Nanocarrier types and their applications in delivering medications by transdermal route

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ABSTRACT

In recent years, there has been a significant growth in the use of nanotechnology in drug administration, with the goal of improving the efficacy and/or lowering the toxicity of currently existing drugs. Promising therapeutic biomacromolecules (such as nucleic acids and proteins) can be delivered more efficiently by bypassing cellular barriers with the help of nanocarriers. On the other hand, the transdermal drug delivery system is another method that was designed to reduce the limitations associated with other modes of administration, particularly the oral route.. The challenge arises from the fact that the stratum corneum layer of skin serves as an effective barrier that restricts medication penetration through the skin and that only a small number of noninvasive techniques are known to considerably increase the ability to penetrate this barrier. The use of nanocarriers is now recognised as an intriguing and beneficial alternative for delivering hydrophilic and lipophilic medications across the stratum corneum with the ability to have a local or systemic effect in the management of a variety of diseases in order to broaden the spectrum of drugs available for delivery through the skin. Liposomes, ethosomes, bilosomes, transferosomes, dendrimers, etc. are examples of nanocarriers that can be created from a wide variety of substances and have extremely varied chemical and structural properties. They can transport the drug to the targeted organ using smaller drug doses as a way to minimise side effects because they become too small for the immune system to identify them.

Key words: Nanotechnology, Nanocarriers, Lipid-based vesicular system, transdermal rout, stratum corneum, applications.

الناقلات النانوية وأنواعها وتطبيقاتها في توصيل الأدوية عن طريق الجلد

الخلاصة

شهدت تقنية النانو زيادة كبيرة جدًا في استخدامها في إدارة الأدوية في السنوات الأخيرة، وذلك بهدف زيادة فعالية و/أو تقليل سمية الأدوية المتوفرة حاليًا. يمكن توصيل الجزيئات الحيوية العلاجية المرتقبة (مثل الأحماض النووية والبروتينات) بشكل أكثر فعالية بمساعدة الناقلات النانوية من خلال التغلب على الحواجز الخلوية. ومن ناحية أخرى، فإن نظام توصيل الدواء عبر الجلد هو وسيلة أخرى تم تطويرها لتقليل القيود المرتبطة بالطرق الأخرى للإعطاء، وخاصة الطريق الفموي. وينشأ التحدي من حقيقة أن الطبقة القرنية من الجلد تعمل بمثابة طبقة فعالة من الجلد. حاجز يقيد تغلغل الدواء عبر الجلد، ولا يُعرف سوى عدد قليل من التقنيات غير الجراحية التي تزيد بشكل كبير من القدرة على اختراق هذا الحاجز. أصبح من المعترف به الآن استخدام الناقلات النانوية كبديل مثير للاهتمام ومفيد لتوصيل الأدوية المحبة للماء والدهون عبر الطبقة القرنية مع القدرة على أن يكون لها تأثير موضعي أو نظامي في إدارة مجموعة متنوعة من الأمراض من أجل توسيع نطاق الأدوية المتاحة للتسليم من خلال الجلد. الجسيمات الشحمية، والإيثوسومات، والبيلوسومات، والترانسوسومات، والتشعبات، وما إلى ذلك. هي أمثلة على الناقلات النانوية التي يمكن تصنيعها من مجموعة واسعة من المواد ولها خصائص كيميائية وهيكلية متنوعة للغاية. يمكنهم نقل الدواء إلى العضو المستهدف باستخدام جرعات دوائية أصغر كوسيلة لتقليل الآثار الجانبية لأنها تصبح أصغر من أن يتمكن الجهاز المناعي من التعرف عليها.

1. INTRODUCTION

Nanotechnology The definition of nanotechnology is the process of creating both inorganic and organic substances, structures, equipment, and systems by manipulating their size and shape on a scale of less than one micron [1].

A lot of diseases and changes in the biological system are present at the nanoscale level, such as infections by different types of viruses or bacteria, mutated genes, and miscommunication. All of these may lead to serious diseases, depending on their nanoscale size. These infections and molecular changes can protect themselves from nuclear pores, so they will be allocated in the biological system [2].

Nanomaterials sizes are similar to or near those of the biological system; this property will help to use nanotechnology and nanomaterials in sensitive and highly precise diagnostic and therapeutic manners due to their ability to cross biological barriers [3].

Nanomaterials can be classified into three classes. First, according to dimension, include: One-dimensional nanoparticles are often found in thin films or surface coatings, while two-dimensional nanoparticles can be nanoparticles bonded to a surface or porous thin films with nanoscale pores. Three-dimensional nanomaterials are substances that are nanoscaled in all three dimensions, including colloids and free nanoparticles with different morphologies. Second, according to morphology, nanomaterials are classified into low- and high-aspect-ratio nanoparticles with various shapes and morphologies. Composition can also influence nanoparticle composition, with pure materials being easily produced through various processes. Also, according to uniformity and agglomeration, nanoparticles are classified as isometric or inhomogeneous, depending on their agglomeration condition. The shape and functionalization of their surfaces can determine their hydrophobicity or hydrophilicity [4],[5].

Medical sciences could greatly benefit from nanotechnology, both in terms of the ability to diagnose illnesses in vivo and in vitro and in terms of the chance to treat them. The use of nanotechnology in medicine is not only confined to the aforementioned fields; it also includes fields linked to the creation of nutraceuticals and the production of novel biocompatible and bioresponsive materials [6].

Nanomaterials are substances that have internal, surface, or external dimensions that are on the nanoscale. Since the majority of the materials in our environment are altered at the nanoscale, they would all be considered nanomaterials by this definition.

A particle having a minimum of one exterior dimension in the nanoscale is referred to as a nanoparticle [4].

2. APPLICATIONS OF NANOPARTICLES:

Nanoscale meters are (10–1000) nm; drug delivery and other pharmaceutical applications should be within these ranges. The aims of using nanotechnology in pharmaceutical applications are:

- Improve specificity during targeting and delivery of drugs, for example delivering medications to tumour tissue which leads to increased drug accumulation in the tumour, minimising damaging adverse effects on normal cells or tissues [7].
- Solving the solubility issues of drugs with low solubility ,for example nanocrystalline suspensions of poorly soluble medicines, such as itraconazole, are simple to make and represent a promising novel therapeutic formulation for oral drug administration for fungal infection treatment [8].
- Co-delivery of the drug with imaging modulating for tracking the drug at the site of action for example magnetic resonance (MR) imaging-guided medication delivery is a promising technique for enhancing or facilitating targeted drug administration to solid tumours. MR imaging can be utilised for screening, scheduling, tracking, and post-procedural therapy outcome evaluation [9].
- Controlling the delivery of a drug from its formulation for example nanocapsules containing atovaquone were created utilising the interfacial deposition approach and various polymers to provide spatiotemporal control of drug release, which contributes to drug toxicity reduction and improved therapeutic efficacy [10].
- Enhancement of the targeting of drugs that have a large molecular weight (macromolecules) at their site of action, for example many protein and peptide drugs like Albumin bound paclitaxel and Denileukin diftitox marketed as a noano-formulations delivering [11].

3. NANOCARRIER

In the last few decades, there has been a lot of research done on nanocarriers since they have shown great promise for drug delivery.

