iron in ferritin and haemosiderin-mediated lipid peroxidation in liposomes. Biochem J 1985; 229:135-139.

29. Gutteridge JM, Quinlan GJ, Clark I, Halliwell B. Aluminium salts accelerate peroxidation of membrane lipids stimulated by iron salts. Biochem Biophys Acta 1985; 835:441-447.

30. Babizhayev MA. The biphasic effect of calcium on lipid peroxidation. Arch Biochem Biophys 1988; 266:446-451.

31. Mishima K, Satoh K, Ogihara T. Optical birefringence of phosphatidylcholine liposomes in gel phases. Biochim Biophys Acta 1987; 898:231-238.

32. Bittman R, Leventhal AM, Karp S, Blau L, Tremblay PA, Kates M. Osmotic behavior of liposomes of phosphatidylcholine and phosphatidylsulfocholine as a function of lipid concentration. Chem Phys Lipids 1981; 28:323-335.

33. Lichtenberg D, Freire E, Schmidt CF, Barenholz Y, Felgner PL, Thompson TE. Effect of surface curvature on stability, thermodynamic behavior, and osmotic activity of dipalmitoyl phosphatidyl choline single lamellar vesicles. Biochemistry 1981; 20:3462-3467.

34. Patel HM, Stevenson RW, Parsons JA, Ryman BE. Use of liposomes to aid intestinal absorption of entrapped insulin in normal and diabetic dogs. Biochem Biophys Acta 1982; 716:188-193.