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A REVIEW ON TRANSFEROSOMES FOR TRANSDERMAL DRUG DELIVERY

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ABSTRACT

Transdermal delivery systems are gaining importance now a day. Transdermal drug delivery has made an important contribution to medical practice, but has yet to fully achieve its potential alternative to oral delivery and hypodermic injections. Various new technologies have been evolved for the transdermal delivery of some important drugs. Physical and chemical means of crossing the lipophilic stratum corneum, the outermost layer of the skin, are being explored. Transfersomes are ultradeformable vesicles possessing an aqueous core surrounded by the complex lipid bilayer. When it is pressed against or attracted into narrow pore. Pre formulation studies like SEM, TEM, DSC and FTIR will be performed to check the compatability between drug and polymers used in the formulation. The prepared transferosomes will be evaluated for particle shape, entrapment efficiency, and skin permeation study. *In vitro* release studies are to be performed using specific dissolution medium.

Key Words: Transfersomes, SEM, TEM, DSC and FTIR, *In vitro* release studies

1.1NOVEL DELIVERY SYSTEMS

Novel drug delivery systems modified a number of drugs in order to overcome several problems. NDDS is the most suitable drug delivery system in which developing the therapeutic efficacy of preexisting as well as new drugs [1][2][3]. Encapsulation of drug in vesicular systems predicted to prolong the presence of drug in systemic circulation the toxicity can be reduced. Novel vesicular systems allow the drug to control or sustain the release of conventional medicines.[4][5][6][7]. Novel drug delivery systems localize the drug action by spatial arrangement of controlled release systems adjacent to disease site or organ [8] [9] [10]. Vesicular systems reduces the cost if therapy by improving the bioavailability of drugs especially poorly soluble drugs. They can incorporate both hydrophilic lipophilic drugs [11][12]. Vesicular drug delivery systems reduces toxicity, reduces dose related side effects, high therapeutic efficacy of drugs for longer periods of time. The key role is to control degradation of drug and loss, availability of drug to the diseased sites. The encapsulation of drug in vesicular systems be predicted to prolong the drug in systemic circulation. Lipids are the type of mainly experimental membranes evolves successfully for controlled delivery [13].

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The conventional chemotherapy for intracellular infections cannot be treated because they cannot permeate into the cells. Hence vesicular delivery systems made a prominence role in penetrating deep into cell membranes.[14][15][16].

1.2 CONTROLLED RELEASE

It refers to delivery of compounds in response to stimuli or time. It is time dependent release in oral dosage formulations. It not only prolongs action but it attempts to maintain drug levels within the therapeutic window.

1.3 SUSTAINED RELEASE

It refers to release a drug at a predetermined rate in order to maintain constant drug concentration for a specific period of time. Amphiphilic, lipophilic, charged hydrophilic drugs can be associated with the vesicle bilayer, by hydrophobic / electrostatic interactions. But hydrophilic drugs to be entrapped into internal aqueous compartments. These vesicular formulations are formulated in order to sustain the release as well as rate limiting membrane for transdermal delivery. Transferosome technology is best suited for noninvasive delivery of drug molecules across open biological barriers. They can transport across the skin that can diffuse over large size molecules eg., insulin, interferon crosses the mammalian skin. The ability of targeting peripheral, subcutaneous tissues minimizes the carrier associated drug clearance through cutaneous blood vessels plexus. [cutaneous blood vessel plexus – nonfenestrated blood capillaries in skin with tight junctions between endothelilal cells]

These plexus preclude the vesicles directly into blood, increases the drug retention time locally and reaches the peripheral tissues.[1]

1.4 THE DIFFERENT HYBRIDS OF VESICLES

1.4.1 LIPOSOMES

Liposomes are usually unilamellar and range of 50-250 nm. Consists of one or more lipid bilayer enclose an internal aqueous volume. Liposomes are capable of carrying drugs differ widely in physicochemical properties such as polarity, charge, size. They are hollow spheres. The main component is dipalmitoyl phosphatidylcholine improve stability. Increases the solubility of insoluble drugs. Both water soluble and water insoluble drugs can be delivered [2]. In the small intestine liposomes are digested in the presence of bile and enzymes. The soluble compound is liberated and further solubilized in bile and lipids.

