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Review Article

Penetration enhancer containing vesicles for dermal and transdermal drug delivery. A review

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ABSTRACT

Dermal and transdermal drug delivery systems are attractive dermatological products of great importance in the pharmaceutical market from conventional to advanced formulations. The skin, the largest organ in our body, has a barrier function to protect our bodies against any harmful external factor. This function may interfere with or inhibit the drug delivery through the skin. Therefore, for efficient drug penetration or permeation two approaches can be applied; adding external penetration enhancers to ease the drug penetration, or encapsulating the drugs in carrier systems that facilitate drug penetration by squeezing through skin-tight junctions hence allowing better penetration of the drug. Hence, researchers have developed novel ultra-deformable nano-vesicles to overcome this barrier function of the skin and deliver the drug to the required action site. Among the most promising developed nano-vesicles are the lipid-based nanocarriers. The penetration enhancer-containing vesicles are lipid-based nano-vesicles containing penetration enhancers hence combining both aforementioned approaches for facilitating drug penetration through the skin. This review gives an overview of one of the novel ultra-deformable vesicles; the penetration enhancer-containing vesicles (PEVs) which are used in dermal and transdermal drug delivery with special emphasis on their composition and method of preparation. A special focus was made on the therapeutic outcome of using penetration enhancers containing vesicles compared to the conventional dosage forms.

Keywords: *Transdermal; cutaneous; nano-vesicles; lipid-based nanocarriers; penetration enhancer vesicles.*

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1. Introduction

The skin is the largest organ of the body, it protects the body through different mechanisms and regulates some body functions. It is formed of two layers, epidermis and dermis. The Stratum corneum (SC), is the outermost layer of the epidermis and the main layer responsible for skin protection as it possesses a barrier function, that acts against many external harmful factors **[1]**. The skin controls not only the entry of harmful substances, but also guards against the loss of water, electrolytes, and important biological molecules. Unfortunately, this barrier function represents an obstacle against dermal and transdermal drug delivery as it protects against drug entry to and through the skin **[2]**. Advantage should be taken of this large area of the skin to

deliver the drugs; dermally, as the drug is applied directly to the required area to produce a local action on the skin and hence high drug amount is deposited at the site of action (the skin), decreasing the amount of drug reaching the circulation hence lower side effects, and transdermally where the drug is delivered to the body organs (the action site) through the skin, so the drug crosses the skin and reach the systemic circulation then the target organs moreover the drug should reach a certain concentration in the target organ(s), which is the therapeutic concentration, to achieve the desired outcome. The effectiveness of both pathways is restricted to the barrier property of the SC. Efficient penetration of drugs through the keratin and lipid bilayer of the SC is crucial for drug delivery. Both dermal and transdermal routes are convenient only for low molecular weight and lipid-soluble drugs, whereas the high molecular weight molecules cannot pass through the SC **[3]**. Many trials were reported to improve the dermal and transdermal drug delivery through the skin such as physical techniques and other chemical approaches (e.g., using penetration enhancer (PE)) or using novel delivery systems. The physical approach is not convenient, and annoying to the patients, the chemical approach can sometimes cause toxicity and decrease the efficacy of the treatment **[4-6]**.

Recently, nano-drug delivery systems have been employed in dermal and transdermal drug delivery. They showed superiority over the conventional topical dosage forms. They can act as reservoirs and help in drug targeting or modifying the drug release. This is achieved by changing the carrier composition or surface, which may help in lowering the drug toxicity and enhancing the drug deposition in the action site **[7, 8]**. Among the most promising nano-drug delivery systems employed recently for dermal and transdermal drug delivery are vesicular carriers. Vesicular carriers have shown good contributions in trans/dermal delivery, surpassing the disadvantages of the physical and chemical techniques **[2]**. The leading vesicular carriers attempted for drug delivery through the skin are the conventional liposomes composed solely of phospholipids and cholesterol as it is considered the basic type of phospholipid-based vesicles from which other types emerged. Liposomes, versatile drug delivery systems, can consist of naturally derived phospholipids with mixed lipids or hydrogenated phospholipids. The primary structural components of conventional liposomes include phospholipids and cholesterol. Liposomes can be categorized based on their structure and application, encompassing conventional liposomes and innovative liposomes (elastic liposomes, long-circulating liposomes, coated liposomes like lipoprotein-, carbohydrate-, PEG-coated, and sterically stabilized liposomes such as Stealth® liposomes). Elastic liposomes include ethosomes, niosomes, Transfersomes®, invasomes. While some liposomes are utilized for parenteral drug administration, conventional and flexible liposomes remain common in dermal and transdermal applications. Conventional liposomes are specifically defined as those composed predominantly of phospholipids (neutral and/or negatively charged) and cholesterol **[9]**.

Several studies proved the poor penetration ability of liposomes, besides their poor stability, through the skin. Studies for liposomes and niosomes have shown inconsistent results the same as the conventional liposomes studies. The findings count on multiple criteria, like the constitution of the particles and the selection of the edge activator, which is of great significance **[9]**. This led Cevc and Blume to develop ultra-deformable vesicles and named them transfersomes, which were able to squeeze themselves between the cells and pass through

the skin-tight junctions to deliver the drugs. Transfersomes are composed of phospholipids and an edge activator. They are liposomes like vesicles so they can incorporate hydrophilic and hydrophobic drugs or both **[10]**. Edge activators are compounds added to impart certain fluidity to the lipid membrane, as they are formed often of one chain, so they have a great curvature radius, which increases the particle's deformation ability. They act by rendering the phospholipids layers unstable, which increases the vesicle's deformation. In 1999, niosomes were developed by van den Bergh et al. They are ultra-deformable vesicles like tansfersomes but contain non-ionic surfactants forming the bilayers instead of phospholipids **[11, 12]**. In 2000, Touitou et al. introduced ethanol-containing liposomes with the nomenclature; Ethosomes. They are composed of phospholipids, ethanol, water, and occasionally propylene glycol **[13-15]**. They were suggested as these particles showed a high ability to promote drug permeation and make the liposomes deformable owing to their high ethanol concentration. Propylene glycol-containing vesicles as a substitute for ethosomes were formulated and assessed too **[16]**. Propylene glycol-containing vesicles were formulated to enhance the performance of liposomes intended for topical administration. They are liposomes containing propylene glycol as an adjuvant to impart some elasticity and reduce the size of the liposomes aiming to enhance the topical drug delivery and they showed superiority over the conventional liposomes in the loading efficiency, prolongation of release, stability during storage, and skin retention **[17]**. Invasomes are composed of phosphatidylcholine, ethanol, and terpenes as PEs, developed by Verma and Fahr et al. **[18, 19]**. These ultra-deformable vesicles have better efficacy in drug penetration/permeation than the classic liposomes **[20]**. Several edge activators were proposed to form these vesicles like Spans and Tweens, potassium glycyrrhizinate. Novel elastic particles containing a small concentration of molecules like oleic acid and limonene were tested to improve the permeation through the skin, also a combination of terpenes and ethanol was tested too. Following this, a cascade of vesicles was developed to improve the dermal delivery. Mura et al., and Manconi et al., first developed Penetration Enhancer-containing Vesicles (PEVs) in 2009, which are liposomes incorporating PEs **[15, 21]**. These particles are composed of Soy lecithin and PE like Transcutol (TRC), Labrasol (Lab), and Cineole which are added in varying concentrations. PE plays a crucial role in easing the transport of drugs through the skin. These substances possess several desirable properties, including being predominantly colorless and odorless, pharmacologically inert, specific in their mode of action, physicochemically stable, and do not cause irritation toxicity or allergy, and their effect is reversible. Their primary mode of action is on the SC, where they can influence drug diffusion through this outermost skin layer or alter partitioning within the SC. Commonly employed PEs encompass fatty acids, alkanes, esters, terpenes, cyclodextrins, surfactants, azone, and other similar compounds **[22]**. Top of Form The PE has helped in lipid membrane fluidization, so gives the vesicles a fluid nature and certain fluidity, that aids their passage through the SC, and hence the drugs **[15]**. The potential mechanisms of action of PEs are diverse, encompassing both direct effects on the skin and modifications to the formulation. Acting directly on the skin, enhancers can: i. Act on the intracellular keratin in the SC, denaturing it or altering its conformation, leading to swelling and increased hydration. ii. Affects the desmosomes responsible for maintaining cohesion between corneocytes. iii. alter the lipid domain between the cells to decrease the resistance barrier of the lipids. iv. Alter the partitioning of the drug in the tissue as many enhancers act as solvents **[23]**.

