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Review Article

Topical Drug Innovation: Past, Present And Future Prospects

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ABSTRACT

Topical delivery is the application of a drug-containing formulation to the skin, mostly to treat cutaneous illnesses such as acne or the cutaneous manifestations of a universal disease such as psoriasis. Topical drug delivery has numerous advantages, including non-invasive delivery, bypass of first pass metabolism, and increased duration of action, reduced dose frequency, stable levels of medication in the plasma, decreased drug toxicity /adverse effects, and enhanced patient compliance. Skin is the largest organ in the human body and the most complex barrier isolating the biological system from the outside environment. Historically, topical therapy was the earliest method of delivering pharmaceuticals to humans in the form of ointments and potions. Our understanding of the anatomy and physiology oAf the skin has increased over the years, allowing us to design technologies that can effectively and quantitatively carry solutes past this barrier to particular target areas in the skin and beyond. Currently, several conventional and novel topical dose formulations are employed to treat skin problems. Also, many physical approaches have been investigated to improve medication penetration in or through the skin. The current review focuses on the evolution of medication delivery via topical application from ancient times to the present, as well as potential future advancements targeted at enhancing topical delivery.

INTRODUCTION

Drugs have been administered to the human body by a variety of ways during the past few decades, including oral, sublingual, rectal, parental, topical, and inhalation. Topical delivery is the process of applying a medication with a formulation directly onto the skin to treat conditions like acne or the skin-related symptoms of a general illness like psoriasis. The goal is to limit the drug's pharmacological or other effects to the skin's surface or inside the skin. [1] Topical formulations, which administer a medicine to a specific spot, are arguably among the most difficult products to design. In order to accept

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several substances that may have distinct, if not incompatible, physicochemical properties, an effective topical formulation must offer a stable chemical environment in an appropriate dispensing container. For a topical formulation to achieve sufficient skin absorption, it must interact with the skin environment after application, which might affect the pace of the compounds' release. [2] The skin makes up around 16% of an adult's total body weight, making it the biggest organ in the body. [3] As a result, it contributes significantly to the preservation of homeostasis and serves as a biological, chemical, and physical barrier against environmental dangers that are external. [4] Although some dermatological diseases can be effectively treated with traditional topical and transdermal formulations like creams and ointments, there are still limitations and drawbacks with regard to bioavailability and targeted drug delivery. [5] As a result, technologies to improve drug permeation and increase drug delivery are being developed and advanced. Due to this, innovative topical and transdermal drug delivery systems, like nano-based technologies, have been developed. These systems greatly enhance dermatotherapy and address some formulation issues, like drug solubility. [6] They also avoid some of the issues that arise with oral drug delivery, such as the hepatic first-pass effect, longer dosing intervals, and patient compliance. [7] The use of chemical enhancers, bio-polymers (such as sodium hyaluronate), liposomes, particulate carriers (microspheres and lipid nanoparticles), topical sprays and foams, occlusion (via dressings and patches), topical peels, temperature (heat), iontophoresis, and ultrasound are some of the current and emerging methods for optimizing the topical delivery of dermatological agents (small and large molecules). [8] The potential benefits of these delivery methods over traditional systems (creams, lotions, ointments, and pastes) include increased efficacy and tolerability, improved patient compliance (including dermatology life quality), and the ability to meet additional unmet needs in the topical dermatology market. [9] This review focuses on the past, present and future prospective of the topical drug delivery system.

Skin: Anatomy and physiology

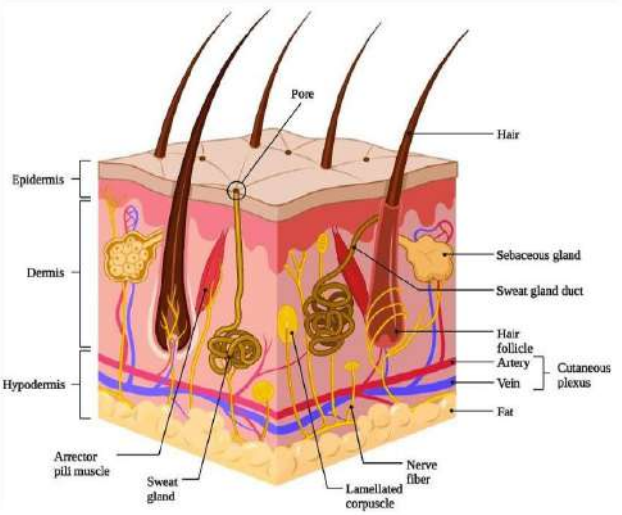


Figure 1: Anatomy and physiology of skin

The skin, which has a surface area of 1.5 to 2 m2, is the largest organ in the human body and serves as the most intricate barrier separating the biological system from the outside world. [10] Skin is biggest external defence system. Skin covers the outside of the body but has other functions beside the defence mechanism. Temperature of skin varies in a range of 30 to 40 °C degree depending on the environmental conditions. [11] It is a three-layered structure made up of the innermost subcutaneous fatty tissue (mechanical cushion), the 250 µm thick dermis (heat barrier), and the 50–150 µm thick outer epidermis (biological barrier). The epidermal region is made up of the stratum corneum's superficial layers, whose distinct cellular architecture acts as a barrier to the passage of molecules larger than 500 Da, offering physical defense against microbial invasion. [10]