1.4.2 NIOSOMES

Niosomes are formed by hydration with or without cholesterol and nonionic surfactants. They are of spherical, unilamellar, multilamellar. They can be used as carriers for amphihilic and lipophilic drugs[3]. Niosomes are preferred because they exhibit high chemical stability and economy. They improve therapeutic performance of drug molecules by delayed clearance from circulation, protecting drug from biological environment and restricts to target cells[4].

1.4.3 PHARMACOSOMES

Pharmacosomes are defined as colloidal dispersions of drugs covalently bound to lipids and exist as ultrafine vesicular, hexagonal aggregates. It depends on the chemical structure of drug lipid complex [5]. It has come up as potential alternative to conventional vesicles [6]. No need of removing unentrapped drug from the formulation. Physical stability such as fusion, aggregation, sedimentation, drug leakage etc., absent in pharmacosomes.

1.4.4 ETHOSOMES

Ethosomes are involved in cellular communication, particle transformation for many years. They are noninvasive delivery carriers that enable drugs to reach systemic circulation. They are composed of phospholipids. Excess of ethanol makes ethosomes unique for the disturbance of skin lipid bilayer organization. The lipid membrane packed tightly than conventional vesicles, allow more malleable structure and improves the good distribution ability in stratum corneum [8]. Ethosomal drug is administered in semisolid preparations gel or creams. High patient compliance.

1.4.5 COLLIDOSOMES

Collidosomes are hollow shell microcapsules of coagulated or fused particles at interface of emulsion droplets. Have great encapsulation efficacy with a wide controls over size, mechanical strength, permeability and compatibility. The shell of collidosomes consists of coagulated or fused colloid particles at interface of emulsion droplets. They were produced first time by encapsulating latex particles adsorbed on the surface of octanol-in-water emulsion drops and removal of oil after fusing monolayers. They can also be template by water-in-oil emulsions. The final hollow shells are obtained by removal of central, spherical colloidal particles [9]. Collidosomes assemble polymer latex colloidal particles into shells around water-in-oil emulsion droplets followed by partial fusion of shell and centrifugal transfer into water to yield capsules in which the shell permeability can be controlled by adjacent of partial fusion conditions. Collidosomes membrane offer great potential in controlling the permeability of the entrapped species and allow the selective & time release.

1.4.6 HERBOSOMES

The term “herbo” means plant, while “some” means cell like. The biological active constituent are polar or water soluble phytoconstituents are poorly absorbed of their large molecular size. Herbosomes often called phytosomes. Exhibit better pharmacokinetic and pharmacodynamic behavior than conventional herbal extracts [10]. Phospholipids form a molecular layer provides continuous matrix which proteins inserted. It increases the absorption of lipid insoluble polar phytoconstituents through topical as well as oral route thereby increases bioavailability.

1.4.7 SPHINGOSOMES

Sphingosomes are defined as concentric bilayered vesicles in which aqueous volume is entirely enclosed by a membranous lipid bilayer mainly composed of natural or synthetic sphingolipid. The sphingolipids are used for formulations of stable liposomes called sphingosomes [11]. Administered through parenteral, intravenous, intramuscular, subcutaneous, inhalation. Provide passage for targeting to tumour passively. Improve pharmacokinetic ability.

1.4.8 CUBOSOMES

Cubosomes are discrete, submicron, nanostructure particles of bicontinuous cubic liquid crystalline phase [12]. Bi continuous water in oil channels are separated by bilayer. The ability of cubic phases to exist as discrete dispersed colloidal particles or phases exist equilibrium with excess water and dispersed. They are produced by high energy dispersion of bulk cubic phase with colloidal stabilization using surfactants. They posses large ratio of bilayer and particle volume and large breaking resistance [13].