Nanocarriers have a high surface area to volume ratio, which can alter the fundamental properties and bioactivity of medications. Nanocarriers can be used in drug delivery systems to improve pharmacokinetics and biodistribution, lower toxicities, increase solubility and stability, provide controlled release, and deliver therapeutic molecules to particular sites.

A nanocarrier is one of the special and deferential ways that are used to improve and enhance drug delivery through the cellular tissue with the assistance of different types of substances that have the ability to deliver drugs to the site of action by different mechanisms depending on the physiochemical properties of nanoparticles. One of these mechanisms that the drug needs to achieve a pharmacological effect is to penetrate through the biological membranes such as the mucosa, epithelium, and endothelium, move on towards the cell membrane, and at the end reach the specific cellular target, so that for drugs that are deposition intracellularly, this will lead to a lowering of the drug's efficacy and increase the adverse effects.

This problem prompted an attempt to devise new solutions for this issue. Many ideas started to emerge on how to deliver the active constituent to the site of action by using nanocarriers, which have different types and forms and also have another advantage of overcoming some of the limitations associated with substances with large molecules or those that are affected by physiological conditions.

The general objective of using nanocarriers in drug delivery is to successfully treat a disease with minimal adverse effects, an important example for nanocarriers have been employed to avoid the drawbacks of traditional anticancer drug delivery systems, such as nonspecificity, severe side effects, burst release, and damage to normal cells. Nanocarriers boost anticancer medication absorption and therapeutic efficacy while offering selective deposition at the desired site [12],[13].

3.1 Types of Nanocarriers Used as Drug Delivery Systems

There are different types of nanoparticles according to the material that is used in the preparation as mention in table 1:

- Polymeric materials (polymeric nanoparticles, polymeric micelles, or dendrimers)
- Viruses (viral nanoparticles)
- Organometallic compounds (carbon nanotubes)
- Lipid-based vesicular systems such as liposomes. Figure 1 illustrate the type of nanoparticles.

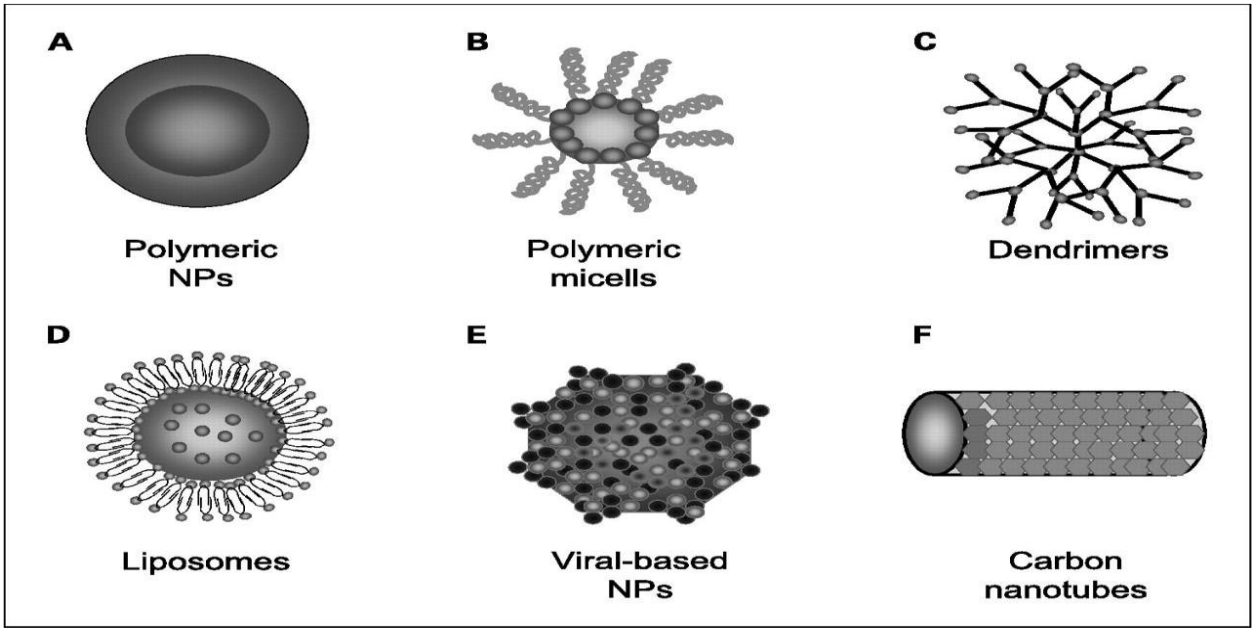


Figure 1 : Fundamental types of nanocarriers for drug delivery. Polymeric nanoparticles (A) Polymeric micelles (B). Dendrimers (C). Liposomes (D)Viral nanoparticles (E). Carbon nanotubes (F) [14].

Table 1. Types of nanocarriers for drug delivery

System	Composition	Examples	Ref.
Polymeric nanoparticles (polymer-drug conjugates)	A linker (cleavable bond) is used to conjugate drugs to the side chain of a linear polymer.	Albumin-Taxol (Abraxane)	[15]
Polymeric micelles	Amphiphilic blocks of polymers join together to produce a micelle with a hydrophobic core and a hydrophilic shell.	polyethylene glycol - pluronic- Doxorubicin	[16]
Dendrimers	Synthetic polymer having a radially developing hyperbranched pattern and repeated units.	poly(amidoamine)-methotrexate	[17]
Lipid-based vesicular systems (liposomes)	Self-assembling lipid bilayer-based closed colloidal structures	Liposomal daunorubicin (DaunoXome)	[18]
Viral nanoparticles	Protein enclosures are multivalent self-assembled nanostructures	cowpea mosaic virus-. Doxorubicin	[19]
Carbon nanotubes	Carbon cylinders with benzene rings	CNT-amphotericin B	[20]

3.1.1 Polymeric materials (polymeric nanoparticles, polymeric micelles, or dendrimers)

According to the method used for preparation and whether the drug will be entrapped physically or covalently bound to the polymeric matrix, polymer-based drug carriers can be divided into:

3.1.1.1 Polymeric nanoparticles

Different types of polymers like heparin, albumin, and chitosan will be united with drugs, DNA, and proteins to produce a capsulated structure (nanocapsules or nanospheres) between them.
Polymeric nanoparticles have several advantages:

- biodegradability,
- surface modification, and
- Ease of implementation of polymers

That will lead to improvements in the pharmacokinetic properties of entrapped drugs and more suitable steady levels [21],[22].

3.1.2 Polmeric micelles

Self-assembled structure, which is composed of polymers that have both hydrophobic and hydrophilic parts (amphiphilic structure) arranged by itself to form micelles where its size will be within the nanorange, hydrophobic parts will be arranged on the inside, and the hydrophobic parts will form the outer shell in aqueous media above the critical micelle concentration (CMC) and critical micelle temperature (CMT) [23],[24].

Polymeric micelles have many advantages.

- Delivering different types of potent hydrophobic drugs, where the chemical and physical properties of the unimers will specify the amount of drug to be loaded,
- High thermodynamic stability in physiological media,
- Can be released rate controlled, [25]
- Suitable for intravenous drug formula, [26]
- Moreover, due to their nanosize, they easily avoid the reticuloendothelial system and pass through the endothelial cells [27].

