Nanomedicine-Based Novel Formulation Strategies for the Management of Skin Disorders: Current Advances and Future Perspectives

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Abstract

Acne vulgaris, wrinkles, hyperpigmentation, premature aging, and inflammatory dermatoses are among the most common skin conditions in the globe. Stratum corneum's morphological barrier characteristic makes it difficult for medications to penetrate and reduces the therapeutic efficacy of conventional topical products such as ointments, gels, and creams. Clinical results and patient compliance are negatively impacted by poor drug stability, poor penetration into deeper skin layers, and repetitive administration. Therefore, developing tailored therapeutic action and maximizing cutaneous bioavailability would necessitate the development of innovative drug delivery techniques. Topical delivery techniques supported by nanomedicine have been proposed as possible ways to overcome these limitations. Various nano-carriers such as transfersomes, ethosomes, liposomes, niosomes, solid lipid nanoparticles (SLPs), nanostructured lipid carriers (NLCs), and nanoemulsions. Beneficial features like helping solubilization of active ingredients drug compounds and preventing the degradation of active components which will result in controlled release 21. In acne treatment, nano-formulations make the delivery of antimicrobial, anti-inflammatory substances to sebaceous glands. In terms of wrinkle reduction and anti-aging, nano-systems facilitate dermal delivery of active ingredients such as antioxidants, retinoids, peptides and collagen stimulating agents to enhance therapeutic efficacy with reduced irritation. The purpose of this study is to give a summary of current developments in topical medication delivery-based nanoenabled formulations for the treatment of wrinkles, acne, and other skin conditions with a particular focus on permeation enhancement mechanisms, therapeutic benefits, safety aspects and developmental bottlenecks. Despite the tremendous potential of nanomedicine in dermato-oncology.

Keywords: Acne vulgaris, Skin aging, Nano-carrier systems, Topical drug delivery, Solid Lipid NanoparticlesIntroduction

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Cosmetic preparations include those that are used immediately to clean the skin, hair, and nails purposes, as well as for protection from damage (and) to enhance one's appearance [1]. Definitions in regulatory bodies indicate cosmetic products are those which are used on the body (for the purpose) of making the person look better; changing their physical appearance but have no effect on the body's structural and functional integrity [2]. The majority of cosmetic product formulas will contain a combination of chemically synthesized or derived from nature chemical compounds, and are prepared specifically for use in the application of skin care and personal care [3].

Although traditional use of cosmetics is for beauty treatments, a significant number of topical products are now being used to treat various forms of dermatitis such as acne, aging of the skin (premature), and wrinkles. Acne vulgaris an inflammatory disease impacting pilosebaceous units and caused by microbial invasion of these structures. Wrinkles are formed due to degradation of collagen and oxidative damage. The conventional methods of topical formulation include creams, ointments, and gels; although they can provide the desired therapeutic effect, there are numerous reasons why they are ineffective including lack of penetration through the stratum corneum and loss of potency of active ingredients. As such, it has become apparent that to improve dermal bioavailability and controlled release, alternative It is necessary to design medicine delivery methods that can get over the stratum corneum's barrier function. With respect this goal, various Drug delivery systems based on nanotechnology have been shown to have the potential to improve the

targeted distribution of medications and, consequently, to produce better therapeutic benefits in therapy of wrinkles, acne, and other skin-related conditions [4]

1.2. Basic Skin Structure

The Skin is used as a barrier between body its surroundings biggest organ in body. Epidermis, dermis, and hypodermis are main layers. (Figure 1). Outermost layer epidermis which has of keratinocytes layers of stratified squamous surface cells. The basale, granulosum, corneum, and spinosum strata are its four primary layers. During differentiation, which typically takes 30 to 40 days, keratinocytes begin in basal layer and gradually move toward surface before undergoing desquamation [7–9]. Surface layer which serves as skin's primary protective shield, formed when keratin production rises and cellular organelles progressively break down during this differentiation process.

Layers of keratin-filled, flattened cells embedded in a lipid matrix make up the stratum corneum. Usually 10–20 µm thick, many external elements, including pharmaceuticals and cosmetic ingredients, cannot pass through this layer's strong barrier [10]. Dermis, a layer of supportive tissue beneath the epidermis, is mostly made up of collagen and elastin fibers made by fibroblasts. The skin's structural stability, flexibility, and mechanical strength come from the dermis [11]. The hypodermis, which is located beneath the dermis and functions to cushion, store energy, and insulate underlying tissues, is mostly composed of adipose tissue. Most of the blood arteries that provide nutrition and oxygen to the surrounding tissues are found in the dermis and hypodermis [12].

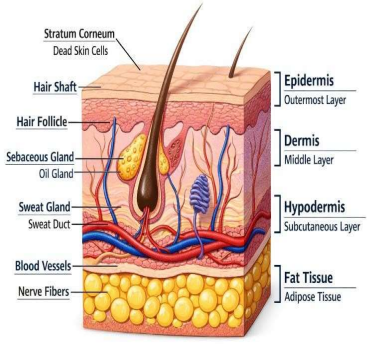


Fig 1: "Cross-sectional diagram of skin layers" Created using AI tools

1.3. The Barrier Function of the Stratum Corneum

The surface layer is primary restricter to medicament movement in skin. It is commonly described by the "brick and mortar" paradigm, where corneocytes (bricks) embedded in phospholipid region contain of ceramides, cholesterol, and free fatty acids (mortar) [13]. As a result, achieving sufficient skin drug concentrations remains a major challenge in topical medication administration. Because molecules intended for effective cutaneous distribution often require to have perfect physicochemical features, such as molecular weight below 500 Da, balanced lipophilicity, and adequate solubility, the choice of drugs suitable for conventional topical treatment is severely limited [14].

2. Factors affecting topical drug absorption

Table gives the different factors how these affects the medicaments release on to the skin surface layer also the effect on absorption.