Terpenes like cineole function as PEs by altering the stratum corneum's solvent properties, thereby enhancing the partitioning of drugs into the tissue. The efficacy of terpenes in permeating human skin is well-established. Furthermore, terpenes may influence drug diffusivity through the membrane, suggesting a diverse role in augmenting drug permeation **[23]**. Oleic acid, a mono-unsaturated fatty acid, has been documented for its ability to enhance the penetration of drugs through the skin. Its mechanism of action involves disrupting the densely arranged intercellular lipid domain of the SC **[24]**. This is done by acting on the hydrogen bonds of the SC lipid bilayer, inducing phase separation and SC fluidization **[25-27]**. Edge activators are characterized by single-chain surfactants with a large radius of curvature, which function by conferring malleability to the vesicles. This is achieved by disrupting the lipid bilayer and facilitating the penetration of vesicles into the deeper layers of the skin **[28, 29]**. TRC operates through a dual mechanism. Initially, it serves as an edge activator for vesicular carriers. Additionally, TRC affects human cells by enlarging the intercellular lipids of the SC without altering their bilayer structure, thereby promoting enhanced intercellular penetration through them **[30, 31]**. TRC also acts by disrupting the SC lipid bilayer by disrupting the lateral and transversal H-bonds of the SC ceramides, increasing the solubility of the drug in the formula, affecting the partitioning of the drug in the skin, hence enhancing the skin permeability and drug retention time **[26, 32]**. Lab (capryl-caproyl macrogol 8-glyceride) is an example of a hydrophilic non-ionic surfactant that acts as a PE by affecting the fluidity of skin membranes and hence improving their permeability to different drugs **[33, 34]**. The lab is well known to possess a high power for improving the drug accumulation in the skin this could be attributed to its amphipathic nature that results in destabilization of the vesicle bilayer. Lab modulates the epidermal tight junctions **[30, 34, 35]**. Tween 80 acts as PE by extracting the lipids from the SC, which leads to fluidization of the SC lipid bilayer **[36]**. PEVs were able to deliver efficiently poorly permeable molecules through different body parts like the eyes, nose, oral route, oral cavity, dermal, and transdermal. Several studies have proved the successful delivery of different medicinal drugs using these particles as a carrier.

Different methods of preparation have been employed for PEVs. They were prepared by thin film hydration method (also called dehydration rehydration method) sometimes followed by sonication or extrusion. Sometimes a small modification is done, where the hydration of the thin lipid film is done in two steps to ensure a more homogenous and monodispersed vesicle **[37]**. Ethanol injection methods, classic mechanical dispersion or mechanical shake method, followed by homogenization at 15,000 min^{-1} were also used to produce PEVs **[38-40]**. Another preparation technique was employed by leaving the sample overnight at room temperature to hydrate the sample and expand the lipids, followed by sonication cycles. Moreover, the fusion method or sonication using an ultrasound disintegrator with high intensity proved their abilities to prepare PEVs. The general composition of PEVs is illustrated in **Fig. 1.** PEVs preparation methods and composition are represented below in **Table 1.** and illustrated in **Fig. 2.** In this review, different studies done on PEVs in different skin diseases and transdermal delivery were highlighted.

2. Drugs delivered dermally using PEVs

2.1. Antifungal drugs

Skin fungal infections are among the most common skin diseases around the world that are increasing recently **[41]**. Local antifungal agents

are usually used for the treatment of fungal infections, but conventional antifungal formulations require a more prolonged time for treatment, with a diminished therapeutic effect, at the same time they produce undesirable local side effects **[42]**. Therefore, several studies have attempted the incorporation of antifungal agents in PEVs.

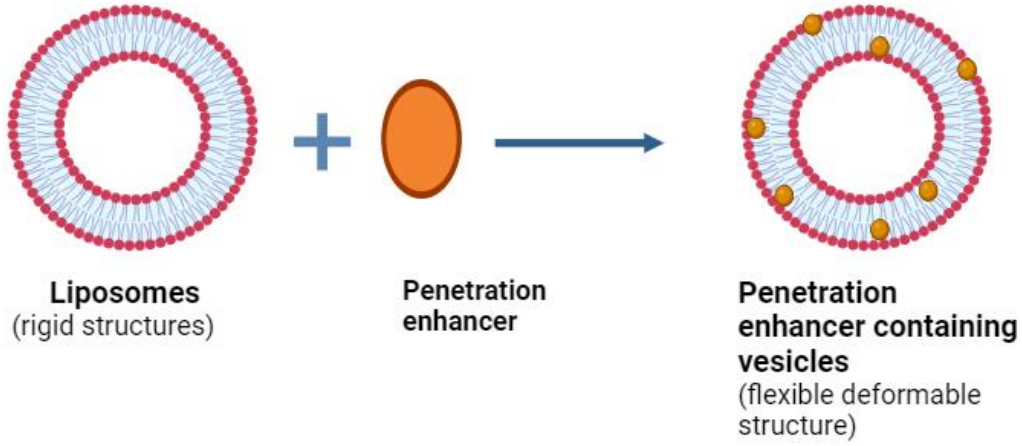

Fig. 1. Penetration enhancer vesicles general composition.

