Biomimetic lipid-based nanosystems for enhanced dermal delivery of drugs and bioactive agents

Niranjan G. Kotla, [*, ¥] **Bhargavi Chandrasekar,** [‡] **Peadar Rooney,** [¥] **Sivaraman Gandhi,** [‡] **Aitor Larrañaga,** [¥] **K. Vijaya Krishna,** [¥] **Abhay Pandit,** [¥] **and Yury Rochev** [*, ¥, †]

[¥] Centre for Research in Medical Devices (CÚRAM), Biomedical Sciences Research Building, National University of Ireland Galway (NUI, Galway), Newcastle, Galway, Ireland

[‡] Institute for Stem Cell Biology and Regenerative Medicine (inStem), GKVK PO, Bellary Road, Bangalore, 560065, India

[†] School of Chemistry, National University of Ireland Galway, Newcastle, Galway, Ireland

Email address of corresponding author(s): yury.rochev@nuigalway.ie; n.kotla1@nuigalway.ie

ABSTRACT

Clinical utility of the conventional oral therapies is limited by the inability to deliver therapeutic molecules at the local or targeted site, causing a variety of side effects. Transdermal delivery has made a significant contribution to the enhanced therapeutic activities over the past two decades. In the modern era, various biomimetic and biocompatible polymer-lipid hybrid systems have been used to augment the transdermal delivery of therapeutics such as dermal patches, topical gels, iontophoresis, electroporation, sonophoresis, thermal ablation, micro needles, cavitational ultrasound and nano or micro lipid vesicular systems. Nevertheless, the stratum corneum still represents the main barrier to the delivery of vesicles into the skin. Lipid based formulations applied to the skin are at the center of attention and are anticipated to be increasingly functional as the skin offers many advantages for the direction of such systems. Accordingly, this review provides an overview of the development of conventional to advanced biomimetic lipid vesicles for skin delivery of a variety of therapeutics, with special emphasis on recent developments in this

field including the development of transferosomes, niosomes, aquasomes, cubosomes and other new generation lipoidal carriers.

KEYWORDS: Nano Lipid Vesicles, Skin Permeation, Transdermal Drug Delivery, Liposomes, Elastic Liposomes, Skin Delivery, Niosomes, Aquasomes and Transferosomes

INTRODUCTION

Over the past few decades, significant attention has been paid to the advancement of biomimetic, biocompatible drug delivery systems to improve patient compliance with low systemic side effects. Conventional pharmaceutical delivery systems (oral delivery systems) for topical applications have limited efficacy with drug metabolism by first pass effect in the liver, ubiquitous enzymatic degradation, and poor patient compliance often hampers the success and efficacy of treatments.[1] Topical delivery is the application of pharmaceuticals to the surface of the skin for the delivery of bioactive agents to disease sites within the skin (dermal delivery) or through the skin into the systemic circulation. Formulations for dermal/transdermal delivery containing bioactive agents are applied to the skin for the treatment of topical diseases like psoriasis, eczema, acne, lupus, warts, vitiligo, dermatomyositis, local anesthesia and for systemic targeting.[2] A transdermal drug delivery system uses the skin as an alternative route for the delivery of systemically acting drugs, and has several advantages over oral drug administration. [2, 3]

However, biphasic carriers such as liposomes, niosomes, or micro emulsions are confined to the skin surface and therefore are not efficient transdermal delivery systems. Currently, to minimize the problem of the stratum corneum barrier, various approaches have been developed.[3] These include augmentation of skin permeability using permeation enhancers, edge activators, size, shape and degree of unsaturation in the vesicles system. Drug delivery

systems using vesicular carriers such as transferosomes, elastic liposomes, aquasomes, sphingosomes and ethosomes have soft, flexible, self-regulating and self-optimizing vesicular characteristics that allow them to penetrate easily into deeper layers of the skin and circulation [4, 5] (Figure 1).

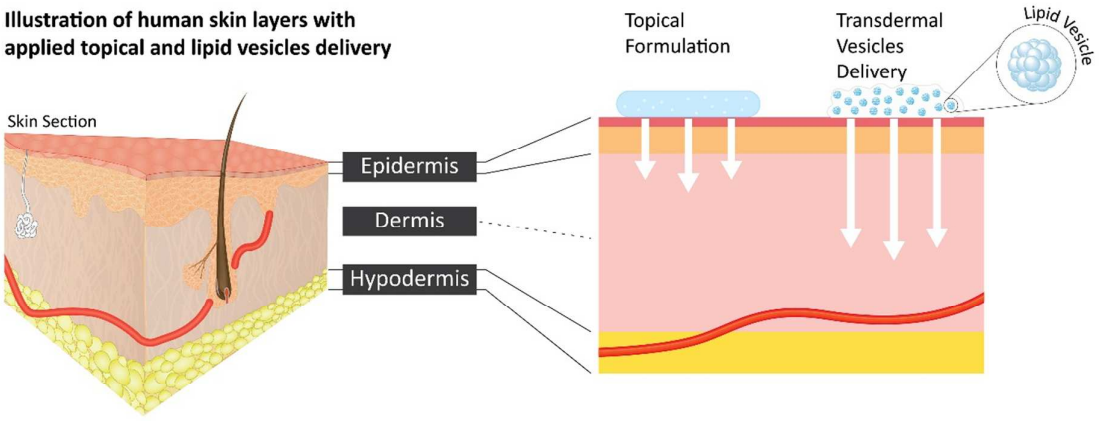

Figure 1. Schematic illustration of human skin layers with applied topical and lipid vesicular delivery showing lipid based vesicular system penetration into deep skin layers.