Table 1: Factors Affecting Topical Absorption

Factor Category	Factor	Effect on Absorption	Supporting Reviews
Physicochemical Properties	Molecular Size / Weight	Smaller molecules penetrate more effectively; larger >500 Da show limited permeation	[1]
	Lipophilicity (log P)	Moderately lipophilic compounds favor partitioning into skin lipids; extremes reduce absorption	[1]
	Solubility	Good solubility in both vehicle and skin enhances absorption	[15]
	Ionization & pH	Non-ionized forms permeate better across the lipid barrier	[15]

	Partitioning & vehicle interactions	Ability to partition from formulation into skin lipids affects penetration	[15]
Formulation Characteristics	Formulation Base / Vehicle Type	Vehicles affect penetration (e.g., occlusion increases hydration and uptake)	[15]
	Release Rate	Slower or controlled release affects the concentration gradient and absorption	[15]
	Penetration Enhancers	Chemical/physical enhancers modify stratum corneum and improve permeation	[16]
Factor Category	**Factor**	**Effect on Absorption**	**Supporting Reviews**
Skin Condition & Physiology	Hydration of Skin	Hydrated SC increases porosity and improves absorption	[17]
	Integrity of Barrier (damage, inflammation)	Compromised skin may allow increased penetration	[18]
	Regional Site / SC Thickness	Differences in thickness alter permeability (face > palm/sole)	[15]
	Age of Skin	Age influences barrier function and uptake	[15]
Environmental/Lifestyle Factors	Temperature & Humidity	Temperature changes can affect diffusion and fluidity of lipids	[18]
	Pollution / Barrier Stress	Pollutants may damage the barrier and change absorption dynamics	[19]

3. Limitations of Conventional Topical Semisolid Formulations

The conventional semisolid formulation like creams, gels, lotions, ointments commonly used in various dermatological and cosmetic applications due to simple usage and better patient compliance. However, conventional semisolid dosages possess a number of limitations, which restrict the therapeutic efficacy of the formulation. The first major problem associated with conventional semisolid formulations is the poor permeation of the formulation. The skin acts as a highly organized lipid structure, which restricts the permeation of the active ingredients. This highly organized structure of the skin, i.e., Surface layer, restricts permeation of active components with an elevated molecular weight hydrophilicity. Retinoids, antioxidants, peptides, and herbal extracts that don't work well on the skin's surface can make a formulation less effective as a medicine [20–21]. 6Another big problem with traditional semisolid bases isthat the active ingredients in medicines and cosmetics can change quickly. Coenzyme Q10, vitamin C, retinol, and other plant extracts are very easy to damage by light, air, and moisture. These active ingredients can break down when the traditional semisolid formulation is used and stored. This could make the formulation less effective. Also, traditional formulations may need more active pharmaceutical and cosmetic chemicals to work better and not break down as quickly. This could make irritation, sensitization, and bad skin reactions more likely, especially in people with sensitive or damaged skin [22]. Also, these systems don't have regulated and long-term drug administration, which shortens the time it takes for the drugs to work and means that the formulations need to be applied more than once. Another problem is that traditional formulations can't effectively and steadily give both hydrophilic and lipophilic drugs. This could be a problem for treating conditions that have more than one cause, like acne and photoaging [23]. All of these problems show that we need more advanced ways to deliver drugs that could improve skin penetration, stability, controlled distribution, and comfort. Recently, the application of nanoparticles-based

carrier methods has considered promising tool in management dermatological disorders [24].

3.1. Drug Penetration Routes Through the Skin

Drug molecules able to penetrate the skin via various routes. Transepidermal route major route for permeation of drug molecules into skin [25]. This route comprises two mechanisms:

- Transcellular pathway: This mechanism of the transepidermal route occurs when the drug molecules pass directly via keratinocytes of Surface layer. This route is more favorable for oil loving drugs due to the presence of a lipid-rich environment in the cell membrane.
- Intercellular pathway: This mechanism of the transepidermal route occurs when the drug molecules pass through the lipid matrix between two adjacent cells of the surface layer. This way is considered the main route for permeation of drug molecules into the skin due to the presence of a highly lipophilic environment between two adjacent cells [26]. Another route is the transappendageal way, in which the drug molecules pass via hair scalp follicles and sebaceous glands. Although route covers a smaller area of the skin, it may be useful in the passage of larger molecules and polar substances that cannot easily pass through the stratum corneum. The complex structure of the skin and the strong barrier function of surface layer are major obstacles in the passage of therapeutic agents [27]. Consequently, a key topic of study in dermatological therapy is
the creation of sophisticated drug

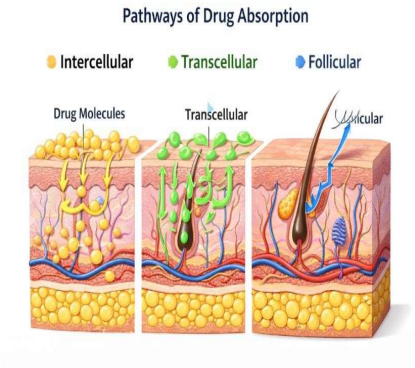


Fig2: Medicament absorption pathways through skin that demonstrate intercellular, transcellular, and follicular routes. *Created using AI tools*

4. Overcoming Solubility Limitation

Different Permeation Enhancers for Drug Administration Via the Skin Substances that momentarily alter the skin's barrier qualities are known as penetration enhancers. This allows for greater absorption of active chemicals without permanently harming the skin. Industries can significantly increase the effectiveness of their formulations by using these enhancers, which guarantee that enough active ingredients enter the circulation or skin at the desired depth to have the desired therapeutic effect. To provide context for terminology that the reader might not be familiar with,

Table 2: presents a summary of technologies that improve penetration.

