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Lipid Carriers in Transdermal Drug Delivery Systems

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Abstract
Transdermal drug delivery systems (TDDS) have emerged as an effective alternative to conventional drug administration routes because they provide controlled drug release, improved patient compliance, avoidance of first-pass metabolism, and reduced systemic side effects. However, the stratum corneum acts as a major barrier that limits the permeation of therapeutic agents. To overcome this limitation, lipid-based carrier systems have been widely explored for enhancing transdermal drug delivery. Lipid carriers such as liposomes, transferosomes, ethosomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and possess excellent biocompatibility, biodegradability, and drug-loading capacity. These carriers improve drug solubility, enhance skin permeation, protect drugs from degradation, and provide controlled release of therapeutic agents. Recent advances in lipid nanotechnology have further improved the effectiveness of transdermal systems and expanded their pharmaceutical applications.
Keywords: Liposomes, SLNs, ethosomes, NLC, transferosomes

Introduction

Transdermal drug delivery systems are pharmaceutical formulations designed to deliver therapeutic agents through the skin into systemic circulation. Compared with oral and parenteral administration, transdermal delivery offers several advantages such as avoidance of hepatic first-pass metabolism, sustained plasma drug concentration, improved patient compliance, reduced gastrointestinal side effects, and non-invasive administration (Barry, 2001; Prausnitz & Langer, 2008). Despite these benefits, the skin acts as a highly efficient protective barrier. The stratum corneum, which is the outermost layer of the epidermis, restricts the penetration of most drug molecules because of its tightly packed lipid structure (Honeywell-Nguyen & Bouwstra, 2005).
To overcome this barrier, researchers have developed lipid-based carrier systems capable of improving drug permeation across the skin. Lipid carriers are biocompatible and biodegradable systems composed mainly of physiological lipids that resemble biological membranes. These systems improve drug solubility, enhance skin penetration, increase drug stability, and provide controlled release of therapeutic agents (Doktorovová & Souto, 2017; Khallouki et al., 2018).

Lipid Carriers for Skin Penetration:

Introduction

Topical and transdermal drug delivery systems have gained significant attention due to their ability to provide localized treatment while minimizing systemic side effects. However, the major challenge is the barrier function of the stratum corneum, the outermost layer of the skin, which limits the penetration of many active pharmaceutical ingredients (APIs). To overcome this barrier, lipid-based nanocarriers have been developed as efficient delivery systems.

Lipid carriers are biocompatible and biodegradable vesicular or particulate systems composed mainly of physiological lipids. They improve the solubility, stability, skin penetration, controlled release, and bioavailability of drugs and cosmetic actives. Due to their close resemblance to skin lipids, they can interact with the stratum corneum, enhance hydration, and facilitate the transport of active ingredients into deeper skin layers. Consequently, lipid carriers are widely employed in pharmaceuticals, cosmeceuticals, and dermatological formulations.Mechanism of Skin Penetration by Lipid Carriers
Lipid carriers improve transdermal drug delivery through several mechanisms. These systems interact with the lipid matrix of the stratum corneum and disrupt its highly organized structure, thereby increasing membrane fluidity and permeability. Some vesicular systems fuse directly with skin lipids, while others improve hydration of the skin and create pathways for drug diffusion (Cevc & Blume, 1992; Khallouki et al., 2018).
Nanosized lipid carriers also increase the surface area available for absorption and maintain sustained release of drugs at the application site. Ethanol-containing vesicles such as ethosomes fluidize skin lipids, while transfersomes penetrate through the skin due to osmotic gradients and membrane deformability .(Touitou et al., 2000; Benson, 2006).(Reference 24to33)

Advantages of Lipid Carriers

Lipid carriers offer several advantages in transdermal drug delivery systems. These carriers improve bioavailability, enhance penetration of poorly soluble drugs, provide controlled and sustained release, reduce systemic toxicity, and improve patient compliance. Their biocompatible and biodegradable nature minimizes irritation and toxicity associated with conventional penetration enhancers (Doktorovová & Souto, 2017; Khallouki et al., 2018).
Additionally, lipid carriers protect drugs from chemical degradation and increase therapeutic efficacy. Nanoparticle-based systems also improve drug targeting and reduce dosing frequency (Prausnitz & Langer, 2008; Patel & Baria, 2011).