3.1.3 Dendrimers

when a number of monomeric or oligomeric polymers are united, they form a new type of macromolecular compound called dendrimers. They are considered synthetic polymers, so they can be formed with different groups and functional ends. Drug entrapment within these polymers is easily achieved by making modifications in branching degree, size, and shape [28],[29].

Dendrimers have many advantages.

- easy change in shape and size, so different properties,
- its size in the nano range,
- easy to prepare,
- can be used for specific targeting, such as in cancer therapy [30].

3.2 Viral nanoparticles

Because of many factors such as size, monodispersity, and diversity in the chemical structure that can be changed to lead to a suitable platform in a nanoscale structure, viral nanoparticles are considered one of the most promising fields in biomedicine, such as delivering drugs and imaging tissues.

For targeted drug and gene delivery, viruses like the Cowpea mosaic virus, the Cowpea chlorotic mottle virus, and bacteriophages have been used.

Viral nanoparticles are well-known, monodisperse structures that can be mass-produced. as a result of their extremely symmetrical structures.They are among the most versatile and sophisticated naturally occurring nanomaterials [31]. The genetic material of viruses is encased in a protein cap (capsid). By interacting with particular cell surface receptors, the capsule facilitates binding, internalisation, and delivery of the encapsulated material into the target cell, resulting in a quick and organised delivery. Many peptides and molecules, including antibodies, transferrin, folic acid, and others, can be displayed on their surfaces using genetic or chemical methods for active targeting in vivo [32],[19],[33].

3.3 Carbon nanotube

Carbon nanotube is one of the nanocarriers that are made from benzene rings in their structure, which is cylinder-shaped. These nanocarriers have different applications in biology, like sensors for discovering DNA for transporting vaccines and proteins inside the body and diagnostic tools for distinguishing between different proteins from serum samples.

In general, carbon nanotubes are insoluble in all types of solvents, so they may pose a big health issue and be toxic to the human body.

Therefore, the ability for chemical modification of carbon nanotubes can change its solubility and make it water-soluble, so it can be crossed with different types of active molecules and active pharmaceutical ingredients. In addition, the chemical structure of carbon nanotubes has the ability to add one or more functions to the same cylinder, so that therapeutic agents and contrast molecules can be loaded along with the targeting agent altogether [20].

3.4 Lipid-based vesicular system

Another type of nanocarrier is composed of vesicles, which are highly organised assemblies made up of one or more concentrated bilayers that arise when amphiphilic building blocks self-assemble in the presence of water. The ability of vesicular drug delivery systems to localise drug activity at the site or parts of action, thus reducing its concentration at other places in the body, makes them especially crucial for targeted drug delivery.

This system has many applications and can be useful to treat and resolve many issues that medications suffer from, like:

- It is simple to encapsulate both hydrophilic and hydrophobic medicines.
- Drug bioavailability can also be increased.
- It is possible to prolong the elimination of quickly metabolizable drugs.
- Drugs may circulate for a longer period of time in the body.
- Targeted drug delivery is frequently possible.
- Problems with related medications' stability can be fixed.
- Problems with medication toxicity tend to be treatable [34].

4. Transdermal drug delivery

This route has become increasingly essential and a focus of research in order to improve it and use it to deliver drugs more effectively than other traditional oral routes because:

Advantages:

- Transdermal delivery has the advantage of avoiding fluctuations that can happen during gastric absorption.
- Because the active ingredient is delivered by transdermal administration, it avoids the liver's process of metabolism and enters the bloodstream directly, increasing the bioavailability of drugs [35].
- It can offer a controlled, regular drug intake, minimising variations in drug plasma concentrations.
- It improves patient compliance by providing a simple administration technique with no risk of tissue injury or stress.

-Disadvantages:

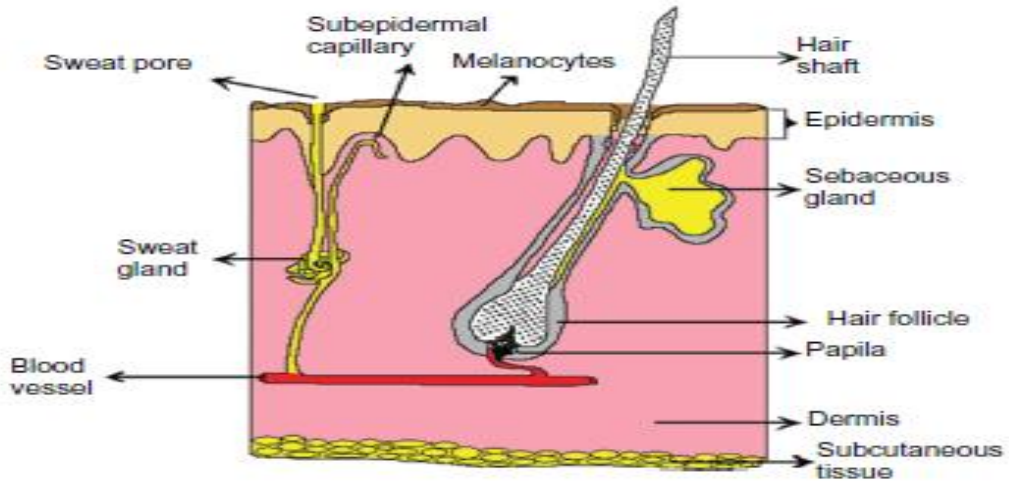
- Drugs larger than 500 Da are unable to be injected beneath the skin.
- Obtaining a high drug level in the blood is challenging.
- High doses of certain medications may cause skin sensitivities or irritation.
- Problems with ionic drug delivery or drugs having a low or high partition coefficient.
- There are differences in skin permeability from person to person based on age, place of application, and other factors [36].

4.1 Skin physiology and natural defenses

The skin is the body's biggest organ, covering more than 10% of total body mass; it allows the body to engage more closely with its surroundings. The skin is made up of four layers in total [37].

1. The stratum corneum, which is the skin's outer layer. It serves as the rate-controlling barriers for practically all chemicals' diffusion. It is made up of dead, flattened out, keratin-rich cells known as corneocytes. These packed cells are surrounded by a complex intercellular lipid mixture that includes ceramides, free fatty acids, cholesterol, and cholesterol sulphate. Their greatest distinguishing feature is that they are organised as ordered bilayer patterns.The intercellular diffusional path appears to be the most common for molecules crossing the stratum corneum [38].
2. Remaining layers of the epidermis (viable epidermis).
3. The dermis.
4. Subcutaneous tissue.

Hair follicles, sweat ducts, glands, and nails are also related appendages, however they only account for roughly 0.1% of the total human skin surface [39].



as displayed in Figure. 2

Figure 2 : Schematic representation of epidermis layer of human skin[40]

4.2 Drug penetration routes through the skin

The medication is transported across the skin by transappendageal, transfollicular, transcellular, and intercellular pathways. Figure (3) depicts different pathways of drug delivery through the skin [35].

Passive routes for molecules to cross the stratum corneum include intercellular (via solubilization in extracellular lipids organised into structured bilayers), transcellular (via corneocytes and lipid bilayers), and transappendageal (via sweat glands or hair follicles). However, while skin appendages occupy 0.1% of the skin surface, the impact of the latter route remains minor. Because of the tortuous passage and rising sweat, sweat glands are not a frequent route for medicines to enter through the skin. In contrast, hair follicles are a common mode of transport for certain ions, polyfunctional polar chemicals, and high molecular weight molecules. Hair follicles, despite their fewer surface area, have been shown to play a crucial role in the absorption of nanoencapsulated compounds because they act as nanoparticle depots [40].