Technological	Explanation	Method/Benefits	References
Enhancement of Permeation	Molecules that make the stratum corneum more permeable	Perform by altering: (i) Lipids (lipid extraction or damage) (ii) Proteins (altering keratin or corneodesmosome conformation)	[28]

		(iii) Drug partitioning into the stratum corneum is inexpensive, scalable, and simple to incorporate into formulations; it may also boost drug thermodynamic activity.	
Hydrogels	Highly pliable three-dimensional polymeric matrices that can transport medications	Strong biocompatibility, a constant humidity environment, and tissue-like characteristics the potential for stimuli-responsiveness and regulated release	[29]
Nanotechnology	Systems of nanoparticles intended to transport and contain medications	Drug encapsulation enables regulated release and protection against degradation; it can accommodate various sources (lipid-based, cell-based, inorganic, polymeric); it may accept many drugs for combination treatment and attach targeting ligands for improved specificity. It is simple to integrate into different systems or formulations.	[30]

anostructures	Pharmaceutical drug-based nanocrystals (100–1000 nm)	Higher saturation solubility and a quicker rate of dissolution; large drug loading (up to 100%) with little stabilizer Improved oral absorption and bioavailability consistency Increased patient compliance with fewer dosages	[31]
Nanoemulsions (1–100 nm) and Microemulsions (100–400 µm)	Colloidal systems made of water and oil	Subcategories: (i) Oil-in-water, or O/W; ii) Water-in-oil, or W/O Both hydrophilic (W/O) and hydrophobic (O/W) pharmaceuticals may become more soluble thanks to the internal area, quicker absorption, and improved dissolution and bioavailability compared to traditional emulsions. Microemulsions exhibit greater stability, but nanoemulsions sometimes need surfactants to stabilize.	[31]

5. Enhancement of Solubility and Stability by Nanocarriers

The limited water solubility of many dermatologically active chemicals is one of the main drawbacks of traditional topical preparations. Vitamins that are lipophilic, include A, D, E, and K as well as bioactive

agents like retinoic acid and linoleic acid, exhibit limited solubility in water-based formulations. As a result, these types of compounds are traditionally formulated in oil-based formulations, which may also result in decreased patient compliance owing to their greasiness and poor aesthetic acceptability. This restriction is made possible by the two separate sections of liposomes and other nanocarrier formulations: the aqueous part contains water loving molecules, while the lipophilic part contains lipophilic and amphiphilic compounds. This overcomes solubility constraints and improves patient compliance and acceptability by enabling the dispersion of lipophilic substances in aqueous formulations [32].

Besides solubilization, nanocarriers also provide better physicochemical stability for labile bioactive compounds. Antioxidants and vitamins are generally labile to oxidation, photo-oxidation, and environmental factors. Nanocarriers in the form of liposomes provide better protection for these types of labile compounds from external factors such as ultraviolet radiation and oxygen [33]. For instance, vitamin C, which is highly labile to degradation in ultraviolet radiation and storage conditions, also demonstrates better stability and retains its antioxidant activity in nanoliposomal formulations [33]. Thus, nanocarrier-based formulations provide better dermal penetration and also address other critical formulation issues.

6. Novel Medicament Transport Systems

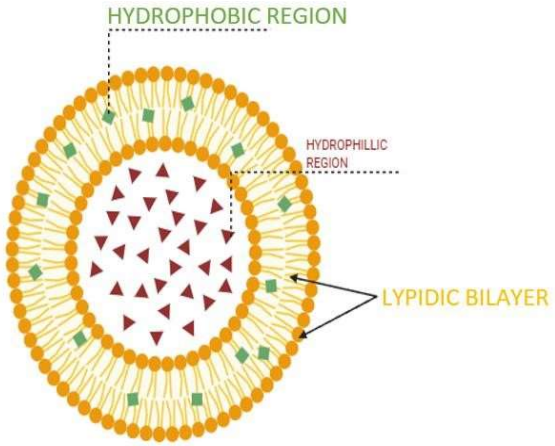
Creation and applied Nano based science is study of materials a nanolevel that have physical and chemical differ in characteristics from those of their equivalents in bulk. This is to main internal structural changes, these novel materials react differently in biological systems and have a greater surface area [34]. By creating nanoproducts, Currently, product innovation is supported by the incorporation of medicaments into novel transport systems that are nanoscale.

Nanoproducts used to provide APIs in skin, like as nanopharmaceuticals and nanocosmeceuticals,[35] had already ways to be successful in treating various skin injuries, including skin carcinoma and atopic dermatitis skin inflamation,[36] burns[37], and UV protection radiation [38-39]. One effective example is the creation of nanoproducts from sunscreens. This method was reported help lessen the adverse effects of chemical filters like benzophenone-3 and UV purifiers that are inorganic in nature like zinc oxide (ZnO) and titanium dioxide (TiO2) [40-41]. Improving consumer security. Additionally, it has been showed adding Because nanoparticles may filter sunlight on their own, sunscreen and solid nanoparticles can work in concert [42]. In recent years, a variety of nanobased particles used to add sunscreens, vitamins, and antioxidants to skin care products. Forty years ago, the first cosmetics developed using nanotechnology were moisturizing lotions containing liposomes [43]. Since then, a number of additional Solid lipid nanoparticles (SLN), nanoemulsions, and nanostructured lipid carriers examples of biocompatible nanomaterials that have been proposed. (NLC), which are particularly interesting because of their lipid content. Additionally, lipid nanoparticles enhance skin hydration by creating a thin lipidic coating on the skin's surface that keeps moisture there for a longer period of time [44,45]. Cosmetics had a significant growth in marketing during the 20th century, increasing their appeal as everyday products [46, 47]. Many cosmeceutical formulas for use on the skin, body, and hair are being proposed to address a variety of issues, including photoaging, wrinkles, hyperpigmentation, and hair damage and/or loss [48]. Over the past few decades, the personal care product industry has experienced the most growth in cosmeceuticals, particularly nanocosmeceuticals. The regulated release of APIs with site-specific targeting and occlusive qualities with improved hydration, which help to boost skin penetration to the API, are the primary benefits of nanocosmeceuticals [49]. Because of these benefits, nanocosmeceuticals should be controlled and put through clinical studies, which is an essential step in ensuring the safety of consumers [50]. Both in vitro and in vivo, nanoparticles can be extremely reactive, increasing the likelihood of harmful events [51,52]. Cosmeceuticals used for a various purpose, such as improving skin texture by promoting the formation of collagen, or as anti-aging formulations because their antioxidants protect the structure of keratin and neutralize reactive oxygen species, resulting in improved skin [53,54]. By creating a protective layer, antiaging nano cosmeceuticals marketed as personal care products (such as shampoos, conditioners, hair length boosters) can extend their contact time with the scalp and follicles. These products include gold nanoparticles, niosomes, microemulsions, liposomes, fullerenes, nanotubes, and poly (lactic-co-glycolic acid

