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Research article

Recent advances in lipid based nanovesicles for transdermal drug delivery

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ABSTRACT

Lipid based nanovesicles are the formulations which are used for the delivery of hydrophilic, hydrophobic and amphiphilic drugs or compounds. They are very helpful for the drugs which are hydrophilic and irritant drugs that can be encapsulated and delivered to the target site. They are very advantageous over conventional formulations. Lipid based nanovesicular systems will efficaciously help the drugs addressing the issues of solubility and penetration thereby promotes bioavailability. Now a days lipid based nanovesicles for transdermal delivery of drug has become very useful especially for hydrophilic drugs. The use of the nanovesicles for transdermal drug delivery will overcome the drawbacks associated with the route of drug delivery, such as oral and parenteral. Lipid based nanocarriers includes liposomes, transferosomes, ethosomes, niosomes, ufasomes, spinghosomes, pharmacosomes etc., This review article describes the types, formulation methods, evaluation and the research works done on lipid based nanovesicles for transdermal delivery of the drug.

Keywords: Lipid based nanovesicles, transdermal, Bioavailability, Absorption, Penetration

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INTRODUCTION

Transdermal delivery of drug is the most advantageous method for delivery of chronic and gastric irritant drugs. Through transdermal drug delivery, the drug levels will be maintained constant and transdermal patches can be easily removed if it doesn't require the drug delivery. But most of the drugs cannot be formulated as transdermal dosage forms due to the physicochemical properties of the drugs as the drug should be transported through different layers of the skin. The drug should be highly lipophilic to transport through the skin. But nowadays, several advancements have implemented to develop the transdermal delivery of the drug like iontophoresis, magnetophoresis, microneedles etc., Drug delivery through the conventional dosage methods was decreasing the penetration of the drug and also the release of the drug so to overcome these problems, novel drug delivery systems were developed like lipid based nanovesicles. Nanovesicles have the smaller size range which will enhance the drug permeation through the skin, site specific drug delivery and encapsulation of the drug to avoid the drug decomposition. Nanomaterials will also deliver the drugs which are highly hydrophilic by encapsulating them in a lipid layer and releasing at the site of action. The different types of lipid based nanocarriers includes liposomes, transferosomes, ethosomes and niosomes etc., the formulated nanovesicles were fabricated into the transdermal drug delivery systems by using different methods to enhance the action of the drug [1].

Types

Liposomes

Liposomes are the concentric bilayered vesicles in which aqueous membrane was enclosed by bilayered lipid membrane. The lipids included may be natural or synthetic. The essential components of liposomes are phospholipid and cholesterol, where cholesterol acts as a fluidity buffer [2]. The advantages of liposomes for transdermal drug delivery includes

Helps in localized delivery of drug at the maximum thermodynamic activity.

Liposomes helps in sustained release of transdermally active compounds.

For the systemic absorption of the drug, they serve as the rate-limiting membrane barrier.

Majorly, steroidal compounds are delivered as liposomal transdermal drug delivery systems [3].

Niosomes

Niosomes are also called as non-ionic surfactant vesicles because of the presence of non-ionic surfactants in their structure. Niosomes are more stable than liposomes. In niosomal formulations, non-ionic surfactants like fatty acids, alkyl esters, amino acids,

cholesterol and other type of lipids are used and then the formulation was hydrated. The formation of vesicle depends on the surfactant hydrophilic –lipophilic balance. The cholesterol in the formulation may or may not be used, but using of cholesterol will increase the rigidity of the bilayered structure and increase the encapsulation efficiency of the drug. Both the hydrophobic and hydrophilic drug can also be formulated as niosomes.[4] The advantages of niosomes for transdermal drug delivery includes

Reduced toxicity of the drug when niosomes formulated as transdermal formulations.

Bioavailability and pharmacokinetic properties can be modified for the drugs.

Improved patient compliance.

For the treatment of rheumatoid arthritis, the drug was delivered as niosomal transdermal drug delivery system [5].

Transferosomes

Transferosomes are the structures which consists of both surfactants and phospholipids in their structure as edge activators which increase the rigidity of lipid layer and has the higher permeability through the skin. In transferosomes, both high and low molecular weight drugs can be encapsulated. The vesicle exists in the form of unilamellar and particle size will be nano range to submicron range [6]. The advantages of transferosomes for transdermal drug delivery includes

Transferosomes are biodegradable and biocompatible, as they consist of natural phospholipids.

Transferosomes are very flexible that they can travel through the small pores of the skin.

The drugs which are having short half life can be used to increase pharmacological and physiological response.

It offers extended release of drugs and decreases the side effect that occurs when drug is administered through oral route.

Transferosomes as transdermal drug delivery will helps to deliver insulin, proteins and peptides, corticosteroids, anesthetics through the skin [7].