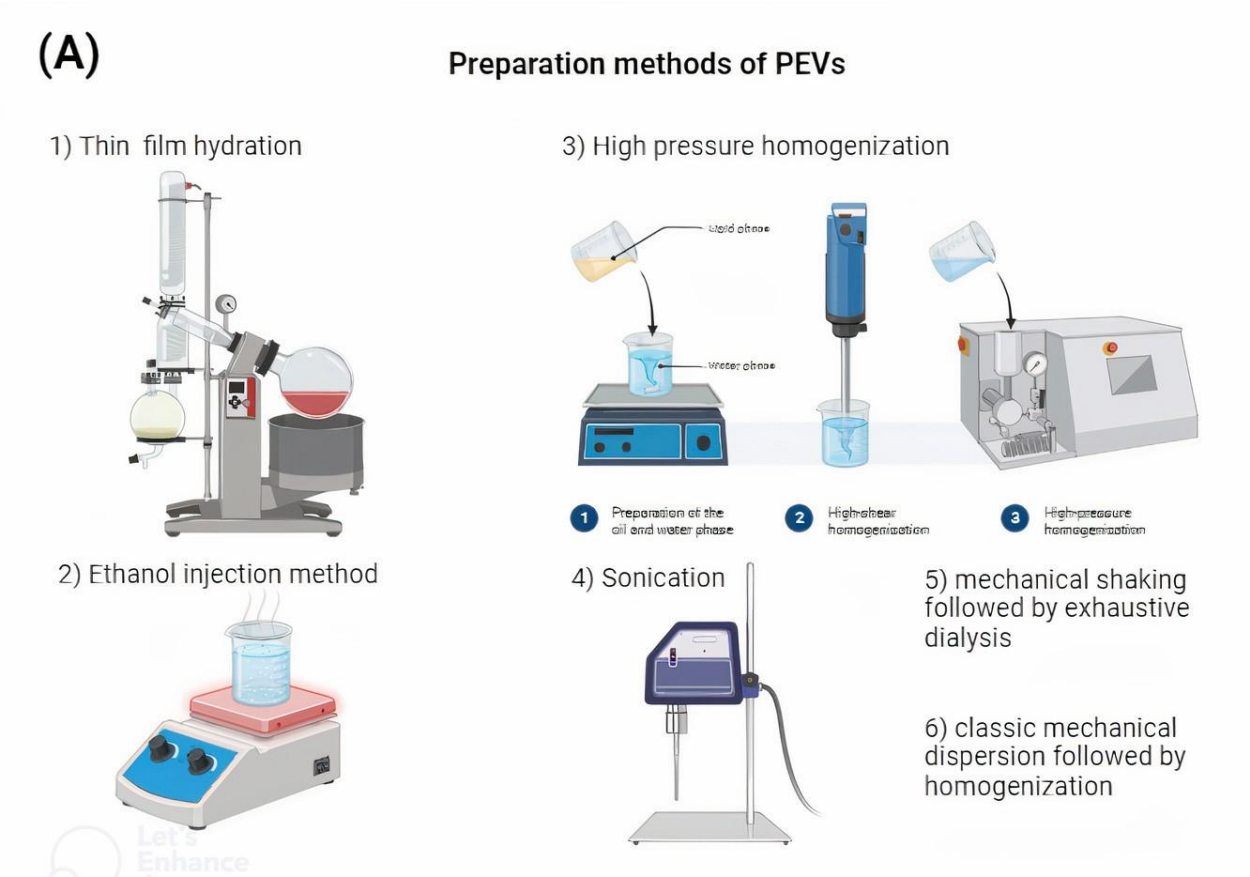

Fig. 2. (A) Different preparation methods of penetration enhancers containing vesicles

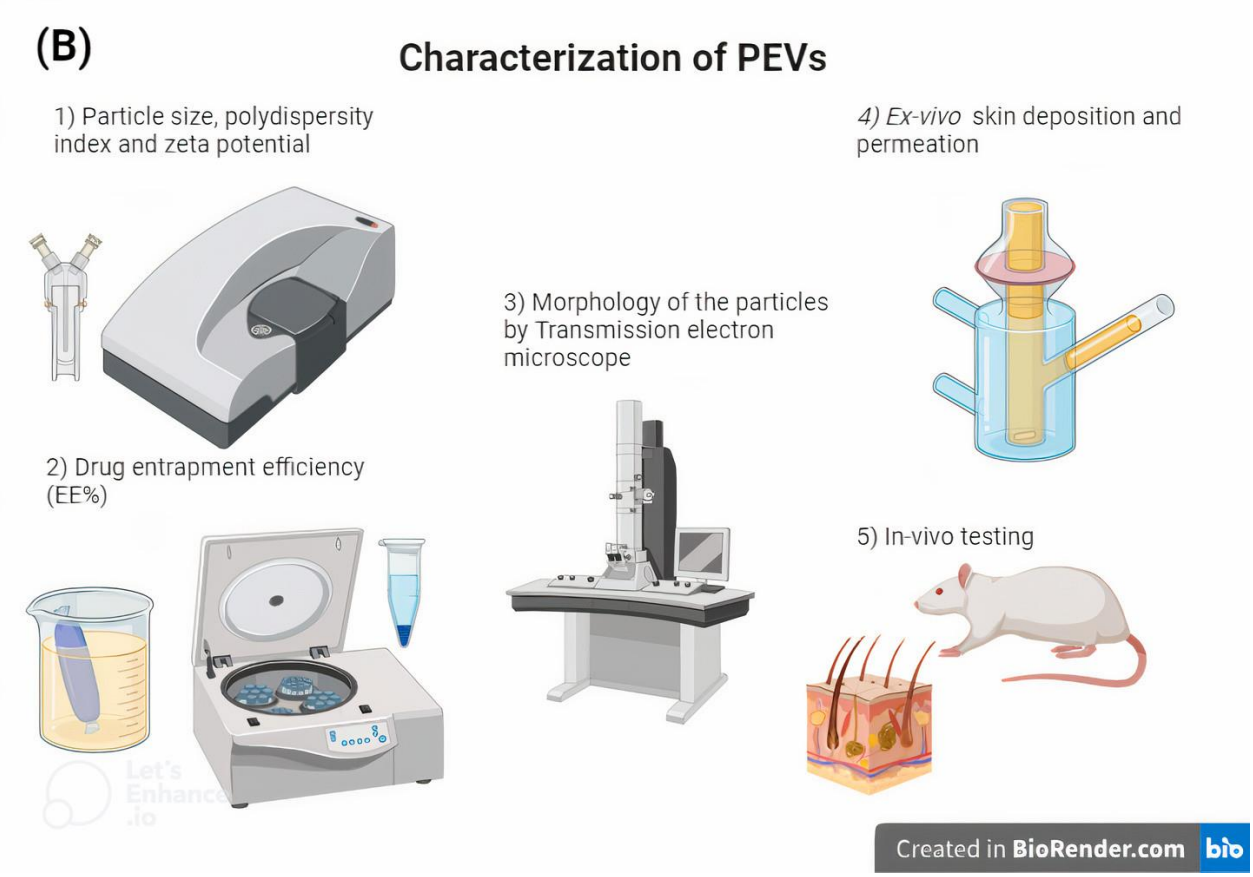

Fig. 2. (B) characterization of penetration enhancers containing vesicles.

Table 1. Summary of penetration enhancers-containing vesicles for dermal and transdermal drug delivery systems

Composition	**Model Drug**	**Preparation method**	**Route**	**Findings**	**Ref.**
PE (5, 10, 15 & 20 %w/w) 1)Oleic acid 2) **Lab 3) *TRC Stearyl amine (charge inducer)	Sertaconazole Antifungal	Thin film hydration method	Dermal	PEVs were better than topical conventional antifungals in either the magnitude or onset of clinical cure.	**[35]**
PEVs (4 & 10% w/v): 1) Lab 2) TRC 3)Limonene 4)Cineole	Terbinafine hydrochloride Antifungal	Classic mechanical dispersion method The formulation (5 mL) was then	Dermal	Limonene nano-vesicular chitosan gel showed a successful eradication of the fungal infections.	**[39]**

		homogenized at 15,000 min^{-1} for 5 min.			
Ethosomes					
Liposomes					
PE: 1) Lab (20 mg/mL) 2) TRC (20 mg/mL) 3) Cineole (10 mg/mL)	Minoxidil Anti-alopecia	Thin film hydration (DRV dehydrated rehydrated vesicles)	Dermal	PEVs were able to increase the minoxidil accumulation in the upper skin layers with no transdermal delivery.	**[15]**
TRC (5, 10, 20, and 30% V/V)	Minoxidil Anti-alopecia	Mechanical shake	Dermal	TRC-containing PEVs can deliver minoxidil to deep skin layers without any transdermal permeation**.**	**[40]**
PE (20 mg/mL) : 1) Lab 2) TRC 3) Cineole	Minoxidil Anti-alopecia	Dehydrated-rehydrated vesicles (DRV) then By thin film hydration method freeze-dried	Dermal	the vesicle formulations with PEs promoted drug deposition into the skin	**[47]**
PE (6 mg/mL): 1) Oramix CG110 2) Labrafac PG 3) Labrasol 4) Labrafac CC	Lidocaine base or lidocaine HCl Anesthetic	Modified thin film hydration method	Dermal	Lidocaine deposition was enhanced by its encapsulation in PEVs.	**[37]**
1)Lipid (15–20–25 % W): 2)TRC (5–10–15 % W) 3)Cholesterol (2 % W) 4)Propylene glycol (3% W)	Tretinoin Anti-acne and anti-inflammatory	Fusion method	Dermal	Tretinoin adverse effects decreased, hence higher patient compliance due to the gradual release of tretinoin from the vesicles.	**[50]**