(PLGA) nanospheres) [55]. Additionally, lipsticks, lip balms, lip glosses, and lip volumizers contain nanocosmeceuticals. improving the lips' suppleness, stopping transepidermal water loss, and preserving the required styling effect (such a color) for an extended amount of time are the objectives of employing nanoparticles in lip care products. Lip volumizers with nanocosmeceuticals depends on liposomes, which fill in the wrinkles in the lip contour and keep the lips moisturized and defined. In the area of nail care, nanocosmeceuticals have also shown promise. Nail polishers improve toughness, dry more quickly than traditional products, are more resilient and long-lasting, and are more stretchy, application become simple [55].

6.1. Liposomes

Liposomes are spherical vesicular structures with an water loving core encircled by one or more phospholipid bilayers. When amphiphilic phospholipids are distributed in an aquatic environment, they spontaneously form. Resulting in bilayer structures that mimic biological membranes. Depending on their preparation method, liposomes varies in range size from approximately 15 nm to several micrometer [56]. Liposomes may encapsulate both hydrophilic and lipophilic active substances because of their unique bilayer structure. Lipophilic molecules are entrenched in the bilayer membrane, whereas hydrophilic molecules are confined in the inner water core. Liposomes are versatile carriers in dermatopharmaceutical and cosmetic applications because they may entrap both hydrophilic and lipophilic compounds [57]. There are several ways in which the use of



liposomes in topical administration systems enhances the drug's skin deposition. The vesicles may fuse with the lipid components of the stratum corneum, disorganize the ordered framework of surface layer improve the partitioning of drug into deeper layers of skin. The phospholipids in the liposomes may also enhance whydration of skin, thus improving the permeation of the drug. The drug's penetration is influenced by the lipid content and vesicle size [58]. Liposomes have been thoroughly investigated as topical delivery methods for retinoids, anti-aging, antioxidants, and antiacne medications. When liposomes are used to treat acne, the drug's topical distribution is increased while its absorption and body irritation are reduced. By boosting the skin penetration of active ingredients like vitamins and peptides, the use of liposomes in anti-aging enhances their bioavailability and therapeutic efficacy [57–58].

- **Classification of Liposomal Vesicles**

Liposomes are commonly classified by vesicle size, lamellae count, and manufacturing method [59]. Depending on how many phospholipid bilayers surround the aqueous core, liposomes can be classified as unilamellar or multilamellar. A single phospholipid bilayer makes up unilamellar vesicles (ULVs), which are further classified into small unilamellar vesicles (SUVs) with a diameter of less than 100 nm and large unilamellar vesicles (LUVs) with a diameter of more than 100 nm [60]. Skin penetration, encapsulation performance, and drug release properties are all significantly impacted by vesicle size. Multilamellar vesicles (MLVs) are made up of several concentric phospholipid bilayers layered in an onion-like pattern. MLVs provide a superior drug loading capacity but often have larger particle sizes. However, multivesicular vesicles (MVVs), which enable segregated drug encapsulation, are composed of several non-concentric internal vesicles contained in a single outer bilayer [61].

- **Advanced Liposomal Systems for Dermatological Applications**

Many modified liposomal systems have been created to increase stability and skin penetration. Hydrophilic polymers like polyethylene glycol (PEG) change the surface of stealth liposomes, increasing stability and decreasing aggregation. Archaeosomes are liposomal vesicles composed of ether lipids produced from Archaea. When compared to traditional phospholipid liposomes, these vesicles show enhanced thermal stability, oxidation resistance, and structural integrity [62].

Fig 3: "Structure of a liposome and drug encapsulation

site"

6.2. Transferosomes

Transfersomes are self-optimized, ultra-deformable aggregates that contain a combination of biocompatible membrane softeners and lipids for transdermal administration. The Transfersome is different from a liposome in that it has an artificial membrane that is softer, more flexible, and more customizable. Transfersomes enter the stratum corneum either intracellularly or transcellularly by creating a "osmotic gradient" as a result of water evaporation. In order to provide proper hydration, a transferosome vesicle put to an open biological surface, like non-occluded skin, tends to break through its barrier and move into the deeper, water-rich layers [63].

6.3. Niosomes

Drug targeting is the ability to direct a medicinal ingredient at the intended site of action with little or no contact with adjacent tissue. Restricted substance. The goal of the delivery system is to achieve a desired drug release profile over an extended duration. Niosomes are one method of obtaining a controlled release system. Hydrated surfactant monomers self-assemble to create niosomes, which are vesicles of non-ionic surfactant with a small lamellar bilayer structure. Niosomes' multilamellar or unilamellar structure is created by combining diethyl ether, cholesterol, and non-ionic surfactant with subsequent hydration in aqueous media [64]. Niosomes are tiny, lamellar structures that range in size from 10 to 1000 nm. The niosome is made up of biocompatible, biodegradable, and non-immunogenic surfactants. Niosomes are more cost-effective than liposomes and have a higher chemical stability of surfactants than phospholipids, which are readily hydrolyzed because of the ester link [64]. Niosomes are tiny vesicles made by dialkyl or alkyl polyglycerol ether non-ionic surfactants. Niosomes are highly beneficial in cosmetics and skin care since they can enhance the product's efficacy and penetration, boosts the bioavailability of components that are poorly absorbed, and improves medication stability [65].