Ethosomes

Ethosomes are the new formulations in which the drug will penetrate into the skin in any condition. Ethosomes consists of phospholipid as an edge activator like transferosomes. High amounts of alcohol solution were used in this formulation to increase penetration into skin. It has the size range from nano to micron and exists in multilamellar and unilamellar forms. Many formulations of ethosomes have shown good results in research [8]. The advantages of ethosomes for transdermal drug delivery includes

Ethosomes can penetrate into deeper layers of the skin and also to systemic circulation.

The presence of ethanol in ethosomes, disturbs the lipid bilayer of the skin and the drug can enter into systemic circulation.

The presence of soft vesicles in ethosomes will enhance the transdermal delivery of drug.

Trihexyphenidyl HCl for Parkinsonian syndrome and insulin for diabetes was delivered through transdermal drug delivery [9].

Sphingosines

These are the formulations which consists of synthetic or natural sphingolipids or cholesterol. Sphingolipids has the size range from nano to submicron and exist in multilamellar and unilamellar forms. It has the better hydrolysis resistance and drug retention than liposomes. The sphingolipids used are sphingosines, glucuronosphingolipids, lysoshihngomyelins etc., The sphingosomes are tuned as ligands to achieve active targeting and these formulations can be administered through many routes [10]. The advantages of sphingosomes for transdermal drug delivery includes

They have the flexibility for the site-specific delivery of the drug.

The efficacy and stability of the drug can be increased.

Helps to control release of the drug through the skin.

Sphingosomes as transdermal drug delivery was mainly used for cosmetics like beclomethasone [11].

Ufasomes

Ufasomes are the nanovesicular systems which consists of unsaturated fatty acids like lanoleic and oleic acid and recently started using saturated fatty acid also along with surfactants. Ufasomes exists in multilamellar and unilamellar forms and particle size ranges from nano or sub-micron range. These are cheaper and have good stability and entrapment efficiency than liposomes. They have skin toxicity as side effect and less entrapment efficiency for hydrophilic drugs [12]. The advantages of ufasomes for transdermal drug delivery includes

The accumulation of the drug in dermis will be enhanced.

The drug will release in a controlled manner, avoiding side effects on the skin.

NSAID's and antifungal drugs are delivered through transdermal route in the form of ufasomes [13].

Pharmacosomes

Pharmacosomes are the vesicular systems in which drug and lipids are bound covalently. These are the colloidal dispersions that consist of phospholipids. When the drug is a herbal ingredient, then pharmacosomes are called as phytosomes. In these systems, polar drug encapsulation efficiency was increased, and particle size will range from nano to micron size. Pharmacosomes can easily pass through the biomembranes and has more encapsulation efficiency due to the covalent bond [14]. The advantages of Pharmacosomes for transdermal drug delivery includes

Oxidative degradation can be decreased through pharmacosomes

as transdermal drug delivery systems.

Sustained release of the drug through the skin can be achieved.

The drug can cross lipoidal structure easily and can attain the prolonged release of drug through topical delivery.

Antineoplastic drugs and proteins are delivered through the skin through the pharmacosomes [15].

Virosomes

Virosomes are similar to liposomes but with combination of viruses and has the size range of nano and sub-micron size. In these, virosomes acts as carrier for the drugs to the target site. Virosomes protect the active ingredient from proteolytic degradation and these are also used as an adjuvant system. They exist in the form of unilamellar and multi lamellar vesicles [16]. The advantages of virosomes for transdermal drug delivery includes

The presence of virus in the virosomes makes drug to deliver to target site through transdermal drug delivery.

They attain sustained release of drug through topical application.

Cerebral tumor can be treated by this route [17].

Quatsomes

Quatsomes are the vesicular forms which are unilamellar and consisting of sterols and quaternary ammonium surfactants. Quatsomes has the longer stability and have homogeneous morphology, which is essential for successful drug targeting. These systems are not expensive. They have capability to encapsulate hydrophobic and hydrophilic substances for site-specific delivery [18]. The advantages of quatsomes for transdermal drug delivery includes

They help in wound healing because of having property of improved protein effectiveness and bioavailability.

The presence of ionic surfactants in quatsomes, protects the skin from infections.

Enhanced drug delivery through the topical route.

Diabetic foot ulcers, venous leg ulcers can be treated by quatsome transdermal route [19].

MATERIALS AND METHODS

Thin film hydration method

In this method, initially dissolve the lipid in suitable organic solvent thoroughly and then the organic solvent was removed without traces by rotary evaporator until it forms as thin film. Dry the thin film and hydrate with aqueous media and agitate thoroughly to produce lipid based nanovesicles. The hydration media include saline, buffer, 5% dextrose etc., In this method the drug is added with lipid phase or aqueous phase based on the hydrophilicity and lipophilicity of the drug [20].