Disadvantages of Lipid Carriers

1. High production cost.
2. Physical instability during long-term storage.
3. Drug leakage during storage.
4. Limited loading capacity in some lipid systems (especially SLNs).
5. Polymorphic transitions of lipids may reduce drug entrapment.
6. Particle aggregation may occur.
7. Scale-up and industrial manufacturing challenges.
8. Sterilization is difficult for nanoparticle formulations.
9. Requires specialized equipment.
10. Sensitive to temperature variations.

Applications of Lipid Carriers :

1.Pharmaceutical Applications
2.Topical drug delivery
3.Transdermal drug delivery
4.Anti-inflammatory therapy
5.Antifungal therapy
6.Antibacterial therapy
7.Antiviral drug delivery
8.Local anesthetic delivery
9.Wound healing
10.Psoriasis treatment

Limitations of Lipid Carriers

Despite their advantages, lipid carriers possess certain limitations. These include formulation instability, aggregation of nanoparticles, drug leakage during storage, high manufacturing costs, and difficulties in sterilization and large-scale industrial production. Some formulations may also cause mild skin irritation due to the presence of surfactants, alcohols, or penetration enhancers (Elsayed et al., 2007; Kim et al., 2020).

Furthermore, phospholipid oxidation and polymorphic transitions in lipid nanoparticles may affect formulation stability and therapeutic performance during storage (Mehnert & Mäder, 2001; Wissing et al., 2004).

Recent Advances in Lipid-Based Transdermal Systems

Recent advances in nanotechnology have resulted in the development of novel lipid-based carriers such as transethosomes, hybrid lipid-polymer nanoparticles, and stimuli-responsive lipid systems. Researchers are also combining lipid nanoparticles with microneedle technology to improve skin penetration and targeted drug delivery (Pardeike et al., 2009; Doktorovová & Souto, 2017). These advanced systems are expected to expand the application of transdermal drug delivery in chronic disease management, pain therapy, hormone replacement therapy, vaccination, and cancer treatment. Continuous research in lipid nanotechnology is likely to improve formulation stability, therapeutic efficacy, and commercial applicability of transdermal systems (Chauhan et al., 2020; Kim et al., 2020).

Types of lipid-based drug delivery systems for transdermal administration :

Liposomes

Liposomes are spherical vesicles composed of phospholipid bilayers surrounding an aqueous core. They were among the first lipid carriers investigated for dermal and transdermal drug delivery. Liposomes can encapsulate both hydrophilic and lipophilic drugs and improve drug localization within the skin layers. Their structural similarity to biological membranes allows them to fuse with skin lipids and improve drug deposition into the epidermis (Sharma & Sharma, 1997; Verma & Fahr, 2020).

Liposomes have been widely used for the delivery of corticosteroids, antifungal agents, anticancer drugs, and local anesthetics. They also reduce drug toxicity and improve therapeutic effectiveness. However, conventional liposomes often suffer from limitations such as poor physical stability, oxidation of phospholipids, drug leakage during storage, and limited penetration through intact skin (Sharma & Sharma, 1997; Honeywell-Nguyen & Bouwstra, 2005).

Formulation:

s.no	Materials	concentrations
1.	Diclofenac sodium	25–100 mg (depending on batch)
2.	Soya lecithin	100mg
3.	Cholesterol	15mg
4.	Chloroform : Methanol (2:1)	Sufficient quantity (to dissolve lipids)
5.	Distilled water	As required

Table 2. composition of liposomes :

Batch	Diclofenac sodium	Soya lecitin	cholesterol
F1	25mg	100mg	15mg
F2	50mg	100mg	15mg
F3	75mg	100mg	15mg
F4	100mg	100mg	15mg

Advantages:
1.Can encapsulate both hydrophilic and lipophilic drugs.
2.Biocompatible and biodegradable.
3.Improve drug localization in skin tissues.
4.Reduce drug toxicity.
5.Enhance therapeutic efficacy.
6.Protect drugs from degradation.
7.Suitable for controlled drug release.

Disadvantages:
1.Poor physical stability.
2.Phospholipid oxidation during storage.
3.Drug leakage.
4.Limited penetration through intact skin.
5.Expensive phospholipids.
6.Short shelf life.

Applications:
1.Corticosteroid delivery.
2.Antifungal drug delivery.
3.Local anesthetic delivery.
4.Anticancer drug delivery.