6.4. Novasomes

Polyoxyethylene fatty acids (as monoester), free fatty acids, and cholesterol combine to form novasomes. The diameter range of novasomes is between 0.1 and 1 micron. These systems have a big amphipathic core with 80–85% drug loading and two to seven bilayers. Furthermore, novasome surfaces can have a neutral, positive, or negative charge. Both hydrophilic and hydrophobic pharmacological compounds can be enclosed by novasomes. Additionally, it is feasible for medications to enter bilayers and so stop medications from having incompatible surface charge characteristics. Particularly for the cosmetic, these systems are capable of delivering large quantities of materials. Numerous vaccines against bacterial and viral illnesses, including the smallpox vaccine, have been patented based on novasomes. Novasomes are non-phospholipid oligolamellar lipid vesicles that range in size from 0.1 to 1.0 microns. They are a type of liposome or modified niosome that are produced by mixing the monoester, cholesterol, and free fatty acids of polyoxyethylene fatty acids. Their ability to cleave to skin or hair shafts makes them even more superior for usage in cosmetic preparations. Additionally, this improves the efficacy and texture of these cosmetics and permits continuous release [65].

6.5. Marinosomes

These types come from marine lipid extracts that are high in omega-3 polyunsaturated fatty acids, including eicosapentaenoic acid and docosahexaenoic acid. They are transformed into their anti-inflammatory and antiproliferative metabolites by the skin's epidermal enzymes, which help treat a number of inflammatory skin conditions. Toxicity testing have shown that this family of liposomes is safe for skin and eye contact[66].

6.6. Ultrasomes

Endonuclease from Micrococcus luteus is one of the DNA-repair enzymes found inside ultrasomes, which are microscopic liposomal systems.These vesicles aid in repairing UV-induced DNA damage in skin cells.They help regulate the release of cytokines and enable enzymes to repair damaged DNA.This can lessen sun-induced indications of aging and shield the skin from harm.Ultrasomes may help protect skin from UV damage and maintain its health [67].

6.7. Photosomes

Typically generated from marine microorganisms like Anacystis nidulans, photosomes are vesicular carriers that contain photolyase enzymes. These systems are mostly employed in photoprotective formulations to aid in the repair of UV-induced DNA damage. In order to limit immunosuppression brought on by UV exposure and lessen photo-induced cellular damage, they are commonly added to sunscreen and after-sun treatments [68].

6.8. Ethosomes

Water, phospholipids, and a somewhat high ethanol content (usually 20–50%) make up ethosomes, which are soft, flexible multilamellar vesicles. Ethosomes' higher ethanol concentration sets them apart from traditional liposomes and is essential for improving skin
penetration [69]. Ethanol increases membrane fluidity and decreases barrier resistance by upsetting the stratum corneum's orderly lipid structure. Ethanol enhances vesicle deformability and promotes deeper penetration of encapsulated active substances into the dermal and epidermal layers when added to vesicular systems. Ethosomes exhibit greater transdermal transport capability and improved skin deposition of medicinal and cosmetic substances as compared to conventional liposomes [70].

6.9. Sphingosomes

Ceramides or structurally related sphingolipids make up the majority of sphingosomes, which are liposomal vesicles. Sphingosomes are especially helpful in formulations intended to restore barrier integrity in dehydrated or injured skin because ceramides are crucial parts of the skin barrier. Sphingosomes are useful in dermatological and anti-aging formulations because they promote skin hydration and barrier repair by restoring lipid deficits within the stratum corneum [71].

6.10. Nanosomes

Nanosomes are ultra-small liposomal vesicles with nanometer-scale particle sizes that are made of highly pure phosphatidylcholine [72]. Nanosomes may have better skin deposition and contact with cutaneous layers because of their smaller size. They are commonly included to anti-aging and skin-rejuvenation formulations to enhance the overall appearance of the skin and help distribute active substances [73].

6.11. Invasomes

Modified liposomal vesicles are called invasomes. Include phospholipids, trace quantities of ethanol, and terpenes mixtures. Together, terpenes and ethanol enhance vesicle deformability and skin penetration. Terpenes increase penetration by altering the lipid packing of the surface layer, while ethanol enhances membrane fluidity. This synergistic effect results in improved dermal administration and greater cutaneous dispersion of encapsulated medicines [74].

Fig4: Nanocarrier-based topical and transdermal drug delivery devices are classified.

- **Mechanisms of Enhanced Skin Penetration by Nanocarriers**

One of the many benefits of transdermal systems is the capability to hold and regulate penetration of medicaments of small shelf life, necessitate regular administration. Proteins, peptides, and oligonucleotides—the recently developed "biotechnology" drugs—are especially vulnerable to this issue. Despite being extremely effective and selective, these treatments cannot be administered by traditional means due to their highly labile nature [75]. Furthermore, the transdermal administration of these medications is severely restricted because they are often big molecules with polar and/or charged groups. Nonetheless, physical improvement technologies (explained below) are attempting to directly address the issues raised and provide innovative and compelling solutions to transdermal application problems [76]. substances that have the ability to alter the skin's barrier in a reversible manner are one of the often used methods. This allows low permeability medication candidates to enter the membrane and systemic circulation. Many other substances have been observed to increase the permeability of the SC. These molecules' structural diversity makes it impossible to develop a single mechanistic theory, but it is still a topic of discussion that is strongly supported by the substantial penetration-enhancer described in the literature. On the other hand, some compounds with a changeable mode of action have been observed to have mechanistic information. For instance, alcohols like ethanol enhance penetration by extracting and

solubilizing the lipid content of SC, whereas fatty acids like oleic acid are engaged to cause phase separation and lipid fluidization within the membrane [76,77].