High shear homogenization method/ultrasonication method

In this method, the drug and lipid solution were combined with hot surfactant solution, which is an aqueous phase for emulsification. The surfactant solution should be maintained at the lipid phase temperature. High shear homogenizer was used for the emulsification process. In the second step, the o/w emulsion formed was ultrasonicated with probe so nicator and thus lipid based nanovesicles are formed on cooling the hot nanoemulsion [21].

Solvent emulsification and evaporation method

This method is very useful for the thermosensitive substances which are active because in this method, application of heat is not necessary and the main drawback of the method is presence of organic solvent residues in the final product. In this, the first step is to dissolve the lipid solution in the organic solvent which is water immiscible and then the lipid solution with organic solvent was emulsified with surfactant solution which is an aqueous phase and the end lipid was precipitated as a result of evaporation of organic solvent resulting in formation of lipid based nanovesicles [22].

Micro emulsification method

In this method, microfluidizer was used to formulate lipid based nanovesicles. First the lipid solution was introduced into the fluidizer where the fluidizer pumps the lipid solution with high pressure into the 5 µm orifice then it is directed towards the microchannels in which two streams of liquid colloid with each other and the resulted solution was recycled so many times until the perfect shape lipid based nanovesicles are formed [23].

Double emulsion method

In this method, the drug containing water phase was dissolved in the excess organic solvent which contains lipid phase that leads to w/o emulsion. In the second step, the formed solution was dissolved in excess of aqueous phase to get emulsified and form the double emulsion, i.e., (w/o/w). The organic solvent should be evaporated to form the lipid based nanovesicles [24].

Solvent emulsification and diffusion method

In this method the organic solution containing polymer, oil and partially water miscible organic solvent and surfactant with aqueous solution are combined by adding drop wise to form o/w emulsion. This is followed by the addition of excess of water to undergo diffusion and to form lipid based nanovesicles [25].

Solvent injection method

In this method, lipid is dissolved in water miscible organic solvent and was injected drop wise into the aqueous phase containing surfactant or without surfactant which is under magnetic stirring and maintained at a temperature that vaporizes the organic solvent [26].

CHARACTERIZATION METHODS

Morphology

The morphological characteristics of the formulation were studied under optical microscope. A small drop of sample was poured on a glass slide and observed under microscope for the morphology of formulation like structure, shape etc. [27].

Particle size, zeta potential and polydispersity index

To analyze these characters, zeta sizer was used which involves dynamic light scattering technique. In this technique, first

the samples are diluted with water and transferred into cuvette and place it into the instrument [28]. Polydispersity index is the measure of size distribution of the delivery system.

Entrapment efficiency

Transfer the specified amount of formulation into the centrifugation tubes and add required amount of buffer and centrifuged at required rpm and temperature until the free drug was separated from the sample. The formed supernatant layer was separated and diluted with distilled water if required and measure the absorbance using UV spectrophotometer at required wavelength and calculate the entrapment efficiency [29].

***In vitro* drug release**

In vitro drug release studies were performed by using a dialysis bag. The dialysis bag was filled with the sample and tied properly with a thread and placed in a buffer solution which is present in a beaker kept on magnetic stirrer. At regular intervals of time, the sample was withdrawn and analyzed in UV at fixed wavelength [30].

Table 1: Research works done on lipid based nanovesicles for transdermal delivery of drug