1.4.9 TRANSFEROSOMES

Because of poor permeability liposomes or niosomes are not suitable for transdermal delivery. To overcome this transferosomes been introduced, which are capable of delivering low as well as high molecular weight drugs [14]. They are optimized ultradeformable lipid supramolecular aggregates able to penetrate mammalian skin. Due to incorporation of edge activators such as sodium cholate, sodium deoxycholate, span 80, tween 80. They consist of atleast one inner aqueous compartment surrounded by lipid bilayer. Transferosomes respond to external stress by rapid shape transformations with low energy. They posses deformability hence they penetrate through the pores and get into the intact skin. Peptides like insulin, bovine serum albumin, vaccines can be delivered. Delivery systems which offers several potential advantages over conventional routes like avoidance of first pass metabolism, predictable improves physiological and pharmacological response is

transdermal drug delivery systems are available for the treatment of various diseases such as cardiovascular disease, Parkinson's disease, Alzheimer's disease, depression, anxiety and postmenopausal bone loss and urinary incontinence. Transferosomes are a form of elastic or deformable vesicle, which were first introduced in the early 1990's [15,16]. The main barrier and rate limiting step for diffusion of drugs across the skin, stratum corneum [17]. Recent advances in modulating vesicle compositions have been investigated to develop systems that are capable of carrying drugs and macromolecules to deeper tissues. These have resulted in the design of two novel vesicular carriers, ethosomes and ultraflexible lipid based transferosomes [18].

Transferosomes are ultradeformable vesicles possessing an aqueous core surrounded by the complex lipid bilayer. local composition and Interdependency of shape of the bilayer makes the vesicle both self regulating and self optimizing [19]. Due to their deformability, transferosomes are good candidates for the non delivery of small, medium and large sized one's. transferosomes can deform and pass through narrow constriction (5-10 times less than their own diameter without measurable loss' flexibility can be achieved by mixing suitable surface active components in the proper ratios. The resulting flexibility of transferosome membrane minimizes the risk of complete vesicle rupture in the skin and allows transferosomes to follow natural water gradient when applied under non-occlusive condition across the epidermis [20].they overcome the skin permeation by squeezing themselves along the intracellular lipids of the sratumcorneum. The high and self optimizing deformability of typical composite transferosomes which are adaptable to ambient stress allow the ultra deformable transferosomes to change its membrane composition locally and irreversibly, when it is pressed against or attracted into narrow pore. The transferosomes components that sustain strong deformation preferentially accumulate while the les adaptable molecules are dramatically lowers the energetic cost of membrane deformation and permits the resulting highly flexible particles, first enter and pass through the pore rapidly and efficiently[21].

1.5 DRUGS CAN BE SUITABLE FOR TRANSFEROSOMES

NSAIDS: Ibuprofen, naproxen, curcumin
Antifungal: Fluconazole, Itraconazole, Nystatin, Voriconazole
Steroids: Oestradiol, Norgestrone, Hydrocortisone
Proteins: Human serum albumin, integral membrane proteins.
Others: Interferons-α, interleukins-2, insulin

1.6 polymers suggested for transferosomes are listed in table

2. PREPARATION METHOD

ROTARY EVAPORATION METHOD

1. A thin film is prepared from the mixture of vesicles forming ingredients phospholipids and surfactant by dissolving in volatile organic solvent (chloroform –methanol). Organic solvent is then evaporated above the lipid transition temperature (room temperature for pure pre vesicles, 50°c for dipalmitoyl phosphatidyl choline using rotary evaporator. Final traces of solvent were removed under vacuum overnight.
2. A prepared thin film is hydrated with buffer by rotating at 60 rpm for 1 hr at the corresponding temperature.
3. To prepare small sized vesicles they were sonicated at room temperature or 50 ° c for 30 min. the sonicated vesicles were homogenized by manual extrusion 10 times through a sand which of 200 and 100 nm.

2.2 MODIFIED HAND SHAKING METHOD

Drug, phosphatidyl choline, edge activators were dissolved in ethanol: chloroform 1:1 mixture. Organic solvent was removed by evaporation while hand shaking above lipid transition temperature (43° c) a thin film was formed inside the flask wall with rotation. The film was kept overnight for complete evaporation of solvent. Then the film is hydrated with phosphate buffer (6.4) with gentle shaking for 15 min at corresponding temperature. The transferosomes suspension further hydrated to 1 hr at 2-8° c [22, 23, 24].