PE (0.06 g): 1) TRC 2) Lab 3) Oramix 4) Propylene glycol	Tretinoin Anti-acne and anti-inflammatory	Thin film hydration method but with a slight modification (hydration on two steps)	Dermal	The presence of a hydrophilic PE in the formulation is critical for improving the dermal delivery of the lipophilic tretinoin.	**[49]**
1) Liposomes 2) Lab-PEVs Lab/water (50:50 v/v) 3) LabEthosomes-PEVs Lab/ethanol/water (45:5:50 %v/v)	Grape pomace extract Anti-psoriatic	Samples were left overnight at room temperature to facilitate the phospholipid swelling and then sonicated.	Dermal	Liposomes and LabEt-PEVs showed superiority over the drug solution since they were able to neutralize the H_2O_2 damaging effects and restore healthy skin condition.	**[34]**
1) Tween 80 (2.5mg/ml) 2) Sorbitol (100, 200, 400mg/ml)	Baicalin Anti-photoaging, anti-oxidant and anti-inflammatory	Sonicated (15 cycles, 5sec on and 2sec off, 13µm of probe amplitude) with a high-intensity ultrasonic disintegrator	Dermal	Vesicles were able to deposit baicalin in the deep skin layers. Sorbitol-PEVs were able to restore the healthy conditions of damaged skin.	**[56]**
PE/water 40%v/v 1) TRC P 2) Propylene glycol (PG) 3) Polyethylene glycol 400 (PEG) 4) Lab (Lab)	Quercetin (QUE) Anti-oxidant and anti-inflammatory	QUE was dissolved in a PE/water solution (40% v/v) and added to the flask containing phospholipon 50 and left to swell overnight. followed by sonication then	Dermal	PE improves drug solubility in vesicle dispersion, to have a synergic effect with phospholipids as PEs, which make PEVs potent nanocarriers for QUE skin delivery.	**[58]**

		purification from the non-incorporated drug by exhaustive dialysis			
Oleic acid (2 mg/ml) PE to prepare PEVs (2 mg/ml): 1) Oramix™ CG110 2) Oramix™ NS10 3) Lab 4) Capryol™ 90 5) Lauroglycol™ 90 6)Lauroglycol™FCC 7)Labrafac™ PG 8)Labrafac™ CC	Resveratrol (trans-3,5,4 -tri hydroxystilbene; RSV) Anti-oxidant and anti-inflammatory	All the components were left to hydrate overnight in 5 ml of Tris–HCl, at pH 7.4, followed by sonication.	Dermal	"Oleic acid prevented the vesicles from aggregation during storage, as it generated a highly negative charge on the particles which caused a repulsion between the particles. RSV antioxidant activity was not affected by its encapsulation in the PEVs, a synergistic action may have occurred between RSV and soy phosphatidyl choline as it is reported to possess antioxidant activity. PEVs were demonstrated to be a stable and efficient carrier for RSV."	**[62]**
-PEG 400 (in PEVs) (10% v/v). -Tween80 (in transethosomes) -Distilled water (in PEVs) or hydroethanolic solution (in ethosomes and Transetosomes)	-)-epigallocatechin-3-gallate (EGCG) Anti-cancer	Thin film hydration method	Dermal	The topical application of EGCG-loaded PEVs demonstrated a potent chemotherapeutic and chemopreventive action for skin cancer and this was confirmed by the in vitro and in vivo studies.	**[8]**
PC, cholesterol (Chol), in a molar ratio of 10: 2, Surfactants (2%w/v) 1) Tween20 2) Lab	Sodium fluorescein (NaFl) Fluorescent dye	The thin film hydration method and the size were reduced by sonication	Transdermal	The NaFl PEVs were small and deformable. Surfactants acted as a PEs to promote the dermal delivery of NaFl.	**[71]**

3) Gelucire 44/14					
1) Lab (6 mg/mL)	Sinapic acid and Crocin Anti-cancer	Thin film hydration method	Dermal	Vesicles have good potential for breast cancer treatment due to the synergistic apoptotic effects of the two drugs.	**[76]**
1) Oleic acid (0.5, 1, 1.5 %w) 2) Lab (0.5, 1, 1.5 %w)	Methotrexate Anti-cancer and anti-rheumatic (DMARD)	Thin film hydration	Transdermal	systemic delivery of MTX from the skin in a sustained manner.	**[89]**
Transfersomes standard edge activators (15% w/w) 1) Sodium cholate 2) Tween 80	Curcumin (Hydrophobic poorly bioavailable) Anti-cancer	Thin film hydration method followed by extrusion.	Transdermal	Oleic acid-containing vesicles proved their success as a potential carrier for curcumin to treat breast cancer effectively.	**[10]**
PEs 1) Lab (15% w/w) 2) TRC (15% w/w) 3) limonene (15% w/w) 4) Oleic acid (5% w/w)					
-Span 60 Tween 80 F1 ratio(1:5) F2 ratio(3:2) Haloperidol Edge activator to form PECS 1) Lab (1%w/v) 2) TRC (1%w/v)	Haloperidol Anti-psychotic	Ethanol injection method	Transdermal	SF hydrogel showed that the transdermal hydrogel exhibited a more sustained and pulsatile release behavior in the blood with high brain levels	**[38]**

3) Tetraglycol (1%w/v)					
TRC P (10%, 20%, 30% v/v)	Diclofenac sodium Non-steroidal anti-inflammatory	Thin film hydration method but by hydration of the film in two steps	Dermal and transdermal	PEVs enhance drug transport by penetrating intact the SC, thanks to a synergic effect of vesicles and PEs.	**[37]**
1) Phospholipid with PBS or 2) TRC/PBS solution (10, 20, 30%, v/v)	Diclofenac (DCF) Non-steroidal anti-inflammatory	Hydration. Sonication for 2 min with a Soniprep 150 ultrasonic disintegrator.	Dermal	New TRC containing close-packed vesicles are good candidates for improving DCF dermal delivery.	**[57]**
PE 1) TRC 2) Propylene glycol (10%, 20%, 30%,40%, 50% v/v)	Diclofenac free acid Non-steroidal anti-inflammatory	Thin film hydration method	Transdermal	These systems were highly stable and delivered DCF in an appropriate amount.	**[21]**

*PEs: Penetration enhancers, **EE%: Entrapment efficiency percentage, ‡PS: particle size. *‡TRC: Transcutol, ***Lab: Labrasol (⁂SC: Stratum corneum)

2.1.1. Sertaconazole

Sertaconzole is a strong antimycotic member of the imidazole class, that can kill or inhibit the growth of fungi. Bseiso et al. was the first group to incorporate antimycotic drugs in PEVs and the first PEVs to be tested on human beings **[35]**. The prepared PEVs were clinically tested on patients suffering from fungal infections (e.g.: Tinea versicolor and tinea corporis). Results showed that PEVs with 20% TRC had exhibited a higher cure rate compared to the marketed product, Dermofix®, although Dermofix® contains 20 folds sertaconazole amount compared to the PEVs. This proved the ability of PEVs to amplify the antifungal effect of sertaconazole. The preparation containing 32% of TRC, which had the same concentration of sertaconazole as the Dermofix® cream, proved faster onset of complete cure. The huge concentration of the antifungal agent deposited in the skin layers may be the cause of the fast onset of action and due to the high concentration of TRC, and positive charge inducer, greater binding of the positive vesicles to the negatively charged skin occurred. For both formulations containing 20% and 32% TRC, sertaconazole was present in the receptor compartment of the Franz diffusion cell although for Dermofix® cream no drugs were present at all. So, this deep penetration capability of sertaconazole PEVs may be explained by the deformability of the vesicles.