Author	Type of nanovesicle	Type of lipid used	Active ingredient	Method used
Mohammed Aslam et al.,	Nanostructured lipid carrier	Glyceryl monostearate, CapryolTM90.	Glibenclamide.	Emulsion-solvent diffusion and evaporation [34].
Sonali Bose et al.,	Nanostructured lipid carrier, Solid lipid nanoparticle	Compritol®888, glyceryldibehenate, Oleic acid,	Quercetin	Probe ultrasonication [35].
Madhulika Pradhan et al.,	Solid lipid nanoparticles	Compritol®888 ATO.	Fluocinolone acetonide (FA).	Emulsification-ultrasonication [36].
R. Sun et al.,	Nano emulsion, Solid lipid nanoparticle, nanostructured lipid carrier.	Solid lipid and Liquid lipid.	Resveratrol	High-pressure homogenization method [37].
Amanpreet kaur et al.,	Solid lipid nanoparticles.	Compritol®ATO 888.	Diflunisal	Hot homogenization [38].
Ponwanit Charoenputtakhun.	Nanostructured lipid carriers, Solid lipid nanoparticles.	Cetylpalmitate, Soybean oil, Medium chain triglycerides, Linoleic acids and oleic acids.	All-trans retinoic acid.	Ultra-sonication method [39].
Amalh. el-kamel, et al.,	Solid lipid microparticles.	Glycerol monostearate, glyceroldibehenate, glyceroldistearate, stearic acid.	Testosterone.	Hot homogenization technique [40].
Tarek A. Ahmed	Transferosomes	L-α-phosphatidylcholine.	Sildenafil	Lipid film hydration [41].
L. K. Omray	Solid lipid nanoparticles.	Glyceryl monostearate.	Testosterone	Solvent injection method [42].
S Brito Raj et al.,	Nanostructured lipid carrier.	Compritol 888ATO, Softigen.	Simvastatin	Hot homogenization technique [43].
P. Jahnavi et al.,	Solid lipid nanoparticles	Stearic acid, CholesterolandGlyceryl monostearate.	Lovastatin	Microemulsion method [44].
Kaisar Raza et al,	Nano-lipoidal carriers.	Glyceryl monostearate, Stearic acid, Cetyl palmitate,	Capsaicin	Micro-emulsification and rotary-evaporation [45].
Phunsuk Anantaworasakul et al,	Solid lipid nanoparticles, Nanostructured lipid carriers.	Compritol®888ATO, Glycerylmonostearate, Glycerylbehenate, Cetylalcohol, Stearylalcohol, isopropyl myristate and jojoba oil.	Capsaicin	Hot high-pressure homogenization and probe sonication [46].
Mallesh Kurakula et al,	Solid lipid nanoparticles	Compritol ATO 888, Cholesterol and castor oil.	Avanafil	Homogenization followed by ultra-sonication technique [47].
Kesavan bhaskar, et al,	Solid lipid nanoparticles and nanostructured lipid carriers.	Dynasan 114, Captex 355 EP/NF, soy phosphatidyl choline.	Flurbiprofen	Hot homogenization followed by sonication technique [48].
Saud Bawazeer et al,	Nanostructured lipid carriers.	Compritol 888 ATO and isopropyl myristate.	Tenoxicam	High shear homogenization and ultrasonication method [49].
Nimra Iqbal et al,	Solid lipid nanoparticles, Nanostructured lipid carriers, nanoemulsion.	Compritol®888 ATO, Stearic acid, Precirol® ATO 5, oleic acid.	Olanzapine	Hot high shear homogenization [50].
S. Babael, et al,	Nanostructured lipid carriers and nanoethosomes.	Glyceryl palmitostearate, Cholesterol	Lidocaine	Hot melt homogenization and modified ethanol injection method [51].

Table 2: Patents on lipid based nanovesicles for transdermal drug delivery

Patent number	Title of patent	Year of patent grant
US 8, 715, 736 B2	Nanoparticle formulations for skin delivery [52].	2014
US 2015/0098986 A1	Method for producing elastic vesicles [53].	2015
US 9,375,388 B2	Nanoparticle Based Cosmetic composition [54].	2016
US20160263047A1	Nano particle compositions and methods as carriers of nutraceutical factors across cell membranes and biological barriers [55].	2018
US 2014/0328898A1	Nano-liposomal formulations and method of use [56].	2014

Table 3: Marketed products of lipid based Nanovesicles for transdermal drug delivery

Product name	Name of the manufacturer
Noicellex	Novel Therapeutic Technologies, Israel
Remodelante	Isabelle Lancray
Nano lipid Basic CLR	Chemisches Laboratorium
Niosome +	Lancome
Nanominox	Sinere, Germany

Kinetic analysis for *in vitro* drug release

To know the mechanism of drug release for the lipid based nanovesicles, the drug release data was characterized with mathematical models like zero order, first order, Higuchi model, korsmeyer-peppas model, Hixson- Crowell model [31].

Scanning electron microscopy

Scanning electron microscopy is used to evaluate the surface morphology of the nanovesicles. In this method, the formulation was frozened and lyophilized and then sample was spreaded on conducting tape and subjected to gold coating in the presence of argon vacuum. Finally, it is examined under microscope [32].

Physical stability

The physical stability of the formulation was studied to evaluate the leakage of drug from nanovesicles on storage. For this study, the formulation was stored at room temperature and in refrigerator for 90 days. The samples were withdrawn at different intervals and analyzed for their stability [33].

CONCLUSION

The cases of maternal near miss and maternal deaths that occur in our tertiary care centre is high because of unbooked emergencies and most of the referred patients are in terminal stage. Our finding also suggests that comprehensive framework should also be developed for complicated cases to prevent maternal mortality. Monthly audit of maternal near miss and maternal death cases should be mandatorily done to strengthen the obstetric care. Proper documentation, analysis and interpretation of maternal near miss and maternal death cases will help in improvement of maternal health.

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