Therefore, considerable attention has been paid to investigating new delivery systems to enhance drug absorption through the skin by using nano-scale lipid technology. There has been much research into lipid vesicular based transdermal drug delivery, and multiple reviews of the research have been reported. [2-6, 9, 12] This review is an attempt to provide a comprehensive insight into the conventional biomimetic lipid vesicles composition, preparation methods, their permeation through skin with recent advancements and their clinical applications.

PERMEABILITY AND INTERACTION OF LIPID-BASED SYSTEMS WITH THE SKIN

The skin, which is the largest organ of the body, accounts for about 15% of the total adult body weight and consists of a series of layers penetrated by hair shafts and gland ducts. Skin is a membranous, flexible and protecting cover, formed mainly by two major layers: an

external, non-vascularized tissue layer (epidermis) and an internal, vascularized tissue layer (dermis).[6] The outer part of human skin (epidermis) is generally in the range of 0.06-0.8 mm. It is a multilayered structure consisting of viable cells and dead keratinized cells.[7] The dermis is approximately 0.3-3 mm thick and forms the bulk of the skin, which contains a network of blood vessels, lymph vessels, hair follicles, sweat glands & sebaceous glands–skin appendages. The hair follicles and sweat ducts open directly into the environment at the skin surface and provide the so-called appendageal route of skin permeation. The hypodermis is present beneath the dermis, which is composed primarily of fibroblasts and adipocytes-subcutaneous fatty tissues.[8, 9]

The exact mechanisms by which lipid carrier systems deliver therapeutics or bioactive agents into intact skin are not yet fully understood. Some proposed mechanisms of permeation through skin are the transappendageal route and the transepidermal route (Figure 2).

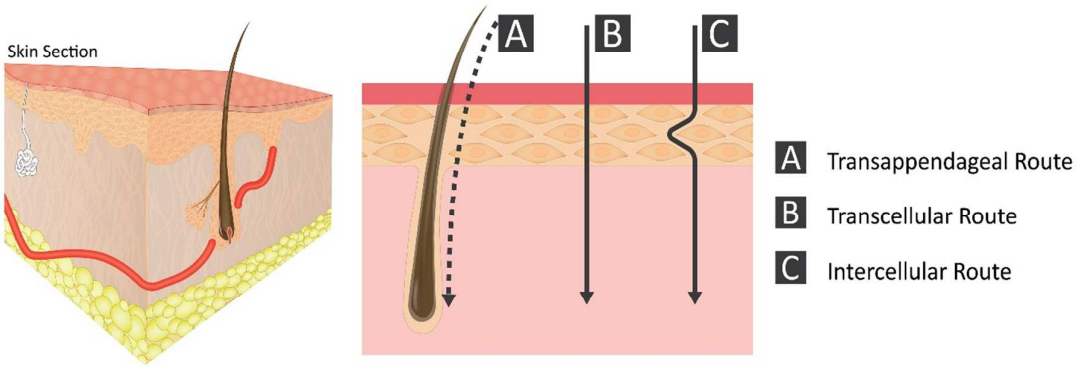

Figure 2. Schematic of major skin permeation routes for topical delivery of cell penetrating bioactive agents. A) Transappendageal route: permeation of the molecules through the sweat glands and across the hair follicles. B) Transcellular route: penetration of bioactive agents through cellular lipids. C) Intercellular route: transports through inter cellular lipids and spaces.

The transappendageal route, or shunt route, includes permeation of the molecules through the sweat glands and across the hair follicles with their associated sebaceous glands. The transepidermal route contains two micro pathways: the intercellular route and the transcellular route. Both pathways need to be partitioned into and diffused through not only the keratin bricks but also into and across the intercellular lipids. Thus, the intercellular lipids play a major role in the barrier function of the stratum corneum. [10, 11] The mechanism of penetration involved is dependent on the type of lipid, surfactant, concentration of permeation enhancer, vesicle size, shape, elasticity etc; however, particles with ≥ 600 nm are not able to deliver their payload into the deeper layers of the skin, whereas particles ≤ 300 nm are able to deliver into the deeper layers of the skin. [12, 13]

CONVENTIONAL LIPID VESICLES AS DELIVERY CARRIERS

In general, vesicles are aqueous fluid (water) filled colloidal particles. The layers of these particles consist of amphiphilic molecules in a bilayer conformation. Lipids are amphiphilic molecules composed of hydrophilic head and hydrophobic tail groups. When lipids are arranged in contact with water, the interactions of the hydrophobic portions of the molecule with the solvent result in the self-assembly of the molecules, generally in the form of liposomes. Liposomes reside at an aqueous core encircled by a lipid bilayer detached from the inner aqueous core from the extent outside. [14, 15]

Liposomes have been used to increase the therapeutic activity and bioavailability of the therapeutics by enhancing drug absorption, decreasing metabolism, extending biological half-life and decreasing toxicity. [15] The specific amphiphilic property of liposomes provides two different cage compartments where hydrophilic and hydrophobic compounds can be loaded in the aqueous cavities and hydrophobic membranes, respectively. Liposomes are

still considered as attractive drug delivery vehicles due to their biocompatibility, non-immunogenicity, biodegradability and ease of surface functionalization. [15-17]

On the other hand, these systems have limitations such as poor encapsulation efficiency for hydrophobic drugs, short half-life and an unstable membrane that results in leaky behavior. Because they have phospholipids as a core material, these systems encounter stability issues, and alterations in temperature (above T_m i.e. melting temperature) lead to phase transition from gel to liquid. The benefits and limitations of liposome drug carriers crucially depend on physicochemical and colloidal aspects such as size, composition, loading efficiency and resistance; likewise their biological interplay with the cell membranes.[17, 18]

The potential for various therapeutic molecules (hydrophilic drugs, hydrophobic drugs, DNA, RNA-polyplexes and surface functionalization with targeted ligands) to be incorporated in liposomal vesicles is illustrated in (Figure 3).