2.1.2. Terbinafine

Terbinafine hydrochloride (TBN HCl) is an antifungal drug with a broad activity range, known for its slight to very slight solubility **[43]**. When applied, it couldn't penetrate the deeper skin layers where the fungus resides. Hence, it was incorporated into ethosomes and PEVs, the PEs used were TRC, Lab, and terpenes (Cineol

and Limonene) (4% and 10% w/v) **[39]**. PEVs showed a high deposition percentage that reached 53% when using Limonene in 4%w/v as PE. This formula also had the best accumulation efficiency and the lowest fungal burden in vivo. The cure rate within 7 days was 20% for the market product versus 86% for the Limonene PEVs formulated into the gel. PEVs particle size (PS) ranged from 95.5 to 525 nm, it showed larger PS than the prepared ethosomes. All vesicular systems including liposomes produced a higher enhancement effect than the hydro-alcoholic solution except for PEVs containing 10% TRC which showed no enhancement. This was attributed to the latter's large size and low deformability index. This ensured the synergistic action between phospholipid, ethanol, and PEs. Vesicles' skin penetration was highly influenced by the synergism between the phospholipid and the PE. Limonene is a lipophilic terpene that produces a high deformability, hence a high penetration enhancement effect. Limonene has a certain antifungal activity. Moreover, the particles were included in chitosan gel to increase the skin contact time. Chitosan is known to have certain antimicrobial activity, so it could have acted concurrently with Limonene and TBN HCl. The addition of these 3 constituents leads to a potent ultra-deformable carrier able to ameliorate TBN HCl dermal delivery **[39]**.

2.2. Anti-alopecia drugs

Androgenetic alopecia is the primary cause of alopecia for people carrying the gene and it is androgen-dependent. Alopecia and hair loss can affect self-confidence and emotional health, especially for women. Minoxidil (MX) is the drug of choice for hair loss and is used locally in both genders for androgenic alopecia. MX acts on the hair follicle dermal papilla cells, causing hair growth, so directly impacts their proliferation and apoptosis. Dermal treatment is effective in stopping the continuous thinning of hair follicles in the case of androgenic alopecia. The required dose is usually twice daily, but this frequency of MX is associated with serious unfavorable side effects. Conventional dermal dosage forms were primarily prepared from solvents like ethanol-propylene glycol-water solutions **[44, 45]**, which resulted in side effects like itching, burning, and allergic contact dermatitis. MX's greatest effect appears after 5 months of treatment, but the effect is reversible upon stopping the treatment. Recurrent intake of MX results in unwanted side effects for patients which lowers their compliance for treatment. Therefore, to minimize these unwanted effects, and to ameliorate the therapeutic outcome, Mura et al., developed a new topical delivery system for MX, which helped in drug build-up in the skin layers and ameliorated the clinical outcome **[15]**. Hydrophilic amphiphiles like Lab & TRC when incorporated in vesicles result in the production of larger vesicles as they increase the vesicle's surface energy **[46]**. These new formulae were highly stable and withstood the lyophilization (without a cryoprotectant) and then the reconstitution. This was apparent by the insignificant change in PS upon lyophilization. The greatest EE% value was 71% and was for cineole (lipophilic terpene) containing PEVs, cineole PEVs also had the greatest deformability index with the lowest PS. Lab and TRC PEVs showed an EE% comparable to the control and was around 60%. These findings showed that the mechanism of action of PEVs is highly correlated to their deformability, which is greatly related to their composition. PEVs showed an increase in the MX deposition in the skin's upper layers, with no transdermal delivery. The PEVs with the greatest deformability could depose a huge amount of MX in the skin, compared to classic liposomes, ethanolic solution of PE and drug solution, and the pretreatment with unloaded vesicles. This proved that PEVs are powerful candidates for dermal MX delivery.

Another study encapsulated the MX in PEVs using 5, 10, 20, and 30% v/v TRC to assess the ability of various PE concentrations to transport MX to the different skin layers **[40]**. These nanoparticles were ultra-deformable and had high power of MX deposition dermally without any transdermal release. TRC-containing vesicles possessed a smaller deformation index and, a smaller ability to transport MX to the skin compared to other PEVs. Usually, MX would be embedded in the lipid bilayer shell of liposomes. As for TRC containing PEVs, TRC affected the dissolution and dissemination of MX within the vesicles. So, lecithin (SL) concentration was critical and if it decreases to less than 180mg/mL particles lose their stability. PEVs were more elastic and stable than the liposomes. TRC-PEVs had the power to transport MX to the deep skin layers without transdermal diffusion of the drug as per the conducted in vitro diffusion studies.

To assess the mechanism of penetration enhancement upon the incorporation of PE in liposomes, skin IR was conducted to assess the in vitro permeation of MX- loaded liposomes compared to its equivalent PEVs **[47]**. Also, the pretreatment of skin with PE followed by the application of MX liposome was attempted. Mx concentration in the skin was greater in the case of the PEVs compared to the pretreated skin samples. MX acted in different manners in the case of the two formulae compared to its equivalent PEVs and this was proved by Fourier-transform infrared spectroscopy (FTIR). The pretreatment showed a lowering of the drug deposition, which was not the case in PEVs. TRC as PE showed a twofold increase in the deposited drug. FTIR showed MX particles scattering in the SC and demonstrated the absorption and adsorption of the vesicles. The analytical findings proved that PEVs assisted in MX dermal deposition in comparison to the control. Mx deposition from PEVs was greater than the control, so PEVs encouraged drug deposition.

2.3. Local anesthetics

2.3.1. Lidocaine

Lidocaine is a rapid onset anesthetic, with high effectiveness, medium action, and low Side effects. It is usually applied in a hydrophilic hydrochloric form. Lidocaine is a lipophilic drug and has poor permeability which results in poor diffusion and penetration through the skin. For optimum activity, it should remain in its lipophilic (unionized) form in the skin for enough time to allow its passage through the SC and desensitization of the pain receptors in the lower skin layers. Therefore, one study worked on formulating PEVs of lidocaine with the aim of its transportation to deep skin layers where the pain neurons are located **[48]**. Surfactants with PE power were expected to ease the transport of the drug to the desired site, ameliorating the neurons' block process. To optimize the formulations for the best drug efficiency, four PEs were tested namely; Oramix CG110, Lab, Labrafac PG, or Labrafac CC. Small spherical vesicles were produced possessing high EE% and stability. The vesicles were oligolamellar. The permeation experiments showed that the hydrochloride form of lidocaine showed better skin accumulation, particularly when incorporated in PEVs. lidocaine's skin deposition was enhanced by its encapsulation in PEVs in addition to the sustained release of Lidocaine imparted by the vesicles. The skin deposition was also enhanced by encapsulating lidocaine as a mixture (the base and salt). These nanocarriers containing both forms of lidocaine were a good way to enhance their topical delivery. Thus, the PEVs are propitious for topical delivery of lidocaine.