3. MECHANISM OF ACTION

The carrier aggregates are amphipathic which aqueous solvents self-assemble into lipid vesicle. By addition of one bilayer flexibility and permeability increases. The flexibility and permeability can rapidly adjust local concentration of bilayer. Transferosomes differ from conventional vesicles primarily by its softer and more deformable and adjustable membrane. An ultradeformable and highly hydrophilic vesicle always seeks to avoid dehydration. When a transferosome vesicle always seeks to avoid dehydration. When a transferosome vesicle applied on biological surface, nonoccluded skin, penetrate its barrier and migrates into deeper layers of stratum corneum to secure its adequate hydration.transferosomes need to enforce its own route through organ. Its usage on its delivery relies on carriers ability to widen the hydrophilic pores in the skin. During transportation to intracellular site involves the carriers lipid bilayer fuses with the cell membranes, or else the vesicles are taken up by the process endocytosis [24].

4. POLYMERS EMPLOYED FOR THE DEVELOPMENT OF TRANSFEROSOMES.

4.1 LECITHIN

It is a yellow-brownish fatty substances occurring in animal and plant tissues composed of phosphoric acid, choline, fatty acids, glycerol, glycolipids, triglycerides and phospholipids. It was first isolated in 1846 by the French chemist and pharmacist Theodore gobley[1][2]. [25][26]He originated lecithin from egg yolk. Established chemical formula of phosphatidyl choline [27]. Available from sources of soybean, milk, marine sources, rapeseed, cottonseed and sunflower. Phosphatidylcholine dissolve in ethanol. Lecithin is

a source of choline an essential nutrient.[28] It can be totally metabolized by humans

Applications

- It acts as wetting, stabilizing, choline enrichment carrier.
- Good dispersing agent
- Helps in emulsification and encapsulation
- Acts as catalyst, colour intensifying agent. Good stabilizing and suspending agent. Eliminates foam in water based paints.
- Used as an anti sludge additive in motor lubricants. Anti gumming agent in gasoline, spreading agent, textile, rubber industries.

4.2 SOYAPHOSPHATIDYL CHOLINE

Phosphatidyl cholines are a class of phospholipid that incorporates choline as a head group. They are major component of biological membranes and can be easily obtained. Phosphatidyl choline is a major constituent of cell membranes and pulmonary surfactant is more commonly found in outer leaflet of a cell membrane, transported between membranes by phosphatidylcholine transfer protein. Phospholipid composed of choline head group and glycerophoric acid with fatty acids. Phospholipase decatalyzes the phosphatidyl choline to form phosphatidic acid and releasing the soluble choline head group into the cytosol. Phosphatidyl choline supplementation slows down aging related processes and improves brain functioning and memory but does not benefit in the patients in dementia.

USES:

Used in the cure of inflammatory bowel disease

4.3 DISTEROYL PHOSPHATIDYL CHOLINE

It appears like a solid substance and stable. Incompatible with strong oxidizing agents. vesicles formed by sonication of saturated chain phosphatidyl cholines in aqueous media have been used extensively as a model for the lipid component in the plasma membrane. The rate of loss of small vesicles and information about the structures to which the small vesicles are converted can be obtained from sedimentation velocity experiments. The kinetic behavior of small disteroyl phosphatidyl choline vesicles is examined. Small single bilayer vesicles are unstable at all temperatures. The vesicles size distributions changed as a function of time at all temperatures below the phase transition temperatures but constant at transition temperature and above. It is to be stored at -20°c.

4.4 DIPALMITOYL PHOSPHATIDYLCHOLINE

It is a phospholipid consisting of two palmitic acids. It is the major constituent of pulmonary surfactant. It is synthesized mainly through remodeling of phosphatidyl choline.1, 2- dipalmitoyl-sn-glycero-3-PC is a zwitterionic phosphoglyceride that can be used for the preparation of liposomal monolayer. The extent of incorporation of the enzyme glutamyl transpeptidase in erythrocyte membranes was five times higher when proteoliposomes were prepared from L-DPPC as compared to control. L-DPPC incorporated vesicles have potential in establishing active immunotherapy with the antigens. [29]