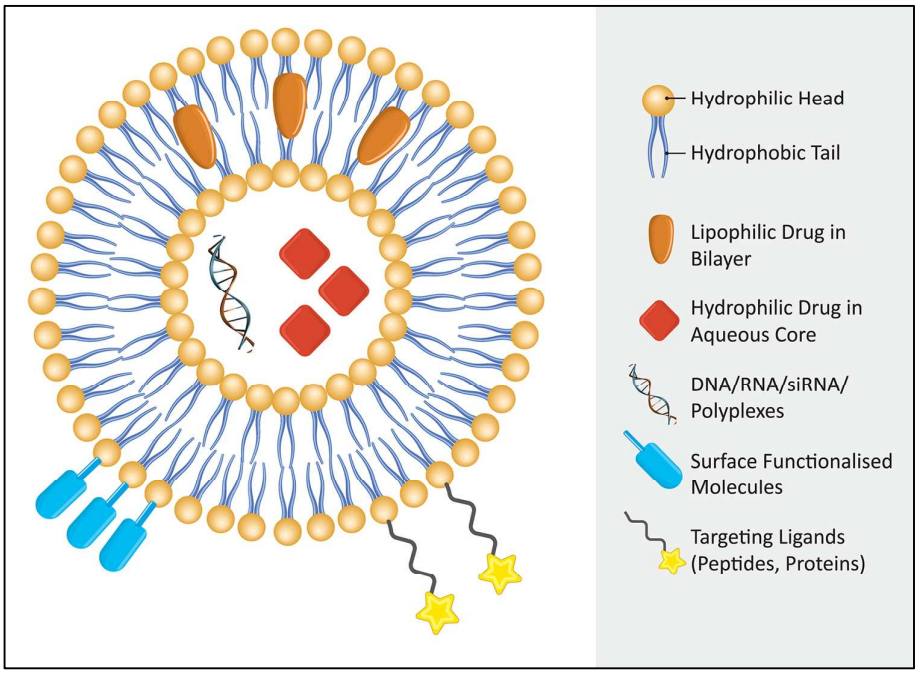

Figure 3. Representation of a typical liposomal vesicle structure with functional modifications showing that a hydrophilic core can load polyplexes, hydrophilic drugs. Lipophilic bilayer embedded with hydrophobic molecules.

Liposome characteristics and use are directly related to the preparation method. Methods reported for preparation of liposomes include mechanical agitation, solvent evaporation, solvent injection and the surfactant (detergent) solubilization method. Even though liposome preparation may be spontaneous, some mechanical mixing is often required. Parameters that are critical for preparation methods include the physicochemical aspects of the material to be involved and those of the liposomal ingredients, the medium in which the liposomes are circulated, the adequate concentration of the encapsulated elements and their potential toxicity. [19,20] Depending on size and number of bilayers, liposomes are classified as small unilamellar vesicles (SUV; with 20-100 nm size), large unilamellar vesicles (LUV; more than 100 nm), multilamellar vesicles (MLV; more than 500 nm), or giant unilamellar vesicles (GUV; more than 1000 nm). The number of bilayers in each system affects drug loading efficiency, permeation efficiency, release kinetics, cell interaction and cell internalization (Figure 4). [21]

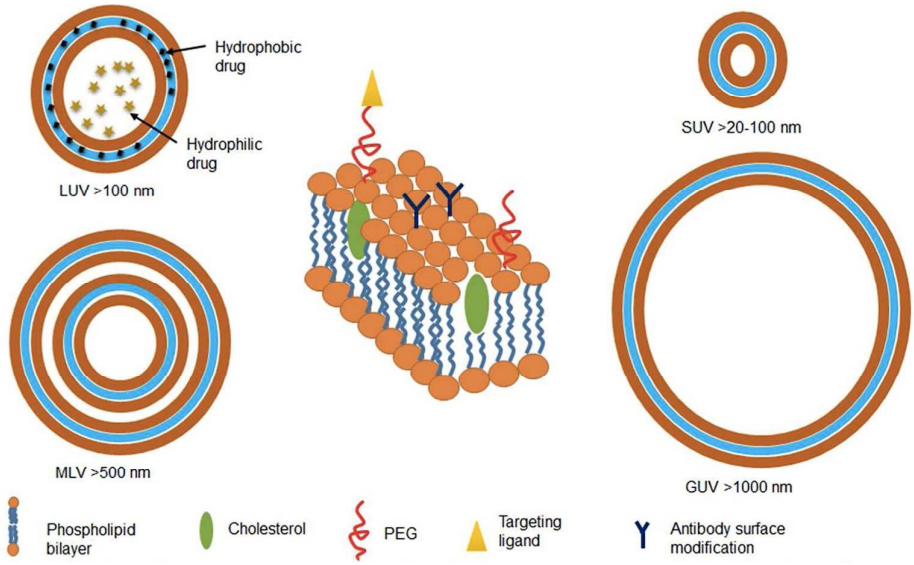

Figure 4. Different type of liposomes based on size and lamellarity (Reproduced with the permission from Ref. 21, Copyright © 2015 American Chemical Society)

Among all the lipoidal delivery platforms, liposomes are a firmly established system with several FDA-approved formulations for cancer treatment, [21] ocular delivery of drugs, [22] pulmonary drug delivery with sustained release, and systemic therapeutic activity [23, 24]. Table 1 illustrates a few reported drugs/genes encapsulated liposomes for various therapeutic applications.