2.4. Anti-acne drugs

2.4.1.Tretinoin (Trans-retinoic acid (TRA))

Tretinoin known as Trans-retinoic acid (TRA), is a naturally occurring retinoid, used to treat proliferative and inflammatory skin diseases

such as psoriasis, acne, photoaging, and epithelial skin cancer. Moreover, it helps in sebum production, collagen synthesis, and regulating the growth and differentiation of epithelial cells. Unfortunately, TRA suffers from several drawbacks that hinder its application. Firstly, it suffers from photosensitivity and degradation upon exposure to light, air, and heat. Furthermore, its topical application may cause irritation and peeling, burning, erythema, and increased susceptibility to sunlight. Also, TRA has a low water solubility **[46]**. Therefore, to surpass the drawbacks and allow its clinical application, TRA was incorporated into nanovesicles. In another study, Manconi et al. proved that the incorporation of TRA in PEVs improved the accumulation of TRA in the skin and reduced transdermal delivery (except for PG-PEVs) **[49]**. The drug accumulation was as follows: control liposomes < Propylene glycol-PEVs < TRC-PEVs ≤ Oramix-PEVs < Lab-PEVs. Scanning electron microscope (SEM) proved that PEVs could strongly interact with the intercellular lipids causing an enlargement of the region. TRA is a lipophilic drug, so the presence of hydrophilic PE in liposomes helped improve its dermal delivery. PEV composition affected the drug deposition and permeation. Moreover, Bavarsad et al. incorporated TRA in PEVs, and it was noticed that they caused lower skin irritation as per the in vivo skin irritation test **[50]**. All the formulations showed a PS of less than 20nm. High drug entrapment values were found which may be due to the lipophilicity of the TRA. TRC had no significant effects on the drug release after 24 h, while the phospholipid concentration of 25% affected positively the drug release. TRA penetration through the skin was higher in the case of PEVs compared to ketrel® (the marketed cream), this may be due to the solubilizing power of TRC. PEVs delivered Tretinoin as the marketed cream but with fewer side effects.

2.5. Antioxidant, anti-inflammatory and anti-psoriatic drugs

Our skin while performing its protective role, is exposed to stress which can be physical, chemical, or mechanical and during this protective process, free radicals and reactive oxygen species are produced which lead to lipid peroxidation, modified gene expression, and DNA deterioration, chronic inflammations and tumors. Antioxidant intake counteracts these processes and restores normal physiology **[34]**.

2.5.1. Grape pomace extract

Grapes are enriched with several useful compounds like anthocyanins, catechins, procyanidins, flavonol glycosides, phenols, and stilbenes. The winemaking procedure of the grapes produces a giant amount of pomaces **[51]**. This grape pomace contains some bioactive compounds **[52]** due to their incomplete extraction. **[53, 54]**. Grape pomaces are a cheap source to recover these polyphenolic bioactive components. These polyphenols act as antioxidants, anti-inflammatory, and antimicrobials, they protect against chronic diseases and cancer. Grape pomaces were formulated in a deformable vesicular delivery system to increase their dermal bioavailability through the skin barrier to enhance their antioxidant activity and protect the skin from oxidative stress **[34]**. Lab was added to these vesicles (with/without ethanol) to improve the physical/chemical characteristics of the vesicles, and bilayer assembly. The vesicle size was homogenous, with a small PS of ≤150 nm and PDI was ≤0.3. This small PS was attributed to the solubilization of the extract constituents and its incorporation within the PEVs **[55]**. The entrapment efficiency (EE%), was high for PEVs (98%), which proved the high ability of PEVs to incorporate the extract efficiently. A Hydrogen Peroxide test was performed to check the ability of the loaded vesicles to protect the human

keratinocytes and fibroblasts, and it was found that the aqueous solution was not able to protect the skin while liposomes and lab-ethanol PEVs (LabEt-PEVs) were able to neutralize the damaging effects of H_2O_2, restoring the normal viability of keratinocytes and fibroblasts.

2.5.2. Baicalin

Baicalin is a flavone glycoside isolated from the roots of the Chinese medicinal plant. It can absorb UV light and scavenge oxygen free radicals, so protects our bodies from solar UV damage, oxidative stress, and inflammation. Since most of the chemical PEs can cause allergy or irritation, sorbitol (a naturally occurring neutral polyhydric alcohol) was chosen. Sorbitol-containing PEVs showed an improvement in the efficacy of baicalin and stimulated the proliferation and migration of cells favoring wound closure in vitro. PEVs caused an enhancement in the ability of baicalin to restore the structural and functional conditions of damaged skin. High amounts of phospholipids have shown an improvement in the particles' stability and EE% **[56, 57]**.

2.5.3. Quercetin

Quercetin is a potent antioxidant, it can induce apoptosis, module the cell cycle, inhibit angiogenesis, and have anti-inflammatory and anti-mutagenesis effects. Quercetin is used topically to stop the skin damage caused by oxidation, and the inflammation caused by the solar UV.

When applied topically, quercetin has poor skin permeability and poor solubility that stands against its formulation. To overcome these challenges, quercetin was formulated in PEVs using a high concentration (40%) of hydrophilic PE namely, propylene glycol, polyethylene glycol 400, Lab, and TRC with high solubilization capability to increase its water solubility and permeability through the skin **[58]**. PE not only helped solubilize the drug in PEVs but also had a synergistic effect with the phospholipids of the vesicles, which made PEVs a very good candidate for quercetin topical delivery. PEVs facilitated the penetration of the incorporated drug to the dermis and epidermis owing to their squeezability and their ability to temporarily disorganize the structure of the upper intracellular lipid sheets forming an occlusive film. In all the samples, the drug accumulation was in the following sequence: SC < dermis< epidermis. The *ex-vivo* study showed a lower drug deposition when using a coarse dispersion with the same composition compared to the PEVs, this proved that they do not just act as a PE but they act as a real carrier for quercetin. Hydrophilic PEs were used in a concentration of 40%, to ease the encapsulation of the drug into the vesicle shell and prevent its precipitation in vesicle dispersions. The findings confirmed the power of the hydrophilic PEs used to promote quercetin solubilization in the PEVs dispersion and their synergistic effect with the phospholipid, which made the PEVs an effective topical delivery system for quercetin.

2.5.4. Resveratrol

Resveratrol (trans-3,5,4-trihydroxystilbene; RSV) is a polyphenol, present in many plant species and food. It acts as an anti-inflammatory, cardioprotective and neuroprotective, chemopreventive, chemotherapeutic, and an exceptionally strong antioxidant so it defends our body against ultraviolet radiation (UV), wounds, and morbific strikes **[59-61]**.

Caddeo et al. prepared RSV liposomal and PEV formulations **[62]**. PEVs were prepared with various compositions to screen the effect of different variables on the prepared vesicles, to obtain the best vesicle composition for the topical delivery of RSV regarding the physicochemical properties, appearance, shape, stability, and antioxidant properties. PEVs were able to deliver

the drug into the deep skin layers, as the PE fluidized the intercellular lipids, and acted synergistically with the nanocarrier **[37, 49, 58]**. To study the effect of the surfactant nature (hydrophilic or lipophilic), eight PEs were used with hydrophilic-lipophilic balance (HLB) ranging from 16 to 1. Non-loaded vesicles had statistically significantly bigger sizes with a low PDI compared to the loaded ones. The addition of hydro miscible PE such as lab and Oramix NS10 during the preparation of the vesicles has shown better deposition of the drug in the skin, extraordinary properties, and mode of action **[63]**. This was attributed to the effect of the oil interaction with the phospholipids, which changed its arrangement, hence affecting the size and the aqueous core capacity. RSV being lipophilic interacted with the phospholipid bilayer, and changed its packing and the aqueous volume, which decreased the vesicle size, particularly when PEs existed. The particle's lamellarity depends on their composition as was shown by transmission electron microscope (TEM) analysis. PEs possessing an intermediate HLB produced oligolamellar vesicles, otherwise, the vesicles were unilamellar. The therapeutic activity of RSV is mainly affected by its antioxidant activity, so a DPPH assay was conducted to determine the antioxidant activity and to ensure that RSV encapsulation in the vesicles did not affect its pharmacological action. RSV showed highly potent antioxidant activity, as it inhibited almost 90% of the DPPH, and its encapsulation in PEVs didn't affect its activity. This topical formulation was propitious and needs further studies on animal and human skin for the dermal application of resveratrol. All dispersions had a long shelf life, which proved that PEVs are effective and stable carriers for RSV **[62]**.