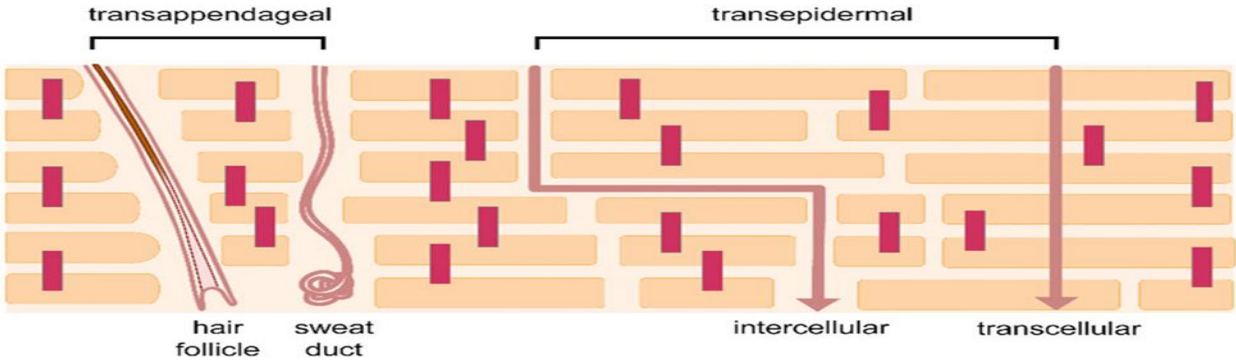


Figure 3 : skin permeation pathways [41].

5. Transdermal nanocarriers

Nearly all routes can be used to deliver nanoparticulated systems into organisms, including transdermal delivery [42],[43]. Which has certain advantages over other administration methods But also has some disadvantages, as shown above. Figure (4) illustrates the most popular and Extensively researched nanocarriers for topical or transdermal drug administration in the pharmaceutical industry [44], based on the material that was utilised to manufacture them.

The current focus of researches into transdermal drug delivery includes lipid-based vesicular systems such as liposomes, transfersomes, ethosomes, niosomes, and others, dendrimers, nanoparticles, and nanoemulsions [40].

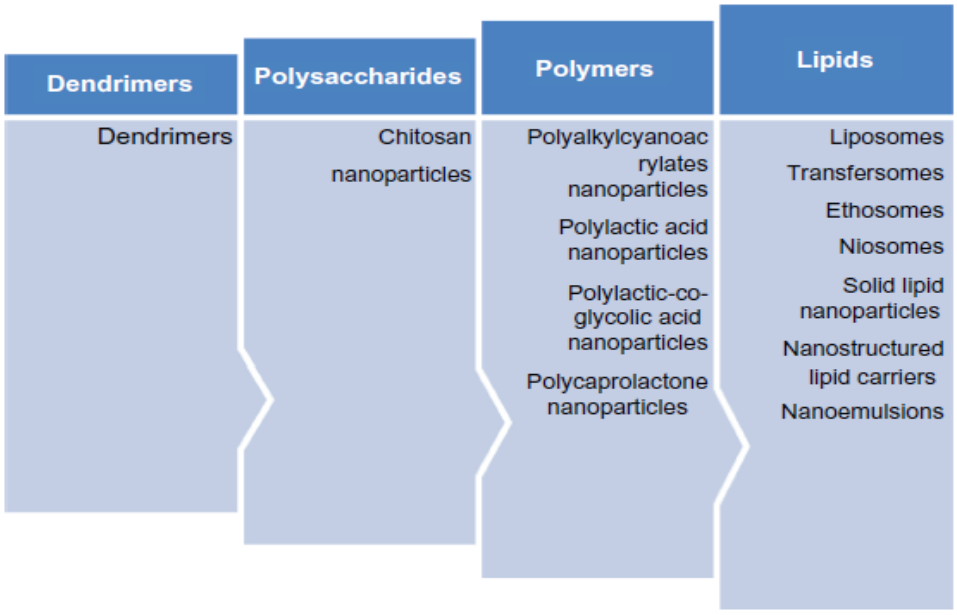


Figure 4 : common carriers for transdermal medication delivery Depending on the material used to make them [40].

5.1 Liposomes

Small, rounded shape made by one or more phospholipids (cholesterol is the most popular one), as displayed in Figure 5 ,Which represents one of the most favourable systems for delivering drugs through the skin layers because of:

- Their size,
- Both hydrophilic and hydrophobic properties
- Can be made by different methods and

Enhancement in the half-life of drugs that are incorporated with liposomes can increase their therapeutic delivery [28].

Liposome weakness:

There are some weaknesses associated with liposomes that limit their widespread use:

- shorter half-lives,
- costly production,
- drug leaking, and
- Phospholipid oxidation [45].

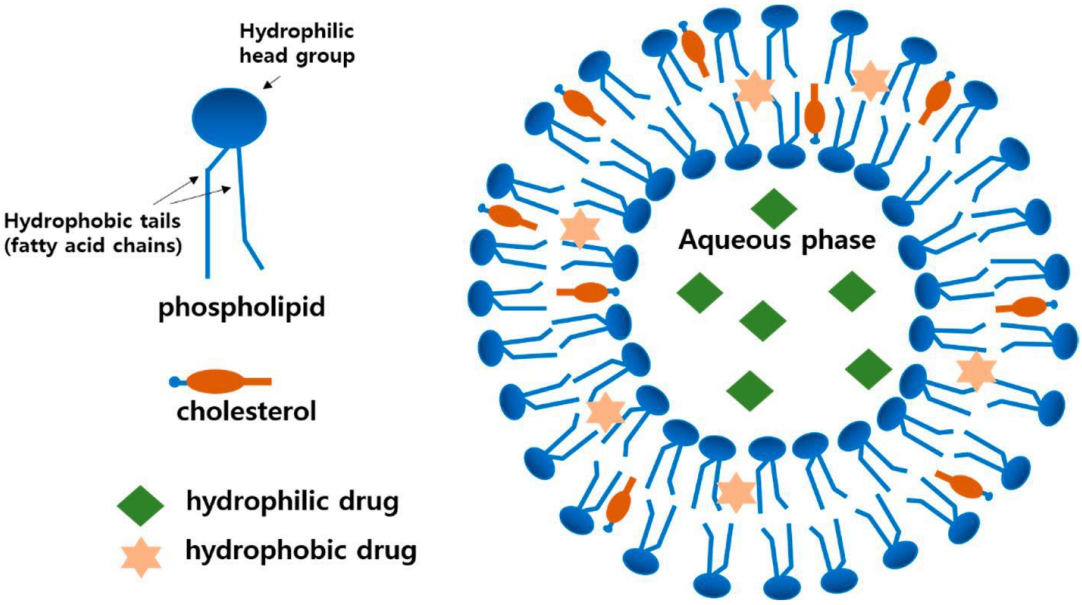


Figure 5 : Structure of conventional liposomes encapsulating hydrophilic and hydrophobic drugs [46].

5.1.1 Liposomes' mechanism for improving skin delivery

By employing liposomes, four processes are proposed to improve skin delivery. These mechanisms are depicted in figure 6

A- The first mechanism includes the liberation of the drug from the liposomes, which is followed by its independent permeation via the skin. Those liposomes serve just as carriers.