Transfersomes

Transfersomes are highly deformable lipid vesicles composed of phospholipids and edge activators such as surfactants. These vesicles possess elastic properties that enable them to squeeze through narrow pores within the stratum corneum that are smaller than their own diameter. This characteristic significantly enhances drug permeation into deeper skin layers and systemic circulation (Benson, 2006; Opatha et al., 2020).

Formulation:

Transfersomes are elastic nanovesicles essentially made of phospholipids and edge activators (EAs) like sodium cholate (NaCo), sodium deoxycholate, Span 60, Span 65, Span 80, Tween 20, Tween 60, Tween 80, and dipotassium glycyrrhizinate.8 This type of vesicle was firstly introduced in 1992 by Cevc9 (transfersomes, a trademark of IDEA AG, Munich, Germany), and it represents the first generation of UDV. The skin permeation and penetration of these elastic vesicles result from a synergic mechanism between the carrier properties and the permeation enhancement ability. Transfersomes can cross the skin layers by different mechanisms depending on their composition, in which these vesicles maintain their intact structure or fuse and mix with skin lipids.10 They can easily change their shape and cross the skin barrier due to the EA action in response to mechanical stress by relocating inside the vesicle to zones with smaller curvature, thus reducing the membrane elastic energy to a minimal level.11

Advantages:
1.Highly deformable vesicles.
2.Excellent skin penetration.
3.Deliver both small and large molecules.
4.High drug entrapment.
5.Improved bioavailability.
6.Suitable for proteins and peptides.
7.Non-invasive drug delivery.

Disadvantages:
1.Oxidation of phospholipids.
2.High production cost.
3.Formulation instability.
4.Sensitive to storage conditions.
5.Difficult large-scale manufacturing.

Applications:
1.Insulin delivery.
2.Ketoprofen.
3.Diclofenac.
4.Vaccines.
5.Corticosteroids.
6.Anticancer drugs.
7.Protein and peptide delivery.

Ethosomes

Ethosomes are modified phospholipid vesicles containing high concentrations of ethanol. Ethanol enhances skin permeation by fluidizing the lipid arrangement of the stratum corneum and increasing vesicle flexibility. This dual mechanism facilitates improved penetration of drugs through the skin and increases drug accumulation in deeper tissues (Touitou et al., 2000; Jain et al., 2004).

Ethosomes have been successfully used for the transdermal delivery of antiviral agents, hormones, anti-inflammatory drugs, and cosmetic compounds. Their high entrapment efficiency and superior permeation capability make them more effective than conventional liposomes for transdermal applications. Nevertheless, high ethanol concentrations may sometimes produce skin irritation and formulation instability (Elsayed et al., 2007; Jain et al., 2004).

Formulation:

Ethosomes are special type of UDV developed by Touitou et al in 1997.20 Due to their size (approximately 150–200 nm) and high deformability, they are also referred to as elastic nanovesicles. Ethosomal systems are vesicles consisting essentially of phospholipids, water, and a high quantity of ethanol. Phospholipids can be used at 0.5%–10% concentration range, and are obtained from natural semisynthetic and synthetic sources such as soybean and egg. Examples of phospholipids include phosphatidylethanolamine, phosphatidylinositol, phosphatidylcholine, and hydrogenated phosphatidylcholine.21 Ethanol can be used at 20%–45%, functioning as an efficient skin enhancer.1 This molecule interacts with the polar head group of the SC lipid molecules, leading to the reduction of the melting point of the SC lipids, thus increasing the fluidity of lipid bilayers and cell membrane permeability.

Advantages:

1.Excellent skin permeation.
2.High drug entrapment efficiency.
3.Flexible vesicles.
4.Better penetration than liposomes.
5.Increased drug deposition.
6.Improved bioavailability.
7.Easy preparation.

Disadvantages:

1.High ethanol content may cause skin irritation.
2.Ethanol evaporation affects stability.
3.Storage instability.
4.Unsuitable for ethanol-sensitive drugs.
5.Possible vesicle leakage.

Applications:

1.Anti-HIV drugs.
2.Hormones.
3.Anti-inflammatory drugs.
4.Antifungal drugs.
5.Antiviral therapy.