Table 1. Drugs encapsulation in different liposomal systems for dermal delivery

Therapeutic agent	System component	Biomedical application	References
Alpha-interferon and cyclosporin A	Nonionic liposomal formulations composed of stearates, cholesterol	For enhanced peptide drug delivery into pilosebaceous of hamster ear via topical delivery	25
Tretinoin	Liposomal gel contaiing carbopol 934 gel base	Potential utility of commercialization of liposomal TRE gel in the treatment of acne.	26
Recombinant human epithelial growth factor	A stable liposomal dry power prepared by purified egg lecithin PC-98T	Ultrasonic spray freeze drying technique applied to prepare a redispersible rhEGF liposomal dry powder for wound healing via dermal delivery	27
Curcumin	Vesicles (propylene glycol liposomes, ethosomes, traditional liposomes) composed of propylene glycol, hydrogenated phosphatidylcholine and cholesterol	Propylene glycol liposomes (PGLs) showed an efficient anti-inflammatory effect by transdermal lipid vesicle skin delivery	28
Fluconazole	Dipalmitoyl phosphatidyl choline (DPPC) liposomes doped by the drug fluconazole	For an effective antifungal fluconazole activity	29
Benzocaine	Multi-lamellar (MLV) and small uni-lamellar (SUV) vesicles entrapping benzocaine contains 50:50 w/w phosphatidylcholine-cholesterol	Improving clinical effectiveness of benzocaine in topical anaesthesia	30
Lidocaine	ELAMax (4% liposomal lidocaine) cream	Liposomal lidocaine cream improves cutaneous analgesia in children before intravenous cannulation	31
5-aminolevulinic acid and its derivatives	Liposomes comopsed of egg yolk phosphatidyl choline (PC), phosphatidic acid (PA) and phosphatidyl glycerol (PG)	Improved delivery of aminolevulinic acid (ALA) and its esterified derivatives ALA-Hexyl ester (He-ALA) and ALA-Undecanoyl ester (Und-ALA) for use in photodynamic therapy (PDT)	32
Tetracaine	Radiolabelled tetracaine loaded liposome formulations and two conventional dosage forms	For an effective local anesthetic effect on skin	33

	(using PEG Ointment USP and Glaxal base)		
Diclofenac	Highly purified soybean lecithin with a mass content of Phosphatidyl choline of up to 90%	To check the efficacy of colloidal structure of a topical formulation and the drug release in vitro as well as the influence of the microstructure on the stratum corneum drug permeability	34
Oestradiol	Liposomes of various ratios of phosphatidylcholine (PC), PC:Sodium cholate, PC: Span 80 and PC:Oleic acid	Oestradiol permeation through human epidermis	35

PROGRESSES IN LIPOSOMAL SYSTEMS FOR ENHANCED DELIVERY

Various attempts including modification of the liposome surface with hydrophilic polyethylene glycol polymers [36], such as cryoprotectants or inclusion of a high amount of cholesterol into the bilayer and a few non-lipoidal carriers have led to a new generation of vesicles (niosomes, aquasomes, transferosomes, sphingosomes, ufasomes, cubosomes etc.) for transdermal delivery. New generation vesicles, their architecture and advantages of the systems, are displayed in Table 2.

Table 2. New generation lipid based vesicles architecture and their specific features

Type	Architecture of the system	Advantage of the system
Niosomes	Non-lipoidal with nonionic amphiphilic surfactants (polyoxyethylene, polyglycerol, Polysorbates, PEG esters)	– Niosomes disrupt the structural, fluidic properties of the stratum corneum for better penetration – Good chemical stability at storage
Transfersomes/ Ethosomes	Lipid supramolecular flocculates (Phospholipids + edge activators /Ethanol)	– Ultradeformable carriers with an edge activity at membrane site – Promotes elasticity and additional flexibility for deep layer penetration
Cubosomes	Bicontinuous cubic liquid crystalline system with two continuous non-intersecting hydrophilic regions divided by a lipid bilayer (Phospholipids and polaxamers or PEG)	– Sustained release of incorporated bioactive agents – Moderate bio adhesive activity – More stable cubic vesicles
Aquasomes	Three-layered structures comprising a solid nanocrystalline core with oligomeric coating	– Preserve structural integrity of protein pharmaceuticals – Induce better immunological responses – Specific targeting with high drug loading, molecular shielding
Sphingosomes	Concentric, bilayered vesicles in which a membranous sphingolipid bilayer encloses an aqueous volume (sphingomyelin, cholesterol)	– Enhance systemic circulation time in in vivo (prolonged release) – Better vesicle stability – Less susceptible to degradation
Ufasomes	Unsaturated fatty acid vesicles (oleic	– Cost effective and better encapsulation