2.6. Anticancer

2.6.1. (-)-epigallocatechin-3-gallate (EGCG)

Skin cancer is a Common malignancy spread all over the world. The main cause of skin tumors is the long subjection to solar UV rays. Nutraceuticals such as (-)-epigallocatechin-3-gallate (EGCG), extracted from green tea, are propitious agents for skin cancer treatment as they lack the disadvantages of the classic treatment. Chemotherapy is the leading treatment for skin tumors **[64]**, but shows severe undesirable effects, and may develop multi-drug resistance **[65]**. Thus, different treatments like safe molecules (nutraceuticals) are of great importance. Green tea contains catechins which are responsible for the highest biological action of EGCG **[66]**. They act as antioxidants, anticancers, and anti-inflammatory **[67]**. Free EGCG is easily auto-oxidized by the air and sun rays, so it is unstable under sun rays which stands against its topical administration **[68]**. Due to its chemical instability and poor bioavailability, it is not delivered properly. EGCG has a large molecular weight which hinders its penetration in the deeper skin layers to exert its action, so to be able to act as a topical anticancer, EGCG should surpass the SC and reach the lower skin layers **[69, 70]**. To bypass these problems, the free EGCG was incorporated in PEVs, ethosomes, and transethosomes (TEs) for topical application. Most of the particles showed good deposition, photostability, and physical stability while keeping the antioxidant activity of the EGCG. Cutaneous administration of EGCG-PEVs showed potent therapeutic and preventive action against skin cancer which was proven by in vitro and in vivo tests. EGCG in PEVs and TEs stopped the tumor in the epidermoid carcinoma cell line (A431) and minimized the tumor mass in vivo experimental models as shown by the histopathological examination and by the skin oxidative stress biomarkers **[8]**.

2.7. Fluorescent dyes

2.7.1. Sodium Fluorescin (NaFI)

NaFl is a hydrophilic fluorescent compound. Rangsimawong et al. assessed the ability of non-ionic surfactants (PEs) containing liposomes to deliver hydrophilic drugs such as NaFl through the porcine skin. It was shown that the hydrophilic nonionic SAA affected the vesicles and NaFl skin permeation properties **[71]**. These highly deformable vesicles were formed of phosphatidylcholine, cholesterol, and different surfactants e.g., Tween 20, Lab, and Gelucire 44/14. Surfactants also can act as PEs to facilitate NaFl delivery through the skin. The surfactant containing vesicles showed smaller sizes ranging from 36 nm to 54 nm compared to the classic liposomes, and were negatively charged. Lab containing vesicles showed the highest EE% for NaFl. Moreover, these new vesicles showed higher flux than the traditional liposomes. These SAA-containing vesicles were smaller and more deformable owing to the surfactant added to their composition. Moreover, Lab vesicles had the highest permeation through the skin after 24 h.

3. Drugs delivered transdermally using PEVs

3.1. Anti-cancer and Anti-rheumatic drugs

3.1.1. Sinapic acid & crocin

Breast cancer is the most common cancer type and the most common mortality cause in females **[72]**. Dual therapy in cancer has synergistic outcomes, such as decreasing the doses and side effects. The use of naturally occurring compounds is growing with the concept of “Back to nature” due to their safety and lower side effects **[73-75]**. The first study investigated the dual therapeutic effect of Crocin and Sinapic acid by encapsulating them in PEVs with the aim of safely and effectively treating breast cancer **[76]**. High entrapment efficiency was achieved for both drugs; Crocin showed an entrapment of 29.54±1.89% while Sinapic acid entrapment was 59.13%±2.44 and this is due to their different nature, crocin is a hydrophilic compound so was loaded in the core of the vesicles, while the lipophilic Sinapic acid was incorporated within the lipid bilayer. The lab was selected as PE for the preparation of PEVs due to its ability to impart flexibility and stealth properties to the vesicles owing to PEs moiety present in its structure. PDI was high for all the prepared vesicles. This may be attributed to the pegylation, which also imparted a neutral charge to the vesicle surface. Both drugs exhibited sustained release from the vesicles. IC50 of the dual therapy was five folds lower than that of sinapic acid and crocin solely. This was attributed to their synergistic effect on apoptosis. The PEVs enabled a promising dual therapeutic outcome for breast cancer. This was attributed to their high penetration ability through the SC, biocompatibility, and the stealth properties which enabled them to avoid the uptake by macrophages. Conclusively, it was found that dual therapy along with the PEVs is a good approach for breast cancer treatment **[76]**.

3.1.2. Methotrexate

Rheumatoid Arthritis (RA) is a chronic autoimmune disease causing continuous severe systemic inflammation, which may cause joint degradation, pain, morning stiffness, and movement troubles. The inflammatory mediators affect tendons, ligaments, fascia, and other organs. Methotrexate (MTX) is the drug of choice in all the modifying anti-rheumatic drugs (DMARD) for controlling RA **[77]**. It stops the proliferation of lymphocytes and decreases the pro-inflammatory cytokines and interleukins **[78]**. So, MTX aids in lowering systemic inflammation and in enhancing movement **[79]**.

MTX may be discontinued despite its efficiency in treatment due to its serious adverse effects like GIT disorders, leucopenia, thrombocytopenia, and anemia due to bone

marrow suppression and liver toxicity **[80, 81]**. So, the transdermal route is an optimum choice to avoid the serious undesirable effects. The transdermal delivery systems should often release the drug in a sustained manner, which permits the drug deposition in the skin layers, and then into the blood vessels. This route is noninvasive, and it avoids the liver metabolism of the drug and bypasses the GIT **[82]**. MTX is hydrophilic and easily ionized at physiological pH which negatively affects its permeation. So chemical and physical permeation enhancers are necessary like iontophoresis, liposomes solid-in-oil nanocarriers, nanostructured lipid carriers, and magnetic silk fibroin nanoparticles **[83-87]**. Local injection of MTX in the joint had low effectiveness due to its fast clearance **[88]**.

MTX was encapsulated in malleable vesicles, then loaded in hydroxyethyl cellulose gel and optimized **[89]**. The dermal toxicity was tested, and it showed no toxicity or irritability. The nano gel produced a low arthritic score and joint damage, lowered the cytokines levels in the blood, and improved the swelling of the hind paw in the model. MTX nano gel formulation depicted sustained systemic delivery up to 48h with lower accumulation in organs inducing toxicity such as the liver, kidneys, and gut. PEVs incorporated in gel successfully delivered the MTX transdermally safely with fewer side effects. The formulae were safe, biocompatible, and therapeutically effective. So, this route for MTX delivery was proved to be promising and more advantageous than the oral and parenteral routes. Also, the MTX incorporation in PEVs permitted its delivery through this route.