Solid Lipid Nanoparticles (SLNs)

Solid lipid nanoparticles are colloidal carriers prepared using lipids that remain solid at both room and body temperatures. These nanoparticles are stabilized using surfactants and possess particle sizes in the nanometer range. SLNs offer several advantages including controlled drug release, enhanced drug stability, protection of sensitive drugs from degradation, and improved skin hydration through occlusive effects (Mehnert & Mäder, 2001; Wissing et al., 2004).

SLNs have been investigated for the delivery of antifungal agents, anti-inflammatory drugs, and cosmetic ingredients. Their ability to form a protective film on the skin surface increases hydration and improves drug permeation. However, SLNs may exhibit low drug-loading capacity and possible drug expulsion during storage because of their highly crystalline lipid structure (Mehnert & Mäder, 2001; Patel et al., 2019).

Formulation:

S.NO	Ingredients	concentrations
1.	Lipid	3.33% w/v
2.	Phospholipids	0.6-1.5%
3.	Glycerol	2-4%
4.	Poloxamer 188	1.2-5% w/w
5.	Soy phosphatidyl choline	95%
6.	Compritol	10%
7.	Cetyl palmitate	10%w/w
8.	Tego care 450 (surfactant)	1.2%w/w
9.	PEG 2000	0.5%
10.	PEG 4500	0.25%

11.	Tween 850	5%
12.	Ethyl oleate	30%
13.	Na alginate	70%
14.	PEG 400	5%
15.	Ethanol/butanol	2%
16.	Tristearin glyceride	95%
17.	Isopropyl myristate	3.60%
18.	Pluronic F 68	40%
19.	Tween 80	50%

Advantages :
1.Controlled drug release.
2.Excellent drug stability.
3.Protect sensitive drugs.
4.Occlusive effect increases skin hydration.
5.Biocompatible.
6.Biodegradable.
7.Low toxicity.
8.Suitable for large-scale production.

Disadvantages:
1.Low drug-loading capacity.
2.Drug expulsion during storage.
3.Highly crystalline lipid matrix.
4.Gelation may occur.
5.Polymorphic transitions.

Applications:
1.Antifungal drugs.
2.Anti-inflammatory drugs.
3.Sunscreens.
4.Cosmetic formulations.
5.Wound healing.
6.Acne therapy.
7.Vitamin delivery.

Nanostructured Lipid Carriers (NLCs)
Nanostructured lipid carriers were developed as second-generation lipid nanoparticles to overcome the limitations associated with SLNs. NLCs are composed of a mixture of solid and liquid lipids that create an imperfect lipid matrix capable of accommodating larger amounts of drug molecules. This structure provides improved drug-loading capacity, enhanced stability, reduced drug leakage, and prolonged drug release (Müller et al., 2002; Chauhan et al., 2020).
NLCs are considered one of the most promising systems for modern transdermal drug delivery because of their superior permeation efficiency and long-term stability. These carriers have been successfully used for the delivery of ibuprofen, curcumin, ketoconazole, and anticancer agents (Pardeike et al., 2009; Chauhan et al., 2020).
Formulations:

S.NO	Ingredients	F1	F2	F3	F4
1.	Resveratrol	0.2gm	0.2gm	0.2gm	0.2gm
2.	Stearic acid	0.8gm	0.8gm	0.8gm	0.8gm
3.	Oleic acid	0.2gm	0.2gm	0.2gm	0.2gm
4.	Tween 20	0.5gm	-	-	-
5.	Tween 40	-	0.25gm	-	-
6.	Tween60	-	-	0.25gm	-
7.	Tween 80	-	-		0.25gm
8.	Propylene	0.25gm	0.25gm	0.25gm	0.25gm
9.	Glycon	q.s to ml	q.s to ml	q.s to ml	q.s to ml
10.	Water	q.s to ml	q.s to ml	q.s to ml	q.s to ml

Advantages:
High drug-loading capacity.
Reduced drug leakage.
Better stability than SLNs.

Controlled drug release.
Excellent skin permeation.
Long-term stability.
Suitable for hydrophobic drugs.

Disadvantages:

Complex formulation.
Expensive equipment.
Difficult optimization.
Possibility of particle aggregation.
Scale-up challenges.

Applications:

1.Ibuprofen delivery.
2.Curcumin delivery.
3.Ketoconazole.
4.Anticancer drugs.
5.Psoriasis treatment.
6.Cosmetic formulations.
7.Anti-aging products.

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