acid, linoleic acid)	– High drug loading, good surface chemistry

Niosomes as Delivery Vehicles

Unlike the conventional liposomes, which are composed of phospholipids, niosomal vesicles consist of non-ionic surfactant molecules (Polysorbates, Polyethylene glycol esters etc.). These amphiphilic surfactant molecules have both hydrophilic and lipophilic parts and self-assemble readily to form either micelles or lamellar structures. Non-ionic surfactants are preferred in most cases as these causes less irritation than the ionic ones do.[37] Major components in a niosomal vesicle include surfactants, cholesterol and charge inducers. Some of the common nonionic surfactants used are ether based, ester-linked surfactants, tweens and spans. In many cases cholesterol is used as an additive. Being a waxy steroidal metabolite, it provides orientation order and rigidity to the bilayer. To induce charge on vesicle surface to help in increasing the stability of the vesicles and also to prevent aggregation of the vesicles, charge inducers were added to the scaffold system. [39] The most common method of preparation used for niosomal vesicles is thin film hydration. For niosome preparation by film hydration, the surfactant with additives dissolved in an organic solvent is evaporated in a rotating evaporator followed by hydration by agitation to form the bilayered vesicles. Other methods include sonication, ether injection, microfluidization, multiple membrane extrusion, bubble method, active and passive trapping methods and reverse phase evaporation. [38, 39]

The stability of niosomes is balanced by many factors; additives like cholesterol and charge inducers not only play a crucial role in balancing the assembly forces on these particles, but also are also crucial for a uniform morphology of spherical particles. While stability is an important parameter, in some cases it comes at the cost of toxicity. For example, while it

seems to be more practical to use ether based surfactants rather than ester-linked surfactants (which are susceptible to enzymatic degradation) purely from a stability based standpoint, previous research has shown that ester-linked niosomes have the least toxicity while ether-linked (especially with single alkyl chain) have high toxicity. Having a balanced formulation of surfactants and additives according to the target application is therefore essential. [40]

Studies by Carlotta et al., in 2016, have shown the effect of pH modification on supramolecular structure and morphology of niosomes. The authors have reported multidisciplinary methodology to study the supramolecular structure and morphology of pH-sensitive non-ionic surfactant vesicles (niosomes), made from commercial polysorbates (Tween 21, 20 etc.) synthesized by modifying the head group of surfactant with different glycine derivatives for inflamed site delivery and tumor targeting applications. [41]

The major advantage of this system is that it has surfactants act as penetration enhancers since they can fluidize the stratum corneum layer and diffuse through them. Niosomes are chemically stable and easier to prepare with higher purity than liposomes since these are vulnerable to oxidative degradation being composed of phospholipids. Because, excipients and equipment used in the preparation of niosomes are much cheaper, mass production of such particles is very cost-effective. Some of the disadvantages encountered with niosomes include physical instability due to aggregation of the particles, leakage and hydrolysis of the entrapped drugs that decrease the shelf life. Various drug-loaded niosomes for dermal delivery are shown in Table 3.

Table 3. Therapeutic agents loaded niosomal formulations

Therapeutic agent	Delivery vehicle	Application	References
Ursolic acid	Niosomal gel	Enhanced transdermal delivery to treat arthritis	42

Tretinoin	Novel diolein- niosomes	Evaluation as a skin delivery system	43
Salidroside	Niosomal vesicles	Dermal and transdermal delivery	44
Simvastatin	Niosomal gels	Pediatric transdermal delivery	45
Buflomedil Hcl	Niosomal patch	Evaluation of transdermal delivery	46
Sulfadiazine sodium salt	Niosomes with hydroxyl groups as additives	Effect of additives on niosomal transdermal delivery	47
Mefenamic acid	Nano-proniosomes	Enhance the penetrability	48
DNA encoding Hepatitis B surface antigen (HBsAg)	Niosome carriers	Topical vaccine for genetic immunization against hepatitis B	49

Transfersomes as Delivery Vesicles

Conventional liposomes often fail to meet the requirements for efficacious transdermal delivery due to their inability to penetrate the deeper layers of the skin; hence there is a need for more non-invasive variants of these liposomes. Transfersomes imitate conventional liposomes in morphology; functionally, they are more elastic and deformable and can penetrate through pores smaller than their own size. [50, 51]

Typical transfersomes for transdermal application consist of a mixture of lipids (mainly phospholipids similar to conventional liposomes) and biocompatible membrane softeners termed as edge activators. Edge activators are single-chain surfactants with the ability to destabilize the bilayer assembly and hence the deformability. This optimal mixture imparts elasticity to the liposomal membrane and makes it suitable for penetration through channels of the skin. Phosphatidyl cholines are used as phospholipids in most cases and common edge activators used are surfactants like sodium cholates, tweens and spans. Other components to improve the vesicle functioning include hydrating agents. [51] These vesicles are also called ethosomes when relatively high amounts of alcohol are used as membrane softeners. The most widely used technique to prepare transfersome formulation is thin film hydration that involves three main steps-mixing components and solvent evaporation,

hydration and sonication. Lipid film hydration modified hand shaking method is another method to prepare these vesicles. [52]

The major advantages of these vesicles include high encapsulation efficiency of the drug, high elasticity which in turn leads to better penetration for transdermal delivery, and the ability to hold both low and high molecular weight drugs. While they are biodegradable and biocompatible, they also have a few limitations that are similar to those of conventional liposomes like chemical instability since they are liable to oxidative degradation, purity issues with phospholipids and expensive formulations. Drug loaded transfersomal vesicles for dermal delivery are showed in Table 4. The major differences in composition and construction of transferosomes with other lipid carriers (conventional, niosomes, ethosomes) are shown in Figure 5.