B- The SC's permeability barrier is reduced by lecithin, which is the second method.

C-The third mechanism is the adherence of liposome lipids to the skin's surface. This adherence causes the liposome lipids to mix with the lipid matrix of the SC, changing the structure of the SC's lipid lamellae and facilitating permeation through it.

D- The last mechanism, A few investigations have shown that only a small number of intact liposomes are able to penetrate the SC layer, which requires undamaged vesicular penetration [47].

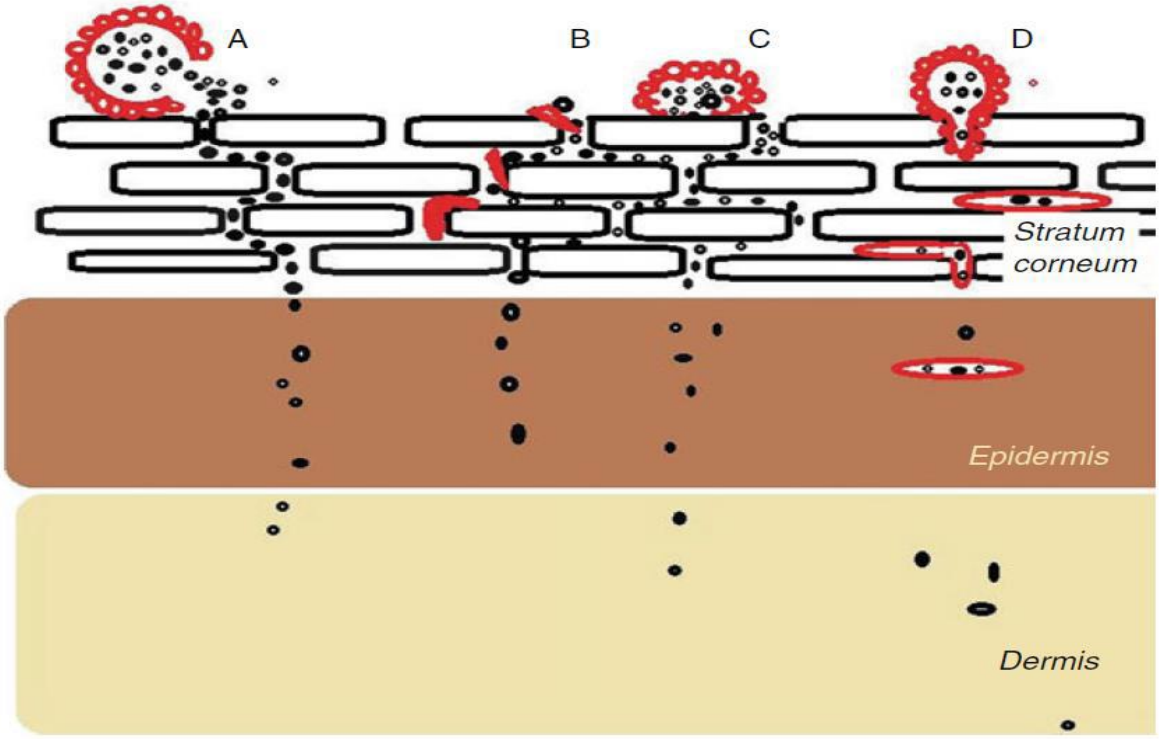


Figure 6: Mechanisms of liposome penetration across the skin [48].

5.2 ETHOSOMES

They are innovative delivery systems for medicines with a low biological membrane penetration rate, especially the skin. Ethosomes are made up of phospholipids, alcohol (ethanol and isopropyl alcohol), in relatively high concentrations, and water. Primarily used for delivering drugs transdermally.

However, the precise process by which ethosomes improve drug penetration into deeper layers of skin is still unclear.

High concentrations of ethanol and phospholipids make up vesicular formulations. The combined effects of these two combinations are what cause more profound penetration and lipid bilayer distribution in the skin. Active loading, passive loading, the hot approach, and the cold method can all be used to produce ethosomes [49].

Ethosomes are used for delivering protein and peptide molecules, which are relatively large molecules, but one of their disadvantages is skin irritation because of the excipients and enhancers used in their preparation [50].

5.3 NIOSOMES

Due to their distinct benefits, nonionic surfactant-based carriers like niosomes and proniosomes are being extensively researched for topical application. The niosomes' amphiphilic moieties allow them to accommodate a variety of pharmacological compounds [51].

Niosomes have the ability to improve drug absorption through the skin, build drug depots, and release the medication in a controlled or gradual manner.

Niosomes production technique and bilayer composition both affect how physicochemically they are made. Enhanced drug loading is possible by changing the ratio of the hydrophilic and/or hydrophobic moiety in the niosome membrane [52].

5.4 Transferosome

The elasticity of the transferosome allows it to pass through a pore that is several times smaller than its size. This makes it an ultra-deformable vesicle. Phospholipids and a combination of surfactants are both components of the transferosome. The ratios of the various surfactants and the total amount of surfactants determine how flexible the vesicle is. The ability to accommodate hydrophilic, lipophilic, and amphiphilic medicines makes this sort of drug carrier system special. Before being injected beneath the skin, these

medications are distributed throughout the elastic vesicle in various locations. Transferosomes can also be used to create formulations for controlled release [53].

5.5 Bilosomes

They are vesicular structures based on liposomes and enhanced with non-ionic surfactants and bile salts. These were referred to as bilosomes, which are differentiated from liposomes and niosomes in terms of their composition, chemical stability, and storage circumstances [54]. Conacher first described bilosomes in 2001. Who reached the conclusion that oral immunization with bilosomes filled with peptide and protein antigens produced an immune response, indicating that bilosomes protected those antigens from the hazardous GIT environment [55].

Bilosomes can be described as closed bilayer vesicles with a structure similar to niosomes and are made of non-ionic amphiphiles, but they also contain bile salts in the bilayer [83]. Bilosomes have drawn attention as a means of orally delivering therapeutic proteins or peptides since Conacher's discovery. Additionally, bilosomes attracted interest for their potential to improve the bioavailability of drugs taken orally, such as acyclovir [56].

6. Transdermal nanocarriers application

Various carrier systems have been developed in an aim to promote drug transport via the skin, allowing drug retention and, in some situations, controlled release. The possible uses of nanocarriers technologies for transdermal medication administration are summarised in Table 2, while Table 3 summarised some examples of special vesicular systems intended for transdermal delivery.

Table 2 Summary of the applications of nanocarriers in transdermal drug delivery.