4.5 CHOLESTEROL

Cholesterol is a sterol or modified steroid which is a lipid molecule biosynthesized by animal cells to maintain integrity and fluidity. It enables no need of cell membrane, ability to change its shape, able to move by the animals. Cholesterol serves as precursor for vitamin D, steroid hormones, bile acids, it is the principal sterol synthesized by humans. Most of ingested cholesterol is esterified and poorly absorbed. The cholesterol modulates membrane fluidity over a range of physiological temperatures**.** The trans confirmation of tetracycline ring decrease fluidity but side chain is rigid and planar**. [30]** In neurons a myelin sheath is derived from Schwann cell membrane, providing insulation for many conducting impulses. Cholesterol is slightly soluble in water, insoluble in blood it transported in blood stream through lipoproteins. High levels of cholesterol termed as hypercholesterolemia. Low levels of cholesterol results hypocholesterolemia

Level (mg/dL)	Level (mmol/L)	Interpretation
Less than 200	Less than 5.2	Lower risk for heart diseases
Between 200-240	Between 5.2-6.2	High border line risk
More than 240	More than 6.2	High risk

4.6 DEOXYCHOLIC ACID

It is also known as deoxycholate, cholanoic acid.deoxycholic acid is one of the metabolic byproducts and secondary bile acids of intestinal bacteria. The two primary bile acids secreted by the liver are cholic acid and chenodeoxycholic acid. Soluble in alcohol and acetic acid. Pure form is in white to crystalline powder form. It functions as detergent and isolating agent for membrane proteins such as “men B”[31] In china, traditional medicine “ Niuhuang” comprises active component DCA used in the treating inflammations and enhances immune system. It can be used as immunostimulant. [32][33] Lyso phosphatidyl choline acyl transferase plays a critical role in its sysnthesis.

Uses:

- Used for research purposes in studying liposomes, lipid bilayers, and biological membranes.
- Used in the production if high density lipoproteins.
- Used in healing of local inflammations

APPLICATIONS

1. Deoxycholic acid used in the emulsification of fats for the absorption in the intestine.
2. Used in the prevention of gallstones.
3. Sodium deoxycholate when mixed up with phosphatidyl choline used for mesotherapy injections.[34]

4. Used as emulsifier in food industry.
5. Deoxycholates and bile acid derivatives used for incorporation in nanotechnology.

4.7 TWEEN 80

It is a nonionic surfactant and emulsifier used in foods and cosmetics. It is also known as polysorbate 80.[35] It is derived from polyethoxylated sorbitan and oleic acid. It is introduced above CMC. It is amber coloured viscous liquid nonionic surfactant, viscous water soluble yellow liquid. It is an excipient that is used to stabilize aqueous formulations of medications for parentral administrant and emulsifier in the antiarrhythmic amidarone. It is used in some eye drops. it is harmful to people in some eye drops it is not carcinogenic. Soluble in ethanol, cottonseed oil. The cosmetic grade of tween 80 has more impurities than food grade [36][37]

USES:

1. As an emulsifier in the preparation of food products.
2. Used to identify the phenotype of strain.
3. Used in icecream as it increases the resistance of melting
4. Prevents milk proteins from coating the fat droplets.
5. Used as surfactant in soaps and cosmetics.
6. Used as a solubilizer in mouthwash.
7. It is used as an excipient to stabilize aqueous formulations of parenteral preparations and emulsifier in antiarrhythmic amiodarone. [38]

4.8 TWEEN 20

It is a clear yellow to yellow green viscous liquid. It is a surfactant whose stability and relative non toxicity used as a detergent and emulsifier in scientific an pharmaceutical applications. It is a derivative of polyoxyethylene derivative of sorbitan monolaurate. [39]

APPLICATIONS

1. Used as wetting agent in flavour mouth drops spreads like alcohol and mint flavour.
2.It has a broad sense of application in biotechnical sciences
3. As a washing agent in immunoassays.
4. Saturate binding sites.
5. Stabilize proteins.
6. Pharmaceutically it is used as excipient to stabilize emulsions and suspensions.
7. It is used to remove stamps from envelopes without harming.