3.1.3. Curcumin

Curcumin is a naturally occurring phytochemical known for exhibiting an anticancer effect **[90]**. Curcumin is poorly bioavailable, hence the transdermal route could be the route of choice, as it can enable its direct delivery to the systemic circulation and can aid the treatment of both topical and subcutaneous tumors e.g. breast tumors. Transfersomes and PEVs of curcumin were prepared to assess their efficacy in the delivery of curcumin through the skin **[10]**. Transfersomes were prepared using Tween 80® and Sodium cholate as edge activators. Lab, TRC, oleic acid and Limonene were used as PEs to prepare PEVs **[10]**. The entrapment efficiency (EE%) ranged between 79% and 93.91% in limonene and Tween80® containing vesicles respectively as the curcumin is hydrophobic so was incorporated within the lipid bilayers. PEVs prepared using TRC and oleic acid had a flux similar to sodium cholate and Tween 80. While PEVs prepared using limonene and Lab had a significantly lower flux. The PE used showed a high ability for transdermal delivery when compared to the ordinary edge activators. Ultra-deformable vesicles containing oleic acid were more cytotoxic compared to sodium cholate when tested on human breast cancer cell lines. It was observed that the type of surfactant and PE significantly affected the PS and zeta potential. Cytotoxicity studies were performed to assess the effect of formulation on the cytotoxic activity of curcumin. MTT assay was conducted and the vesicles containing oleic acid showed an IC50 of 20 µg/mL while sodium cholate showed an IC50 of 78.27 µg/mL. Oleic acid-containing vesicles exhibited a more potent cytotoxic activity compared to sodium cholate-containing vesicles.

This study proved that curcumin ultra-deformable vesicles containing oleic acid as PE are a very good candidate for transdermal breast cancer treatment.

3.2. Anti-psychotic drugs

3.2.1. Haloperidol

Haloperidol is a typical antipsychotic; it is a dopamine D receptor antagonist and is poorly

bioavailable as the liver metabolizes almost half of the dose **[91]**. It has a low effective therapeutic concentration (2-13 ng/mL) and a Log P of 4.3. Its water solubility is 14 µg/mL **[92]**.

Although the transdermal route has been proved to be a promising non-invasive route alternative to the oral route, Vaddi et al., proved that haloperidol applied for transdermal delivery bound strongly to SC and did not permeate deeply to the systemic circulation **[93]**, so to avoid this problem, penetration enhancer-containing spanlastics (PECSs) were prepared to enhance its transdermal delivery and sustain its release, hence decrease the frequency of the application and increase the patient compliance. Previously, PECSs were proved to enhance the drug delivery of drugs as ketoconazole through different routes such as; ocular and dermal, and pravastatin sodium through the intestinal route **[94-96]**. Based on this, PECSs were prepared to improve the delivery of haloperidol through the transdermal route. The chosen formula was composed of Span 60 and Tween 80 in a ratio of 4:1. This formula showed the greatest permeation of Haloperidol and when incorporated in the hydrogel, it showed a more sustained release, higher concentration in the brain, longer time in the blood with pulsatile manner than its oral dispersion form. So this formula is propitious as a maintenance therapy for Haloperidol due to the decreased dose and frequency of administrations compared to the classic oral one.

The permeation studies showed a lag time of 4 h before the drug appearance in the blood for some formulae and of 24 h for the haloperidol solution, and this was attributed to the high binding affinity of Haloperidol to the SC **[93]**. The formulation of the drug in classic spanlastics or PECSs increased the rate of permeation and flux of the drug compared to the drug solution **[38]**. PECS having TRC and Lab in their composition showed a higher cumulative amount of permeated drug compared to their corresponding ones containing tetra glycol, as it is a secondary PE with a lower PE power.

4. Drugs delivered dermally and transdermally using PEVs

4.1. Non-steroidal anti-inflammatory drugs

4.1.1. Diclofenac sodium (DCFNa)

Diclofenac (DCF), a strong non-steroidal anti-inflammatory drug (NSAID), is mostly used to treat rheumatic diseases and chronic inflammations like arthritis. A topical route for DCF is desired because it reduces its systemic noxious effects, and increases its local effectiveness. However, it has some hurdles like the barrier function of the SC which reduces the absorbed amount of DCF, and it is very important to penetrate and permeate through the skin to reach the effective concentration, but this was not achieved using the conventional dosage forms. To avoid this, and improve diclofenac delivery through the skin, several trials have been made like using lipid nanocarriers **[97, 98]**. Manconi et al. prepared PEVs to encapsulate DCF to improve its skin delivery. In this study they used two water miscible PEs; TRC or propylene glycol with different concentrations 10%, 20%, 30%, 40% and 50%W/W the synergism between the lipid and PE aided its penetration. PEs resulted in a size decrease of the vesicles compared to the corresponding liposomes. High EE% was found in 10 and 20% TRC compared to liposomes and propylene glycol PEVs with the same concentration. These systems were highly stable and delivered DCF in an appropriate amount **[21]**.

Thereafter, Manconi et al. conducted another study to show how the composition and preparation method of vesicles might affect their morphological features and delivery performances utilizing DCF as a model drug. TEM and Small and Wide-Angle X-ray

Scattering also proved the liquid status of the vesicular bilayer. They showed that the diverse preparation methods as well as the presence of different TRC concentrations did not significantly affect drug loading, although a slight reduction was observed when the highest TRC amounts (20% and 30%) were used in the sonicated samples **[21]**.

Another study was conducted, and it was found that the best carrier for DCFNa was the PEVs prepared with 20% and 30% TRC which improved both deposition into and diffusion through the pig skin in comparison to liposomes. Even better results in dermal and transdermal DCFNa delivery have been obtained here using phospholipon 50 in both 10% and 20% TRC-PEVs ($p > 0.05$). Therefore, even upon changing the lipid mixture, a lower amount of TRC is enough to promote drug delivery into and through the skin. Although the TRC is a well-known and safe PE, a reduction of the amount used in the formulation might be useful to reduce any potential skin damage. Results suggested that the encapsulation of DCFNa within the PEVs was able to enhance dermal and transdermal skin delivery **[37]**.

Manca et al. conducted dermal/transdermal *ex vivo* studies and showed that upon encapsulation in PEVs, DCF settling in the skin layers was ameliorated twice than traditional liposomes mainly for PEVs containing TRC in concentration 10 and 20% w/w. The results indicated the ability of PE to modify the physicochemical properties of the vesicles and improve dermal/transdermal delivery **[57]**.

Conclusion

Dermatological products are emerging fast nowadays owing to their great importance and advantages in replacing the conventional dosage forms which cannot deliver different types of drugs. Therefore, in the last decades, researchers investigated different ways to overcome this challenge and to bypass the skin barrier to deliver the drugs effectively. Conventional vesicles were prepared but they suffered from some drawbacks, a few years later scientists developed new ultra-deformable vesicles, that were able to deliver different drugs successfully, especially the vesicles incorporating penetration enhancers called PEVs. This review reports the different PEVs incorporating different drugs designed for dermal and transdermal drug delivery and their superiority over the conventional topical dosage forms and the first-generation vesicles (liposomes). As research in this area continues to evolve, PEVs are poised to play a pivotal role in advancing clinical strategies for dermal and transdermal drug delivery, addressing the challenges associated with conventional formulations. The clinical outcome was enhanced as PEVs helped in the drug accumulation and deposition in the skin. Sertaconazole PEVs exemplify an improvement in the clinical outcome. These were tested on patients and the TRC PEVs showed superiority over the marketed product in the cure rate, although PEVs contained 20 folds less in sertaconazole. However, the scaling up of these formulae showed some challenges such as their long-term instability. Therefore, future work should be focused on developing these vesicles in terms of stability and marketability.

Declarations

Consent to publish

All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Availability of data and material

All data generated or analyzed during this study are included in this published article in the main manuscript.

Competing interests

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Author contribution

Conceptualization was performed by Mahmoud Eid Soliman and Riham Elgogary. Data preparation and collection of the draft was performed by Fatma Abdelkader Sarhan and revision of the first draft was performed by Mahmoud Eid Soliman, Manal Yassin, and Riham Elgogary. All authors have read and approved the final manuscript.

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