Type of transdermal nanocarriers	Type of transdermal nanocarriers
Liposom	Drugs that are both lipophilic and hydrophilic can be stabilised in liposomes. Many liposome-based medications have also received approval for use in clinical settings. Positively charged liposomes are currently being employed in gene therapy to transport DNA. Additionally, a variety of antifungal and anticancer uses exist for liposomes [57].
Ethosomes	It gives superior skin permeability than the other lipid vesicles. Ethosomes are simple to make, stable, and safe to use. Ethosomes have already demonstrated their potential to transmit medicinal chemicals via the skin without negative effects after two decades of development. The incorporation of ethosomes in appropriate vehicles such as creams, gels, and patches improves skin permeability and therapeutic effects.[58]
Niosome	Niosomal formulations have a higher potential for medication cutaneous targeting and may be a viable option for topical application of minoxidil in conditions like hair loss. Additionally, topical administration of niosomes can prolong the period that medications remain in the epidermis and the stratum corneum while decreasing the amount of drug that is absorbed systemically [59].
Transferosome	Deformable liposomes have been shown in numerous studies to be able to deliver various medications to the skin more effectively in vitro [60],[61], and to penetrate intact skin in vivo [62], transferring therapeutic doses of pharmaceuticals with an efficiency that is comparable to subcutaneous administration [63].
Bilosome	Vaccine administration using bilosomes, The delivery of conventional tiny medicines and biological medicines may be accomplished via bilosomes, such as tenoxicam [64], Bilosomes can be used for oral Hepatitis B vaccination.and Bilosomes can be employed as a tetanus toxoid for immunological stability [47].

Table 3 Some examples of special vesicular systems intended for transdermal delivery

CONCLUSION:

Nanotechnology is going to become increasingly used in pharmaceuticals, and more specifically, drug delivery. Pharmaceutical scientists have used nanoparticles to lessen the toxicity and adverse effects of medications for many years. There are already many different types of nanoparticles, and numerous synthesis techniques have been developed.

Many researchers are interested in investigating the delivery of drugs through the transdermal system because of its many significant benefits. Today, a lot of fresh research is being done to incorporate newer medications using this technique.

Aiming to prevent immune system resistance and reach target areas, nanocarriers have been developed and tested to get across the SC barrier and increase transdermal permeation.

Vesicular Carrier-Based Dosage Form	Drug	Category of Drug	Dosage Form	Outcomes	Reference
Ethosome gel	Carvedilol	Antihypertensive	Transdermal delivery system	Enhances skin permeation of drugs and reaches into the systemic circulation.	[58]
Ethosome and liposomes	Rosmarinic acid (RA)	Anti-aging, antioxidant, anti-collagenase, anti-elastase	Transdermal delivery system	improved and increased RA skin penetration significantly improve skin permeation and retention	[65]
Transfersomal gel	Miconazole nitrate	Antifungal	Transdermal delivery system	Transfersomal gel showed higher antifungal activity than marketed conventional formulation.	[66]
Ethosomes and transferosomes	Sulforaphane	Anticancer and antiproliferative	Transdermal delivery system	Enhanced percutaneous permeation.	[67]
Ethanol-based malleable liposomes	Cytarabine	Anticancer	Transdermal delivery system	Alternative delivery of drugs for the treatment of leukemia, with low side effects and sustained release.	[68]
Niosomes gel	Lopinavir	antiretroviral	Transdermal delivery system	Improved systemic availability	[69]
Bilosomes gel	Lornoxicam	nonsteroidal anti-inflammatory	Transdermal delivery system	Improving skin permeation, enhanced anti-inflammatory and antinociceptive activities	[70]

Reference:

[1] N. Tirelli, "(Bio)Responsive nanoparticles," Curr. Opin. Colloid Interface Sci., vol. 11, no. 4, pp. 210–216, 2006, doi: 10.1016/j.cocis.2006.09.002.

[2] "2 nanomedicin".

[3] H. Sciences and A. Almalik, "Hyaluronic acid-coated nanoparticles as biofunctional pharmaceutical carriers," 2013.

[4] C. Buzea, I. I. Pacheco, and K. Robbie, "Nanomaterials and nanoparticles: Sources and toxicity," Biointerphases, vol. 2, no. 4, pp. MR17–MR71, 2007, doi: 10.1116/1.2815690.

[5] Andreas Öchsner, L. F. M. da Silva, and H. Altenbach, Advanced Structured Materials EMR/ESR/EPR Spectroscopy for

Characterization of Nanomaterials. 2017.
[6] W. H. De Jong and J. B. Paul, “Drug delivery and nanoparticles : Applications and hazards,” Int. J. Nanomedicine, vol. 3, no. 2, pp. 133–149, 2008.
[7] J. Li et al., “Recent Advances in Targeted Drug Delivery Strategy for Enhancing Oncotherapy,” Pharmaceutics, vol. 15, no. 9, p. 2233, 2023, doi: 10.3390/pharmaceutics15092233.
[8] M. Nakarani, A. Misra, J. Patel, and S. Vaghani, “Itraconazole nanosuspension for oral delivery: Formulation, characterization and in vitro comparison with marketed formulation,” Acta Pharm. Sci., vol. 52, no. 3, pp. 305–314, 2010.
[9] A. S. Mikhail, A. Partanen, P. Yarmolenko, A. M. Venkatesan, and B. J. Wood, “Magnetic Resonance-Guided Drug Delivery,” Magn. Reson. Imaging Clin. N. Am., vol. 23, no. 4, pp. 643–655, 2015, doi: 10.1016/j.mric.2015.05.012.
[10] E. Cauchetier, M. Deniau, H. Fessi, A. Astier, and M. Paul, “Atovaquone-loaded nanocapsules: Influence of the nature of the polymer on their in vitro characteristics,” Int. J. Pharm., vol. 250, no. 1, pp. 273–281, 2003, doi: 10.1016/S0378-5173(02)00556-2.
[11] S. Srivastava, V. Sharma, B. Bhushan, R. Malviya, R. Awasthi, and G. T. Kulkarni, “Nanocarriers for protein and peptide delivery: Recent advances and progress,” J. Res. Pharm., vol. 25, no. 2, pp. 99–116, 2021, doi: 10.29228/jrp.1.
[12] F. U. Din et al., “Effective use of nanocarriers as drug delivery systems for the treatment of selected tumors,” Int. J. Nanomedicine, vol. 12, pp. 7291–7309, 2017, doi: 10.2147/IJN.S146315.
[13] H. Hillaireau and P. Couvreur, “Nanocarriers’ entry into the cell: Relevance to drug delivery,” Cell. Mol. Life Sci., vol. 66, no. 17, pp. 2873–2896, 2009, doi: 10.1007/s00018-009-0053-z.
[14] K. Cho, X. Wang, S. Nie, Z. Chen, and D. M. Shin, “Therapeutic nanoparticles for drug delivery in cancer,” Clin. Cancer Res., vol. 14, no. 5, pp. 1310–1316, 2008, doi: 10.1158/1078-0432.CCR-07-1441.
[15] W. J. Gradishar et al., “Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer,” J. Clin. Oncol., vol. 23, no. 31, pp. 7794–7803, 2005, doi: 10.1200/JCO.2005.04.937.
[16] E. V. Batrakova et al., “Anthracycline antibiotics non-covalently incorporated into the block copolymer micelles: In vivo evaluation of anti-cancer activity,” Br. J. Cancer, vol. 74, no. 10, pp. 1545–1552, 1996, doi: 10.1038/bjc.1996.587.
[17] K. A. Candido et al., “Nanoparticle targeting of anticancer drug improves therapeutic response in animal model of human epithelial cancer.,” Cancer Res., vol. 65, no. 12, pp. 5317–5324, 2005, [Online]. Available: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med5&NEWS=N&AN=15958579
[18] E. Rosenthal et al., “Phase IV study of liposomal daunorubicin (DaunoXome) in AIDS-related Kaposi sarcoma,” Am. J. Clin. Oncol. Cancer Clin. Trials, vol. 25, no. 1, pp. 57–59, 2002, doi: 10.1097/00000421-200202000-00012.
[19] P. Singh et al., “Bio-distribution, toxicity and pathology of cowpea mosaic virus nanoparticles in vivo,” J. Control. Release, vol. 120, no. 1–2, pp. 41–50, 2007, doi: 10.1016/j.jconrel.2007.04.003.
[20] A. Bianco, K. Kostarelos, and M. Prato, “Applications of carbon nanotubes in drug delivery,” Curr. Opin. Chem. Biol., vol. 9, no. 6, pp. 674–679, 2005, doi: 10.1016/j.cbpa.2005.10.005.
[21] D. O. Nutter and T. Ratts, “Direct actions of prostaglandins E1, A1, and F2α on myocardial contraction,” Prostaglandins, vol. 3, no. 3, pp. 323–336, 1973, doi: 10.1016/0090-6980(73)90071-3.
[22] L. Brannon-Peppas, “Recent advances on the use of biodegradable microparticles and nanoparticles in controlled drug delivery,” Int. J. Pharm., vol. 116, no. 1, pp. 1–9, 1995, doi: 10.1016/0378-5173(94)00324-X.
[23] N. Nishiyama and K. Kataoka, “Current state, achievements, and future prospects of polymeric micelles as nanocarriers for drug and gene delivery,” Pharmacol. Ther., vol. 112, no. 3, pp. 630–648, 2006, doi: 10.1016/j.pharmthera.2006.05.006.
[24] E. V Batrakova, T. K. Bronich, and J. A. Vetro, Nanoparticulates as Drug Carriers, no. July 2014. 2010. doi: 10.1142/9781860949074.
[25] R. Savić, L. Luo, A. Eisenberg, and D. Maysinger, “Micellar nanocontainers distribute to defined cytoplasmic organelles,” Science (80-.)., vol. 300, no. 5619, pp. 615–618, 2003, doi: 10.1126/science.1078192.
[26] V. P. Torchilin, “Structure and design of polymeric surfactant-based drug delivery systems,” J. Control. Release, vol. 73, no. 2–3, pp. 137–172, 2001, doi: 10.1016/S0168-3659(01)00299-1.
[27] A. Rösler, G. W. M. Vandermeulen, and H. A. Klok, “Advanced drug delivery devices via self-assembly of amphiphilic block copolymers,” Adv. Drug Deliv. Rev., vol. 64, no. SUPPL., pp. 270–279, 2012, doi: 10.1016/j.addr.2012.09.026.
[28] A. H. Faraji and P. Wipf, “Nanoparticles in cellular drug delivery,” Bioorganic Med. Chem., vol. 17, no. 8, pp. 2950–2962, 2009, doi: 10.1016/j.bmc.2009.02.043.
[29] C. C. Lee, J. A. MacKay, J. M. J. Fréchet, and F. C. Szoka, “Designing dendrimers for biological applications,” Nat. Biotechnol., vol. 23, no. 12, pp. 1517–1526, 2005, doi: 10.1038/nbt1171.