Table 4. Reported transfersomal vesicles for various therapeutic applications

Therapeutic agent	Delivery vehicle	Application	References
Sildenafil	Transfersomal vesicles	Testing the potential of these vesicles for transdermal delivery	53
Sildenafil citrate	Nano-transfersomal films	Enhanced transdermal permeation and bioavailability of the drug	54
Buspirone HCl	Transfersomal gel	Increasing the transdermal permeation	55
Pentoxifylline	Elastic transfersomal vesicles	Treatment of intermittent claudication and chronic occlusive arterial diseases	56
Asenapine maleate	Nano-transfersomal vesicles	Enhanced permeation and bioavailability for treating bipolar disorders	57
Clindamycin phosphate	Gel and vesicles	Enhanced permeation of the antibiotic	58
GinsenosideRhl	Ethosomal and trasnfersomal vesicles	Potential for encapsulation and permeation in transdermal delivery	59
Doxorubicin	Hyaluronic acid modified transfersomes	Transdermal lymphatic delivery for tumor metastasis	60

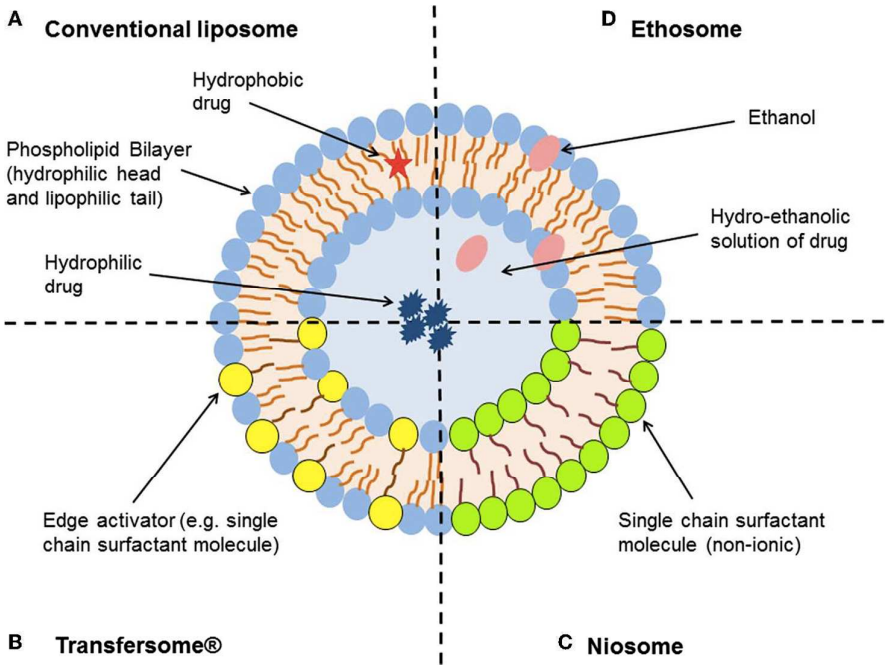

Figure 5. Schematic representation of different types of lipid-based vesicular delivery systems (A) Conventional liposomes generally consist of a lipid bilayer composed of phospholipids and cholesterol which encloses an aqueous core. Both the lipid bilayer and the aqueous space can incorporate hydrophobic or hydrophilic compounds, respectively. Liposome characteristics can be modified by the addition of surfactants to form (B) Transfersomes and (C) Niosomes (depending on the ratio of phospholipid to surfactant), or relatively high concentrations of ethanol to form (D) Ethosomes (high amounts of alcohol used as membrane softeners. (Adopted with the permission from Ref. 61)

Cubosomes as Delivery Vesicles

Unlike solid nano-vesicles, cubosomes exhibit a bicontinuous cubic liquid crystalline phase that has uniform molecular orientation and symmetry in structure. This thermodynamically stable phase is typically exhibited by the hydrophobic regions of amphiphilic molecules in polar solvents. The structure consists of two continuous but non-intersecting hydrophilic regions divided by a lipid bilayer (Figure 6). These structures, that are different from their micellar cubic structures, offer the unique ability to be dispersed into particles called cubosomes of 10-500 nm in size. The internal cubic structure and composition vary with different drug-loading modalities. [62, 63]

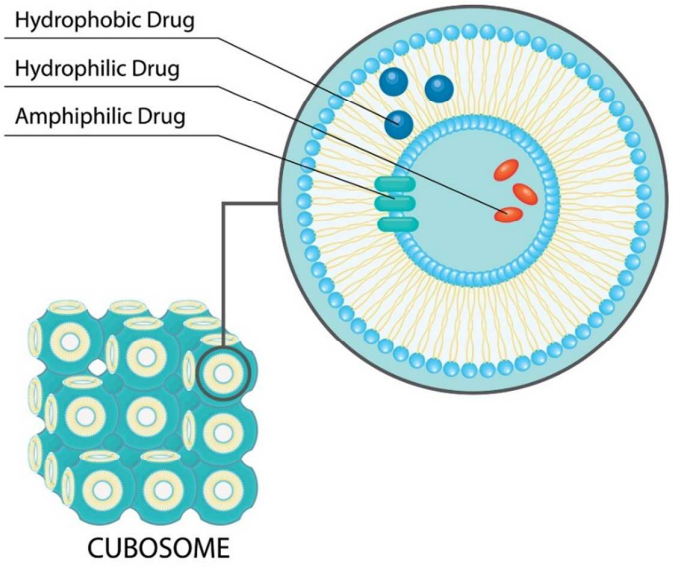

Figure 6. Illustration of a Monoolein based 3D network of typical cubosomes: self-assembled, bicontinuous cubic liquid crystalline system (Reproduced from Ref. 62).