6.12. Solid Lipid Nanoparticles (SLNs)

Drugs of BCS Class II and IV are employed in SLNs, which are colloidal carrier systems made of a solid core of a high melting point lipid covered in an aqueous surfactant. Unlike other solid lipids, SLNs replace liquid lipids in colloidal carriers. Lipid pellets for the administration of oral drugs, such as Mucosolvan® retard capsules, are a well-known example of the utilization of solid lipid as a matrix material. Triglycerides, partial glycerides, fatty acids, hard fats, and waxes are all included under the general term "lipid." Because SLN's lipid matrix is made of physiological lipids, there is less chance of both immediate and long-term harm. It has been shown that employing solid lipid instead of liquid lipid promotes control over the release kinetics of encapsulated compounds and enhances the stability of included chemically-sensitive lipophilic components. These potentially beneficial effects are caused by a variety of physicochemical characteristics related to the physical state of the lipid phase. First, because reactive chemicals are less mobile in solid matrices than in liquid ones, the rate of chemical breakdown processes may be slowed. Second, by regulating the microphase separations of the active substances and carrier lipid within individual liquid particles, it is possible to prevent the accumulation of active chemicals close to the surface of lipid particles, where chemical breakdown reactions usually occur. Thirdly, it has been shown that adding bioactive substances that are poorly absorbed to solid lipid nanoparticles improves their absorption. Numerous studies have shown that employing a solid matrix instead of a liquid matrix can slow down lipid breakdown and allow for a longer-lasting release of the encapsulated component. Another crucial element of SLNs is aqueous surfactants. They are mostly used as emulsifiers to make o/w type emulsions and stabilizers for the dispersion of SLNs; the route of administration largely dictates their choice [79].

Composition

SLNs generally consist of:

- Solid lipids (e.g., triglycerides, fatty acids, waxes)
- Surfactants or emulsifiers (to stabilize the dispersion)
- Water (continuous phase)
- Surfactants mainly act as emulsifying and stabilizing agents in oil-in-water (o/w) dispersions, and their selection depends on the intended route of administration [79].

Preparation Methods

SLNs are primarily prepared by:

- Hot and cold high-pressure homogenization techniques
- Ultrasonication / high-speed homogenization
- Emulsification or solvent evaporation techniques
- Methods based on microemulsions [80]

The most popular method among them is high-pressure homogenization. The drug-loaded lipid melt is emulsified in a heated aqueous phase and homogenized above the lipid melting point in hot homogenization. The drug-lipid combination is solidified, pulverized, and then homogenized below melting temperature to reduce thermal degradation [81,82]. Because of their nanoscale size and biocompatible lipid matrix, solid lipid nanoparticles have a number of benefits in dermatological and cosmetic applications. By reducing the possibility of systemic toxicity and cutaneous irritation, physiological lipids enhance patient safety [83]. SLNs provide controlled and extended drug release due to their solid lipid core, which limits drug diffusion and improves therapeutic effectiveness. They stop the degradation of chemically sensitive active ingredients by limiting exposure to external environmental conditions [83].

Table 3: Comparative analysis of nanocarriers

Parameter	Liposomes	Solid Lipid Nanoparticles (SLN)	Nanoemulsions
Permeability	Moderate – Integrate into skin via phospholipid bilayers.	Low – Solid core limits deep skin penetration.	High – Tiny droplet size improves skin absorption.

Stability	Low – Prone to oxidation and breakdown of phospholipids.	High – Solid lipid matrix enhances physical and chemical stability.	Medium – Stabilized with surfactants; moderate physical stability.
Bioavailability	High – Mimics cell membranes for effective active delivery.	Moderate – Provides sustained release, though with limited permeability.	High – Excellent absorption due to nanometric size and low surface tension.
Scalability & Cost	Low – Costly and requires complex technology.	Moderate – Easier and more cost-effective production.	High – Economical with simpler formulation methods.
Cosmetic Use	Enhances delivery of Vitamin C and prevents degradation.	Suitable for Coenzyme Q10 for improved antioxidant stability.	Frequently used for Retinol, promoting deep delivery and reducing irritation.

7. Evaluation Parameters

7.1. *In vitro* and *Ex vivo* Skin Permeation Studies

Each KM mouse's dorsal area was shaved using a hair trimmer and depilatory cream prior to the experiment. ROLs were administered to the rear skin of the mice the following day (at a dose of about 0.1 g/cm2). Blood samples were taken retro-orbitally and separated the plasma by centrifuging it for ten minutes at 3000 rpm, which was then stored at -80 °C, following the treatment for 0, 1, 2, 4, and 24 hours. Pentobarbital (180 mg/kg) was then injected intraperitoneally to put the mice to sleep. Surgical scissors were used to cut dorsal skin samples, which were then kept at -20 °C [84].
Each SD rat's back was shaved using a hair trimmer and hair removal cream prior to the experiment. Rats' back skin was treated with ROLs the next day (the administration area was approximately 3 x 3 cm2, and the dose was approximately 0.1 g/cm2). At 0, 1, 2, 4, and 24
hours following administration, blood samples were taken. After centrifuging the blood for ten minutes at 3000 rpm, the plasma was extracted and kept at -80 °C for future use [85].

7.2. Particle Size Analysis, Zeta Potential, and Encapsulation Efficiency

The proportion of a material that is effectively contained inside the system in comparison to the entire quantity of the material that was first used during the preparation procedure is known as the encapsulation efficiency (EE%) of a liposome. Centrifugation at 20,000 × g for 60 minutes was used to separate the loaded liposome particles from the free phenolic extract to evaluate the EE of specific phenolic compounds in OBB in an indirect manner. HPLC used to identify and measure the free phenolic compounds in the supernatants, as explained in the section on "In vitro bioactive potential" [86]. A Zetasizer Pro (Malvern Instruments Ltd., Worcestershire, UK) was used to measure the liposomes' Particle size distribution by intensity, zeta potential, and polydispersity index at predefined intervals over a 20-day storage period in a refrigerator at a regulated temperature of 7 °C (Liebherr-International AG, Bulle, Switzerland). To track changes in these parameters and evaluate the formulations' stability over time, measurements were taken on days 0, 1, 3, 6, 10, 15, and 20. Prior to analysis, 100 µL of each sample was diluted in 10 mL of ultrapure water, homogenized on a stirring plate at 400 rpm, and left to stand for five minutes [87]. Encapsulation efficiency is the proportion of the active substance that is successfully contained within the liposomal vesicles. It is calculated by separating the free medicine from the encapsulated medicament using techniques like centrifugation, dialysis, or ultrafiltration, followed by quantitative analysis [88,89].