4.9 SPAN 20

It also known as sorbiton monolaurate. It is a mixture of partial esters of sorbitol and its mono and dianhydrates with edible lauric acid. It is an amber coloured oily viscous liquid, light cream to tan beads or flakes or a hard, waxy solid with a slight odour. Soluble in hot and cold water. [40]

4.10 SPAN 80

Also known as sorbiton oleate. It is a nonionic surfactant induced at CMC. Highest skin permeation can be achieved if we use 10 % span 80. Cationic lipid vesicles were developed of mainly of span 80. Microemulsions can be formulated by span 80 as lipophilic linker. When lactobacillus cells care grown in a medium supplemented with span 80 showed viability and acid producing activity. Addition of increased concentrations of span 80 to suspensions caused marked changes in stability. Span 80 served as a coaservating agent in microspheres . [41]

4.11 ETHANOL

Ethanol also called as ethyl alcohol, pure alcohol phytoactive drug. It is a volatile, colourless liquid that has a slight odour. Ethanol is produced by fermenting sugars with yeast [42] Ethanol causes alcohol intoxication. Ethanol's hydroxyl group is able to participate in hydrogen bonding rendering it more viscous and less volatile than polar organic compounds such as propane. Ethanol was first used as lamp fuel in US 1840. It remains a common fuel for spirit lamps. It has a complex mode of action and affects multiple systems in brain.

USES

1. It is used in scents, thermometer as a solvent.
2. Intended for flavourings, colourings and medicines
3. As motor fuels & fuel additive, rocket fuels.
4. As it dissolvers hydrophobic flavours compounds used as beverages in cooking.

4.12 METHANOL

Also known as methyl alcohol, wood alcohol, simplest alcohol, light, volatile, colourless, flammable liquid.[43] It is produced naturally in the anaerobic metabolism. When methanol is ingested in large quantities methanol is methanol is obtained from pyrolysis of wood. It is produced in anaerobic metabolism of bacteria. At room temperature it is used as polar liquid, antifreeze, solvent, fuel, denaturant for ethanol. If ingested in large quantities it metabolized in to formic acid or formate salts.

Toxicity

Methanol has toxicity, if ingested 10ml of methanol can break down into formic acid causing permanent blindness. It may be fatal due to its CNS depressant activity.

USES

- Used as a solvent for laboratory purposes especially for UV spectroscopy, HPLC LCMS due to its low UV cut off.
- Used as fuel in German military rockets.
- Used as denaturating agent in polyacrylamide gel electrophoresis
- Methanol used as fuel in camping and boating stoves
- Used, as traditional denaturant for ethanol known as denaturated alcohol or methylated spirit, used to discourage the consumption of bootlegged liquor and stopped many deaths.[44]
- It was used as automobile antifreeze in the early 1900s. [45]

4.13 CHLOROFORM

It is one of the four chloromethanes . It is a colourless, sweet smelling, dense liquid trihalomethane which is considered as hazardous.it is soluble in water, benzene, acetone, DMSO, diethyl ether, oils, ethanol. It is estimated that over 90% of atmospheric chloroform is of natural origin.[46] it is produced by brown seaweeds, red seaweeds and green seaweeds.[50] Chloroform can be produced by heating a mixture of chlorine and chloromethane or methane. Dueterated chloroform is an isotope logue of chloroform with single deuterium atom.

USES

1. The major use of chloroform today is the production of chlorofluoromethane which is a major precursor to tetrafluoroethylene. Chlorofluoromethylene used as popular refrigerant.
2.It is used as a solvent in laboratory as it is unreactive miscible with organic liquids not flammable and conveniently volatile .[47] Longer storage of chloroform in polypropylene containers is not advised.[48]
3.Used as a reagent for dichlorocarbeneCCL_2 groups which affects ortho formylation of activated aromated rings. Phenols and aldehydes in riemer tiemann reaction.[49]
4.Used as anaesthetic as it depresses CNS system.
5. It increases the movement of K^+ ions through the potassium channels in nerve cells [50]

Safety

Oral dose of chloroform should be less than 10 ml [14.8g] as it may cause death or respiratory or cardiac arrest if exceeds.