The most common technique to prepare cubosomes is that in which the bulk phase is subjected to high-energy dispersion followed by colloidal stabilization using surfactants. [64] In alternative approach, the cubosomes are formed or crystallized from precursors or by using a spray-drying technique from powdered precursors. [65]

Some advantages of this system include high drug loading due to internal surface area and structure, easy preparation, high stability at any dilution level, and the possibility to encapsulate hydrophilic, hydrophobic and amphiphilic drugs. A drawback is that large-scale production is difficult because of high viscosity. Yallappamaharaj et al., in 2014, evaluated the transdermal delivery potential of diclofenac sodium cubosomes. In this study, authors have used varying ratios of drug, lipid emulsifiers and penetration enhancers to obtain an optimized cubosomal formulation for enhanced transdermal delivery.[66] Peng et al., in 2015 characterized cubosomes for transdermal delivery of capsaicin where a sustained release profile was seen and the penetration studies indicated that these vesicles are ideal candidates for the transdermal delivery of capsaicin.[67] Also Li et al., in 2015, characterized

the transdermal delivery potential of Paeonol loaded cubosomes, where the authors concluded that the paeonol cubic liquid crystalline nanoparticles could reduce the irritation in the skin stimulating test against the commercial ointments with better penetration abilities. [68]

Aquasomes as Delivery Vesicles

Aquasomes translates as "water bodies", and these vesicles use their water-like properties to preserve and deliver fragile bioactive molecules at the desired site. These are three-layered structures comprising a solid nanocrystalline core that provides structural integrity to the vesicle and an oligomeric coating that protects against dehydration and also stabilizes the bioactive molecules that are adsorbed to it. The layers are self-assembled by non-covalent and ionic bonds. [69]

Polymers (acrylates, gelatin) and ceramics (calcium phosphate, diamond particles or tin oxide) are being used for the nanocrystalline core preparation. The oligomeric coating can involve compounds like sucrose, cellobiose, citrate, chitosan, etc. Commonly used methods for core fabrication are colloidal precipitation and sonication, plasma condensation and inverted magnetron sputtering, depending on the material used. The oligomeric layer is adsorbed onto the core material by addition of carbohydrate to an aqueous dispersion of the core material under sonication. Finally, coated particles are dispersed in a solution containing the bioactive molecules for adsorption. [70, 71]

The major properties that led to the use of these particles as ideal carriers include preservation and protection of some fragile bioactive molecules, conformational stability, large size and excellent surface chemistry that helps in higher drug loading. [71]

Sphingosomes as Delivery Vesicles

Conventional liposomes present problems such as degradation due to hydrolysis or oxidation, sedimentation, leakage of drug or fusion of particles during storage, which affect the overall stability of the formulation.[72, 73] Degradation is mainly caused by the hydrolysis of ester bonds in phospholipids in conventional liposomes. This could be avoided if a lipid containing ether or amide bond is used instead. Hence, sphingosomes consist of such sphingolipids to form stable liposomal carriers. [73-75]

Sphingolipids are a cell component which consists of a polar head attached to a hydrophobic tail. Different types of sphingosomes can be prepared from different types of sphingosomes including sphingosine, ceramide, sphingomyelin, glycosphingolipid etc. Sphingosomes are typically defined as a concentric, bilayered vesicle in which a membranous sphingolipid bilayer encloses an aqueous volume, and consist of sphingolipid (commonly sphingomyelin) and cholesterol with an acidic pH inside. [74,75] The most common methods of preparation of sphingosomes are those of mechanical dispersion and film hydration. Other methods include sonication, reverse phase evaporation, solvent injection, microfluidization, freeze-thaw, etc. The sphingosomes produced can be unilamellar, mutilamellar, oligolamellar or multivesicular. In addition to carrying over the various advantages of conventional liposomes, sphingosomes bring major benefits such as increased drug loading efficiency, longer circulation time *in vivo* and, in addition, are less susceptible to degradation due to the presence of amide or ether bonds instead of ester linkages.[72-75]

Unsaturated Fatty Acid Vesicles (Ufasomes) as Delivery Vesicles

Ufasomes are enclosed lipid bilayered structures that are derived from long chain fatty acids. These fatty acid vesicles contain two types of amphiphiles in their structure: the nonionized neutral form and their ionized counterpart which are negatively charged soap molecules. [76] The ratio between these will determine the vesicular stability. Structurally, the

fatty acids containing the carboxyl groups are in direct contact with the water, whereas the hydrocarbon chains are aligned towards the interior of the membrane. [77]

These structures are prepared from various unsaturated fatty acid chains like oleic acid, linoleic acid, palmitoleic acid, etc. Recent studies have shown that vesicles can also be prepared using saturated fatty acid chains. In the preparation, several factors affect the formation of these vesicles including the type of fatty acid, buffer solution, pH, electrolyte, addition of cholesterol, etc. Recently, several modifications to these factors have been introduced to make ufasomes more effective delivery vehicles.[77, 78]

The major advantages of these vesicles over conventional liposomes include cost effectiveness, increased entrapment and loading efficiency and suitability for penetration. Although these are more stable than conventional liposomes, they are sometimes susceptible to oxidation that raises stability issues.[79] In 2013, Rajkamal et al. evaluated ufasome mediated delivery of dexamethasone in carrageenan-induced rat edema models. They have concluded that the transdermal penetration and skin partition was significantly higher in ufasome mediated delivery than in plain drug and plain gel formulations.[80] The permeation of drug for ufasome-mediated delivery was found to be 4.7 times greater than that for plain drug suggesting ufasomes to be a promising mode of transdermal delivery.