8. Applications of liposomes in various skin treating formulation

8.1. Liposomes in Acne Therapy

Acne, which is appropriately characterized by its prolonged appearance, sequential advancement with intervals of remission and return, negative consequences on the patient's social and psychological well-being as well as capacity to integrate into their community, is included in the WHO's list of chronic diseases.

Over 85% of teenagers have acne, according to WHO data, but it can also affect adults and, in rare cases, babies. This makes acne extremely important from a medical and social standpoint. Acne-related physical changes may have a detrimental impact on psychology, life quality, and self-esteem. In order to obtain a delayed pharmacological preparation, an emulsion containing encapsulated microcapsules could be a future alternative [92]. In contrast to other colloidal
transport systems and controlled release of active principles, liposomal systems show remarkable adaptability in terms of changing their structural and functional characteristics to suit therapeutic objectives. The earliest type of liposomes employed in the pharmaceutical sector are called conventional liposomes. They are often derived from cholesterol and/or phospholipids. Despite controlling factors including size, quantity of lipid bilayers, lipid content, and fluidity; the production of these liposomes exhibits a relatively low blood circulation and is quickly removed by macrophages. Long-lasting liposomes are able to stay in the bloodstream for an extended amount of time. It is produced by covalently bonding linear hydrophilic polymer chains (PEG) to the outside of traditional liposomes. The resulting liposomes have outstanding solubility in aqueous conditions and are also referred to as sterically stabilized liposomes. Some cutaneous adverse reactions necessitate long-term topical or systemic therapy, like antibiotics, steroids, or repair creams [92,93]. Like other common treatments, anti-inflammatory drugs like ibuprofen or other cyclo-oxygenase inhibitors can occasionally result in unexpected side responses [94,95].

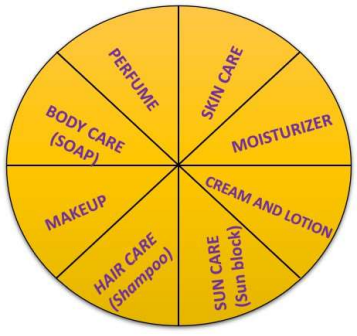


Fig 5: Represents the different formulation in novel basis

Sebum suppressant, keratolytic, antibiotic, and hormonal treatments are among the acne remedies. Long-term use of antibiotics including narrow-spectrum erythromycin, minocycline, and broad-spectrum tetracycline leads to the development of resistance against microorganisms that cause acne. To preserve the effectiveness of antibiotics, Antibacterial medications with a broad spectrum of action that work equally well against both susceptible and resistant pathogen strains must be used concurrently [96]. The Minimum Inhibitory Concentration (MIC) value for both Tetracycline and tretinoin-encapsulated liposomes based ondipalmitoylphosphatidylcholine (DPPC) were reported to have an antibacterial activity of
0.016 mcg/ml against strains of Staphylococcus epidermidis ATCC 35984 and Staphylococcus aureus ATCC 29213. For S. aureus and S. epidermidis, the MIC values for a simple medication combination solution were found to be 0.063 mcg/mL and 0.125 mcg/mL, respectively. This showed that the liposome formulation outperformed the standard medication combination solution at a lower concentration [97]. Based on the Blackheads (open comedones) were safely removed in 33.3% of patients treated with liposomes, but only 8.33% of patients treated with plain clindamycin solution, according to anti-comedogenic efficacy testing of 1% plain clindamycin solution and 1% clindamycin liposomes. exhibited improvement. Papules, pustules, and closed comedones all responded well to liposomal clindamycin. The acne lesion decreased by 42.9%, 48.3%, and 62.8%, respectively, in another clinical investigation that used the same drug's liposomal lotion, non-liposomal lotion, and traditional solution.The study demonstrated that the liposomal formulation was more effective [98]. For *P. acnes*, azelaic acid ethosomes were found to have a Minimum Bactericidal Concentration (MBC) of 250 mcg/ml. The commercial cream, Zelface cream, was found to have MIC and MBC values of 250 mcg/ml and 500 mcg/ml, respectively. It was demonstrated that the commercial cream was less effective than the azelaic acid ethosomes [99].

Table 4: An overview of anti-acne medications, including their properties, adverse effects, method of action, and stability concerns.

Actives	Mechanism	Side effects	Physicochemical characteristics	Stability	References

Clindamycin	efficient against P. acnes and bacteriostatic. inhibitors of leukocyte chemotaxis and lipase synthesis.	Skin rashes.	Poor aqueous solubility. Low logP value	amine and thioglycoside hydrolysis-induced degradation at pH 4.	100
Tretinoin, isotretinoin	suppression of excessive cornification, metalloproteinase enzyme normalization, and Toll-like receptor (TLR-2) inhibition.	Skin irritation, burning.	low solubility in water. Compared to its geometric isomer, isotretinoin, tretinoin penetrates human skin more quickly.	Photodegradation, affected by oxygen, light, acids.	102,103

8.2. Melasma & Pigmentation

Asia has the highest percentage of people who spend money on skin whitening, at about 15%. When exposed to extremely powerful UV-B and less energetic UV-A, melanocytes in the skin generate melanin. Excessive melanin synthesis is the source of skin conditions such sun lentigines, melasma, freckle cancer, and post-inflammatory strong pigmentation.Tyrosinase is a crucial component in the manufacture of melanin, while skin-lightening agents lower melanin levels [103]. Because of their positively charged surface, Kojic acid-encapsulated liposomes N-[(2-hydroxy-3-trimethylammonium) propyl] chitosan chloride (HTCC) coating shown improved fusibility and penetration with the membranes of B16-F10 melanoma cells and L929 fibroblast cells. In melanoma cell lines B-16-F10, HTCC-coated liposomes showed more melanin production inhibitory action than uncoated liposomes[104].