[30] M. El-sayed, M. Ginski, and C. Rhodes, “Transepithelial transport of poly(amidoamine) dendrimers across167-5,” vol. 81, pp. 355–365, 2002.
[31] N. F. Steinmetz, “Viral nanoparticles as platforms for next-generation therapeutics and imaging devices,” Nanomedicine Nanotechnology, Biol. Med., vol. 6, no. 5, pp. 634–641, 2010, doi: 10.1016/j.nano.2010.04.005.
[32] I. Yildiz, S. Shukla, and N. F. Steinmetz, “Applications of viral nanoparticles in medicine,” Curr. Opin. Biotechnol., vol. 22, no. 6, pp. 901–908, 2011, doi: 10.1016/j.copbio.2011.04.020.
[33] M. Manchester and P. Singh, “Virus-based nanoparticles (VNPs): Platform technologies for diagnostic imaging,” Adv. Drug Deliv. Rev., vol. 58, no. 14, pp. 1505–1522, 2006, doi: 10.1016/j.addr.2006.09.014.
[34] S. Jain, V. Jain, and S. C. Mahajan, “Lipid Based Vesicular Drug Delivery Systems,” Adv. Pharm., vol. 2014, no. i, pp. 1–12, 2014, doi: 10.1155/2014/574673.
[35] D. Singh, M. Pradhan, M. Nag, and M. R. Singh, “Vesicular system: Versatile carrier for transdermal delivery of bioactives,” Artif. Cells, Nanomedicine Biotechnol., vol. 43, no. 4, pp. 282–290, 2015, doi: 10.3109/21691401.2014.883401.
[36] S. Dhiman, T. G. Singh, and A. K. Rehni, “Transdermal patches: A recent approch to new drug delivery system,” Int. J. Pharm. Pharm. Sci., vol. 3, no. SUPPL. 5, pp. 26–34, 2011.
[37] J. J. Escobar-Chávez et al., “The tape-stripping technique as a method for drug quantification in skin,” J. Pharm. Pharm. Sci., vol. 11, no. 1, pp. 104–130, 2008, doi: 10.18433/J3201Z.
[38] P. M. Elias, “Epidermal barrier function: intercellular lamellar lipid structures, origin, composition and metabolism,” J. Control. Release, vol. 15, no. 3, pp. 199–208, 1991, doi: 10.1016/0168-3659(91)90111-P.
[39] A. M. Nevill, “The need to scale for differences in body size and mass: An explanation of Kleiber’s 0.75 mass exponent,” J. Appl. Physiol., vol. 77, no. 6, pp. 2870–2873, 1994, doi: 10.1152/jappl.1994.77.6.2870.
[40] J. Escobar-Chavez et al., “Nanocarriers for transdermal drug delivery,” Res. Reports Transdermal Drug Deliv., p. 3, 2012, doi: 10.2147/rrtd.s32621.
[41] A. Rahma and M. E. Lane, “Skin Barrier Function in Infants: Update and Outlook,” Pharmaceutics, vol. 14, no. 2, pp. 1–25, 2022, doi: 10.3390/pharmaceutics14020433.
[42] F. Andrade, M. Videira, D. Ferreira, and B. Sarmento, “Nanocarriers for pulmonary administration of peptides and therapeutic proteins,” Nanomedicine, vol. 6, no. 1, pp. 123–141, 2011, doi: 10.2217/nnm.10.143.
[43] Y. C. Cheng, T. S. Li, H. L. Su, P. C. Lee, and H. M. D. Wang, “Transdermal delivery systems of natural products applied to skin therapy and care,” Molecules, vol. 25, no. 21, pp. 1–21, 2020, doi: 10.3390/molecules25215051.
[44] C. Pailler-Mattei, S. Bec, and H. Zahouani, “In vivo measurements of the elastic mechanical properties of human skin by indentation tests,” Med. Eng. Phys., vol. 30, no. 5, pp. 599–606, 2008, doi: 10.1016/j.medengphy.2007.06.011.
[45] H. Mishra, V. Chauhan, K. Kumar, and D. Teotia, “Journal of Drug Delivery and Therapeutics A comprehensive review on Liposomes : a novel drug delivery system,” vol. 8, no. 6, pp. 400–404, 2018.
[46] M. Lee, “Liposomes for Enhanced Bioavailability of Water-Insoluble Drugs : In Vivo Evidence and Recent Approaches,” 2020, doi: 10.3390/pharmaceutics12030264.
[47] “Overview on different organic nanomaterials in medical,” vol. 12, no. 7, pp. 973–977, 2020.
[48] N. Dragicevic and H. I. Maibach, Percutaneous Penetration Enhancers Chemical Methods in Penetration Enhancement.
[49] D. Mohanty, A. Mounika, V. Bakshi, M. Akiful Haque, and C. Keshari Sahoo, “Ethosomes: A Novel Approach For Transdermal Drug Delivery,” Int. J. ChemTech Res., vol. 11, no. 8, pp. 219–226, 2018, doi: 10.20902/IJCTR.2018.110826.
[50] B. Godin and E. Touitou, “Ethosomes: New prospects in transdermal delivery,” Crit. Rev. Ther. Drug Carrier Syst., vol. 20, no. 1, pp. 63–102, 2003, doi: 10.1615/CritRevTherDrugCarrierSyst.v20.i1.20.
[51] Z. Sezgin-Bayindir, M. N. Antep, and N. Yuksel, “Development and Characterization of Mixed Niosomes for Oral Delivery Using Candesartan Cilexetil as a Model Poorly Water-Soluble Drug,” AAPS PharmSciTech, vol. 16, no. 1, pp. 108–117, 2014, doi: 10.1208/s12249-014-0213-9.
[52] K. Kedar, B. Pratiksha, S. Suchita, and S. S. V, “REVIEW ARTICLE ON NIOSOMES : A FUTURE OF TARGETED DRUG DELIVERY,” vol. 10, no. 6, pp. 603–614, 2022.
[53] V. Kalyani and M. Kishore Babu, “Transferosomes: An emerging tool for effective transdermal drug delivery,” J. Chem. Pharm. Sci., vol. 7, no. 3, pp. 236–241, 2014.
[54] A. Shukla, B. Singh, and O. P. Katare, “Significant systemic and mucosal immune response induced on oral delivery of diphtheria toxoid using nano-bilosomes,” Br. J. Pharmacol., vol. 164, no. 2 B, pp. 820–827, 2011, doi: 10.1111/j.1476-5381.2011.01452.x.
[55] M. Conacher, J. Alexander, and J. M. Brewer, “Oral immunisation with peptide and protein antigens by formulation in lipid