Other evolving lipoidal carriers

Apart from the aforementioned vesicles, there are numerous lipoidal carriers which are either simple modifications of liposomes or derived from different sources and structures. Most of these evolving carriers are an alternative to eliminate various drawbacks associated with conventional liposomes. At present, there are no available drug delivery systems that make satisfy achieving all the lofty objectives, but strenuous efforts have been made to achieve them for better efficacious delivery systems. These vesicles, which include

cochleates, pharmacosomes, archaesomes, genosomes, lipospheres, crytosomes, virosomes, emulsomes etc., are enumerated in Table 5.

Table 5: Some emerging lipoidal carrier systems for delivering bioactive agents

Vesicle Type	Description	Benefits of the system	References
Cochleates	Long rolled up sheets (cigar like) of lipids formed as a result of addition of multivalent cations to phospholipids	Devoid of aqueous compartment which leads to better stability	81, 82
Archaesomes	Vesicles with one or more bilayers of Total Polar Lipids (TPL) extracted from microorganisms of archaea domain	Better internalization in cells, thermal and pH stability, effective for antigen/adjuvants	83, 84
Lipospheres	Drug dispersed in solid lipid core which as a whole is surrounded by phospholipids	Better encapsulation, more control on drug release, high dispersibility in aqueous medium, higher physical stability	85-87
Virosomes	Preformed liposomes coated with virus glycoprotein spikes	Can be used to target specific cell types to deliver nucleic acid, drugs, peptides etc., better fusibility with cell membrane	88, 89
Genosomes	Complex of suitable genetic material (DNA) with lipids	Higher biodegradability and stability in blood stream and better transfection due to DNA-lipid complex	90, 91
Cryptosomes	Liposomes that incorporate polaxamers and polyethylenegycol (PEG) as a stabilizer	Long circulation times *in vivo*, evade the host immune reactions	92, 93
Emulsomes	Colloidal carriers composed of solid lipids surrounded by phospholipids	Increase the solubility and bioavailability of poorly water soluble bioactive agents	94-97

CONCLUSION AND FUTURE PROSPECTS

Over the past few decades, considerable attention has been paid to the development of advanced biomimetic, biocompatible lipid-based vesicular delivery systems. In recent years in particular, topical delivery via skin using pharmaceutical lipid vesicles for different clinical applications has emerged for treating various topical diseases such as psoriasis, eczema, acne, vitiligo, dermatomyositis and topical anesthesia. Efforts have been focused more on

optimization protocols with new combinations for better stability and efficacy of the systems. In the modern era, lipid-based systems have become one of the easiest and widely used delivery vehicles in various topical therapeutic and biomedical applications due to their proficient properties, biocompatibility and functions including selective targeting. These lipid vesicle systems have been examined in the clinic for hydrophilic, hydrophobic, amphiphilic molecules (drug, gene, vaccine, polyplexes) delivery for a variety of skin treatments, dermal anesthesia and imaging.

Even though there was significant progress in lipid delivery vehicles, conventional lipid vesicles are still considered a controversial class of transdermal carriers for topical delivery of therapeutics. This is because they lack potential utility as a carrier and reservoir for controlled release and lack penetrability within various layers of the skin. Recently developed lipid carrier systems exhibit an amalgamation of different specific properties, such as elasticity, penetrability, targetability and longevity. This new generation of biomimetic lipid carrier systems can load more than one therapeutic agent for combinatorial therapies. Currently, a number of various lipid-based formulations have received clinical approval [98] and a few have been used in clinical trials. [99-101]

Among the advanced lipid vesicles discussed above, the choice of the best vesicle is application specific in most cases. Niosomes and transfersomes are among the oldest alternatives to the liposomes that are used. Although advanced modifications of liposomes have emerged, each of these has a slight disadvantage compared to the other. Niosomes have good chemical stability but questions remain as to the physical aggregation of particles. While a transfersome constitutes a modified liposome in terms of penetration, the fundamental issues of degradation still has to be looked into to make it better. Replacement of phospholipids with sphingolipids to overcome the major problem of degradation has

improved the stability but the extended periods of exposure in the body raises concerns about toxicity. The other recent modifications of liposomes like cubosomes or ufasomes have stability issues or problems in other respects such as drug loading and encapsulation. For a given transdermal delivery, a combination of factors including type of drug, period of release, intensity of disease, degree of toxicity etc. play a role in determining a more effective lipid based delivery system.

Numerous methods have been developed to produce novel lipid based delivery systems of desired characteristics such as enhancing penetrability, promoting elasticity, ultra deformability for an effective penetration and controlled release etc., Nonetheless, the application of these methods for developing surface functionalized lipid vesicles at large scale continues to be debated. However, formulation scientists encounter numerous challenges in the development process, in scale-up, shelf life stability and commercialization of these systems. In the future, in the development of bioactive agents loaded lipid vesicle formulations, researchers as well as manufacturers will be required to create developments, which are state-of-the art in the current pharmaceutical area. The need for progress in designing, surface functionalization and stability of lipid vesicles as delivery systems will continue to demand more effective lipid based pharmaceuticals in the market in the future.

AUTHOR INFORMATION

Corresponding authors

* E-mail: yury.rochev@nuigalway.ie

n.kotla1@nuigalway.ie

Notes

The authors declare no competing financial interest.

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Manuscript title: Biomimetic lipid-based nanosystems for enhanced dermal delivery of drugs and bioactive agents

Authors: Niranjan G. Kotla, Bhargavi Chandrasekar, Peadar Rooney, Sivaraman Gandhi, Aitor Larrañaga, K. Vijaya Krishna, Abhay Pandit and Yury Rochev