Compared to conventional liposomes, BounsphereTM, a flexible liposome containing niacinamide (NA), had the maximum skin permeability and improved skin whitening. Human participants with melasma were used to test BounsphereTM's skin-whitening effectiveness. In comparison to the M-values prior to NA treatment, The skin's melanin content (M-values) increased significantly by 9.96% and 16.80%, respectively, after 4 and 8 weeks, with very little likelihood for discomfort [105,106].

8.3. Dryness & Wrinkles (Liposomes as Moisturizer)

The skin on the face is more hydrated and contains Natural Moisturizing Factors (NMF). Water alone cannot keep the skin sufficiently elastic if NMF is lacking in the horny layer. The moisturizers preserve the barrier function, prevent skin damage, and restore skin elasticity [106]. Trans-Epidermal Water Loss (TEWL) is reduced because The horny layer's phospholipids from liposome vesicles interact with creatinine to strengthen the skin's barrier.57. With the help of their lipidic additions, the liposome vesicles can increase skin hydration, delaying the aging process [105]. A 28-day study on healthy human subjects revealed that a liposomal gel reduced TEWL and increased skin moisture. During the first seven
days of the research, there was a 6.3% increase in skin moisture. However, following the Skin moisture levels rose by 14.1%, 30.3%, and 33.5%, respectively, during the second, third, and fourth weeks of gel application, with low erythemal index. Additionally, by raising the pH of the skin, it strengthens resistance to bacterial infections [105].

8.4. Barrier Repair (Liposomes in Sunscreen)

Sunburn, actinic keratosis, melanocytic hyperplasia, solar lentigines, immune system suppression, pre-carcinoma, and skin lesions, mostly on exposed skin,are all consequences of prolonged exposure to high energy UV light.63. Although some traditional formulations have been known to be absorbed systemically upon topical administration, the sunscreens are not intended for systemic absorption. By keeping these candidates in the skin's horny layer, encapsulating them in liposomes increases SPF and inhibits systemic absorption. The horny

layer contained 22.64 ± 7.55 mcg/cm2 of Octyl p-methoxycinnamate (OMC) enclosed in liposomes. It shows that there is little systemic absorption of OMC. On the other hand, 14.57 ± 2.30 mcg/cm2 was the figure found for the conventional formulation [105].

The protective effect of the liposomal suspension with SPF 50+, 30, 25, and 15 at the allowed concentration of 2 mg/cm2 was tested on Fitzpatrick skin type II adult skin. When the skin was exposed to these conditions, the SPF 50+ of the liposomal sunscreen formulation was demonstrated to have drastically dropped to 97% in ordinary water, 96% in salt water, and 99% after perspiration. But another liposomal sunscreen's SPF 30 dropped to 97% in regular water, 96% in saltwater, and 99% after sweating. Even though the SPF of the liposomal sunscreen formulation was 25, it dropped to 90% in regular water, 83% in salt water, and 91% after perspiration.
The SPF-15 liposomal sunscreen formulation's SPF dropped to 95% after perspiration, 96% in salt water, and 96% in ordinary water. The study found that SPF 50+ demonstrated greater resistance than SPF 15, although liposomal sunscreen with SPF 15 demonstrated greater resistance against regular water, salt water, and perspiration than the in-house control with SPF 15 [106].

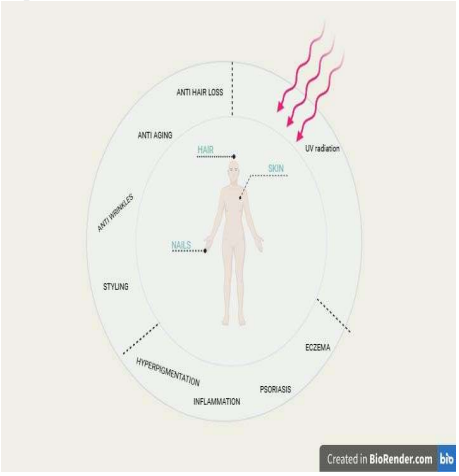


Fig 5: Advanced topical drug delivery systems are targeted towards treating multiple dermatological and cosmetic skin conditions. Nanocarrier-based formulations are mainly focused towards skin, hair and nail disorders such as hyperpigmentation, inflammation, psoriasis, eczema, wrinkles, skin ageing and UV induced skin disorders.

9. Conclusion

The liposomal and gel formulations are a recent addition to dermatologic therapy. They have definite advantages over conventional topical vehicles owing to their ability to promote cutaneous penetration, modify release rates, and improve chemical stability and thus become suitable vehicles for many different skin disorders, such as psoriasis, atopic dermatitis, contact dermatitis, and actinic keratoses. Among them, liposomal vehicles are helpful since they are similar in structure to biological membranes, are highly biocompatible, penetrate the skin more deeply, can be used to encapsulate hydrophilic and lipophilic drugs, and can limit unintended systemic effects, together with providing localized therapeutic action of application, which helps to decrease the toxic effects. Because of this property, they are widely used in the treatment of microbial infections, inflammation and various types of skin cancer. Modification of polysaccharide-nanoparticles surface, such as PEGylation and ligand functionalization could improve their bioavailability and specificity towards customized and advanced dermatological applications. Despite their advantages, several barriers such as formulation, physical and chemical stability, and large-scale production limit the potential use of polysaccharide-nanoparticles for dermatological formulations, which require further optimization of this nanocarrier. Gel formulations are also used as controlled drug delivery formulations and as moisturizers. Gel formulations have been used for the treatment of open wounds and burns as well as dermatological diseases including chronic inflammatory skin diseases such as psoriasis and eczema, where the moisturizing and bioadhesion properties can increase patient compliance.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No humans and animals were used for studies that are the basis of this research.

AVAILABILITY OF DATA AND MATERIALS

The authors confirm that the data and supportive information are available within the article.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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