5. CHARACTERISATIONS FOR TRANSFEROSOMES

5.1 ENTRAPMENT EFFICIENCY

It is expressed as the percentage entrapment of the drug. Entrapment efficiency was determined by centrifugation method, the vesicles were disrupted using triton-100(0.1%) or 50% n-propanol.
Entrapment efficiency = amount entrapped / amount added × 100 [51]

5.2 VESICLE SIZE AND SIZE DISTRIBUTION

Analysis of the transferosomes vesicle size before sonication determined by using a micrometer scale. The polydispersibility index measurement was carried out by dynamic light scattering with zetasizer HAS 3000. The samples are sonicated before PDI determination.[52]

5.3 TURBIDITY MEASUREMENTS

The turbidity measurements were diluted with distilled water to give a total lipid concentration of 0.312m. sonicate for 5 min. Measure turbidity at 274 nm with UV visible spectrophotometer.[53]

5.4 NUMBER OF VESICLE PER CUBIC mm

It is an important parameter for optimizing the composition and other process variables. Transferosome formulations can be diluted for 5 times with 0.9% sodium chloride solution and studied with optical microscopy. [54]

5.5 CONFOCAL SCANNING LASER MICROSCOPY STUDY

The problems associated with problem of fixation, sectioning and staining. Often misinterpretation can be minimized by confocal scanning laser microscopy. In this technique fluorescence markers are incorporated into formulations and light emitted by these markers are used for the determination of mechanism of penetration across the skin. [55]

5.6 DEGREE OF DEFORMABILITY

The deformability study is done against the pure water as standard. Transferosome preparations are passed through a large number of pores of known size distributions are noted after each pass by dynamic light scattering measurements.[56]

5.7 OCCLUSION EFFECT

For traditional topical preparations, but also can be determined for elastic vesicles. Hydrotaxis is the movement of water in direction is major driving force for transferosomes, from dry surface to deep regions with water rich area. Due to hydration forces the evaporation of water be prevented from skin surface.[57]

5.8 RELATIVE DEFORMABILITY

The relative deformability of transferosomes was determined by flexibility which observed by extrusion of vesicles through 0.22 μ m nylon 66 syringe filters (filtration area 1.3 cm^2, at a constant pressure of 0.2 Mpa. The extrusion volume in 5 min was recorded for transferosomes and compared to liposomal formulations. Deformability index was coumted using

$$DI = J * rv/rp$$

Where,

J – Volume of transferosomes extruded during 5 min

r_v- size of vesicles

r_p- pore size of the filter. [58]

5.9 DRUG CONTENT

The drug content can be determined using HPLC method using UV detector, column oven, auto sample, pump, computerized analysis program depending upon the analytical method of pharmacoepial drug.[59]

5.10 INVITRO SKIN PERMEATION STUDIES

Invitro drug study was performed by using goat skin in phosphate buffer (7.4). Modified franz diffusion cell with a receiver compartment volume of 50 ml and effective diffusion area of 2.5cm used for this study. Abdominal skin hair is removed and hydrated with saline solution. The adipose tissue layer removed by rubbing with a cotton swab. To perform study, treated skin was mounted horizontally on receptor compartment with the stratum corneum facing upwards towards the donar compartment of franz diffusion cell. The area of donar compartment is 250 cm and capacity of receptor compartment 50 ml of phosphate buffer of 7.4) at 37± 5° c and stirred at a magnetic bar for 100 rpm. Formulation

equivalent to 10 mg was placed on the skin and top was covered. At appropriate intervals 1ml aliquots were withdrawn and immediately replaced by fresh volumes. Analyzed by any instrumental technique. [60]

5.11 INVITRO DRUG RELEASE

Is performed for determination of permeation rate.Transfersomes were incubated at 320°C and the samples are taken at different times and free drug is separated by mini-column centrifugation. The amount of drug released is then calculated indirectly from the amount of the drug entrapped at zero time as initial amount [61]

5.12 PHYSICAL STABILITY

The initial percentages of drug entrapped in the formulation determined were stored in sealed glass ampoules. The ampoules were placed at 4±20°C (refrigerator), 25±20°C (room temperature), and 37±20°C (body temperature) for atleast 3 months. Samples-analyzed for 30 days to determine drug leakage. Percent drug lose was calculated by keeping initial entrapment of drug as 100%. [62][63]

6.

ADVANTAGES

1. High entrapment efficiency can be achieved
2. Biocompatible and biodegradable.
3. Protects drug product from metabolic degradation.
4. As they act as depot the release will be slow and gradual.
5. Transferosomes consists of both hydrophilic and hydrophobic substances posses a higher solubility range.
6. Carriers for high molecular weight drugs such as analgesic, anaesthetics, corticosteroids, insulin, albumin etc., [64][65][66]

7.