vesicles incorporating bile salts (bilosomes),” Vaccine, vol. 19, no. 20–22, pp. 2965–2974, 2001, doi: 10.1016/S0264-410X(00)00537-5.

[56] M. H. Aburahma, “Bile salts-containing vesicles: promising pharmaceutical carriers for oral delivery of poorly water-soluble drugs and peptide/protein-based therapeutics or vaccines,” Drug Deliv., vol. 23, no. 6, pp. 1847–1867, 2016, doi: 10.3109/10717544.2014.976892.

[57] B. Robert and E. B. Brown, No 主観的健康感を中心とした在宅高齢者における 健康関連指標に関する共分散構造分析Title, no. 1. 2004.

[58] T. M. Ibrahim, M. H. Abdallah, N. A. El-Megrab, and H. M. El-Nahas, Transdermal ethosomal gel nanocarriers; a promising strategy for enhancement of anti-hypertensive effect of carvedilol, vol. 29, no. 3. Taylor & Francis, 2019. doi: 10.1080/08982104.2018.1529793.

[59] N. Mali, S. Darandale, and P. Vavia, “Niosomes as a vesicular carrier for topical administration of minoxidil: Formulation and in vitro assessment,” Drug Deliv. Transl. Res., vol. 3, no. 6, pp. 587–592, 2013, doi: 10.1007/s13346-012-0083-1.

[60] M. Trotta, E. Peira, F. Debernardi, and M. Gallarate, “Elastic liposomes for skin delivery of dipotassium glycyrrhizinate,” Int. J. Pharm., vol. 241, no. 2, pp. 319–327, 2002, doi: 10.1016/S0378-5173(02)00266-1.

[61] R. R. Boinpally, S. L. Zhou, S. Poondru, G. Devraj, and B. R. Jasti, “Lecithin vesicles for topical delivery of diclofenac,” Eur. J. Pharm. Biopharm., vol. 56, no. 3, pp. 389–392, 2003, doi: 10.1016/S0939-6411(03)00143-7.

[62] G. Cevc and G. Blume, “New, highly efficient formulation of diclofenac for the topical, transdermal administration in ultradeformable drug carriers, Transfersomes,” Biochim. Biophys. Acta - Biomembr., vol. 1514, no. 2, pp. 191–205, 2001, doi: 10.1016/S0005-2736(01)00369-8.

[63] G. Cevc, A. Schätzlein, and H. Richardsen, “Ultradeformable lipid vesicles can penetrate the skin and other semi-permeable barriers unfragmented. Evidence from double label CLSM experiments and direct size measurements,” Biochim. Biophys. Acta - Biomembr., vol. 1564, no. 1, pp. 21–30, 2002, doi: 10.1016/S0005-2736(02)00401-7.

[64] A. M. Al-Mahallawi, A. A. Abdelbary, and M. H. Aburahma, “Investigating the potential of employing bilosomes as a novel vesicular carrier for transdermal delivery of tenoxicam,” Int. J. Pharm., vol. 485, no. 1–2, pp. 329–340, 2015, doi: 10.1016/j.ijpharm.2015.03.033.

[65] Ç. Yücel, G. Şeker Karatoprak, and İ. T. Değim, “Anti-aging formulation of rosmarinic acid-loaded ethosomes and liposomes,” J. Microencapsul., vol. 36, no. 2, pp. 180–191, 2019, doi: 10.1080/02652048.2019.1617363.

[66] M. Qushawy, A. Nasr, M. Abd-Alhaseeb, and S. Swidan, “Design, optimization and characterization of a transfersomal gel using miconazole nitrate for the treatment of candida skin infections,” Pharmaceutics, vol. 10, no. 1, 2018, doi: 10.3390/pharmaceutics10010026.

[67] M. C. Cristiano et al., “Sulforaphane-loaded ultradeformable vesicles as a potential natural nanomedicine for the treatment of skin cancer diseases,” Pharmaceutics, vol. 12, no. 1, 2020, doi: 10.3390/pharmaceutics12010006.

[68] R. Raj, P. M. Raj, and A. Ram, “Nanosized ethanol based malleable liposomes of cytarabine to accentuate transdermal delivery: formulation optimization, in vitro skin permeation and in vivo bioavailability,” Artif. Cells, Nanomedicine Biotechnol., vol. 46, no. sup2, pp. 951–963, 2018, doi: 10.1080/21691401.2018.1473414.

[69] N. Nainwal, S. Jawla, R. Singh, and V. A. Saharan, “Transdermal applications of ethosomes–a detailed review,” J. Liposome Res., vol. 29, no. 2, pp. 103–113, 2019, doi: 10.1080/08982104.2018.1517160.

[70] S. Ahmed, M. A. Kassem, and S. Sayed, “Bilosomes as promising nanovesicular carriers for improved transdermal delivery: Construction, in vitro optimization, ex vivo permeation and in vivo evaluation,” Int. J. Nanomedicine, vol. 15, pp. 9783–9798, 2020, doi: 10.2147/IJN.S278688.