LIMITATIONS

1. Transferosomes are chemically unstable because of it undergo oxidative degradation.
2. They are expensive.
3. The purity of natural phospholipids effect vesicles hence it is bit difficult for formulation of transferosomes. [67][68][69]

8.

APPLICATIONS

- Protein and peptides are large biogenic molecules are difficult to transport in body. Orally they get damaged in GIT. Protein suspensions when given subcutaneous injection. Delivery of protein and peptides through transferosomes is same by subcutaneous injection. Gap junction protein or human serum albumin was effective when delivered by transdermal route. Drug molecules which have physicochemical properties that prevent from diffusing across stratum corneum can be transported effectively through transferosomes.
- The proteo transferosomes induced strong response after the repeated epicutaneous application after several dermal challenges as active as injected through proteotransferosomes. Administration of insulin through subcutaneous route is inconvenient as the molecular weight is large. Hence insulin encapsulated in transferosome vesicles made a significant result i.e., the first sign of hypoglycemia after 90-180 min been observed after application on intact skin.
- elivery of interleukins and interferons. Transferosomes have the ability for providing controlled release for the drugs and increases the stability of Labile drugs. They act as carriers for interferone (INF-α) which is a derivative of leukocyte exhibits antiviral, immunomodulatory effect. Transferosomes trap INF., provides controlled release of the active ingredient increase the stability of labile drugs and also provides immune therapy.
- naesthetics can be applicable in the form of suspensions through highly deformable vesicles known as transferosomes. They showed good effect as compared to subcutaneous administration with in 10 mts. The effect of anaesthetics delivered through transferosomal suspensions last longer.
- NSAIDS because of its GI side effects can be overcome if administered through transferosomes, ultradeformable vesicles. Diclofenac and ketoprofen proved their effect transdermally. Ketoprofen gained marketing approval as transferosomes by swiss regulatory agency.
- erbal drugs can also be incorporated into transferosomes as they can penetrate stratum corneum supply nutrients locally to maintain its functioning. Curcumin, Capsaicin showed topical administration through transferosomal formulations.
- elivery of anticancer drugs through transferosomes gained much importance provided a new approach for the treatment of cancer.

9. CONCLUSION

May prolong the release and increase the transdermal flux, improves the site specificity of bio active moieties. Due to their high deformability can incorporate large molecular weight drugs, both hydrohilic and lipophilic drugs. Transferosomes are stable at low temperatures compared to high temperatures.

HYBRIDS OF VESICLES AND THEIR COMPOSITION

Type	Composition
Liposomes	Negatively charged phospholipids and cholesterol
Virosomes	Viral glycoprotein is incorporated into bilayers of lipids
Ufasomes	Vesicles are been enclosed by fattyacids
Aquasomes	Vesicles are formed by lipids
Ethosomes	By the addition of ethanol water and phospholipids,
Genosomes	Formation of macromolecular complexes
Photosomes	The enzyme photolase is encapsulated in liposomal formulations
Erythrosomes	Human erythrocytes are chemically cross linked
Hemosomes	Liposomes consists hemoglobin
Proteosomes	
Vessome	Lipid bilayers are being nested
Archaeosome	Glycerolipids are bilayered
Phytosomes	Herbal extract is incorporated into lipid membranes by chemical bonding
Transferosomes	Formed by the fusion of phospholipids, chloroform, methanol, phosphate buffer, chloroform, dyes.
Cubosomes	Monolein, polaxomer -407, phosphate buffer, chloroform are combined

POLYMERS SUGGESTED FOR TRANSFEROSOMES

Class	Example	Uses
Phospholipids	Soyaphosphatidyl choline Dipalmitoyl phosphatidyl choline, disteroyl phosphatidyl choline	Vesicles forming component
Surfactants	Sodium cholate, sodium deoxy cholate, tween 80, span 80	Flexibility
Alcohol	Ethanol, methanol	Solvent
Buffering agent	Saline phosphate buffer ph(6.4)	Hydrating medium
Dye	Rhodamine-123, rhodamine DHPE, flourescein DHPE, nile red	CSLM study

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