Epidermis:

The entire outer surface of the body is covered in the epidermis; a continuously renewing squamous epithelium composed primarily of squamous cells and live cells or cells of the squamous layer (existing epidermis), corneal layer dead cells, referred to as the stratum corneum. [12]

Viable epidermis is further divided into four unique layers:

- The stratum lucidum
- The stratum granulosum
- The stratum spinosum
- The stratum basale [13]

Stratum corneum; The stratum corneum, as it is also called, is the outermost layer of skin. It is a barrier to flow restriction that limits the flow of substances in and out. The stratum corneum's barrier properties are largely influenced by its composition, which consists of 515% lipid, 510% ondansetron, and 7580% protein on a dry weight basis. When completely hydrated, the stratum corneum will enlarge several times its dry thickness of approximately 10 mm. It is somewhat waterproof but still flexible. It is possible to model the architecture of the stratum corneum (Figure 2) as a wall made of protein bricks and lipid mortar. It is composed of keratinocytes, or corneal cells, joined by desmosomes, which are the protein-rich ends of cell membranes. A lipid matrix in which the corneal cells are embedded has a significant impact on how permeable this material is through the skin. [14]

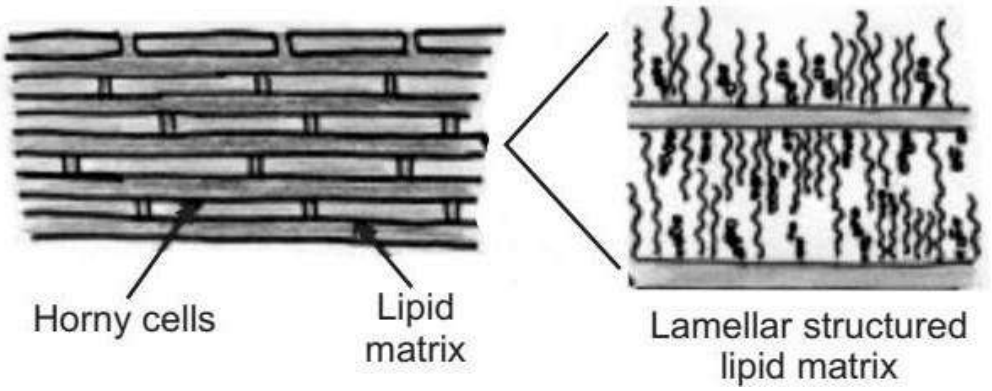


Figure 2: Schematic Diagram of Micro-Structure Of Stratum Corneum

Viable epidermis: Its thickness ranges from 0.06 mm on the eyelids to 0.8 mm on the palms, and it is located beneath the stratum corneum. Inside, there are several layers including the lucidum layer, seed layer, organism layer, and substrate layer. Cell division in the basal layer constantly regenerates the epidermis, and this growth makes up for for the removal of dead keratinocytes from the skin's surface. The cells generated by the basal layer move outward, changing morphologically and histologically as they go. They then go through keratinization to form the stratum corneum's outermost layer, as seen in Fig. 3. [15]

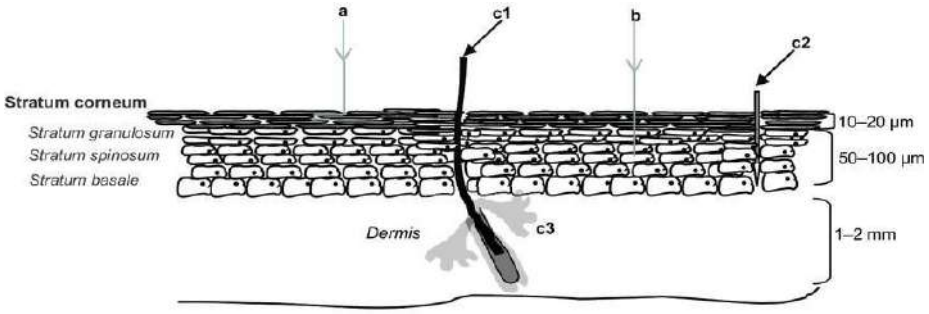


Figure 3: Schematic Diagram of Different Layers Of Viable Epidermis

Stratum lucidum:

The stratum lucidum is composed of epithelial cells that have been compressed. The nucleus of many cells is deteriorated, and in some cells it is gone. Because of the glossy nature of these cells, the layer resembles a uniform translucent zone. Thus, stratum lucidum is the name of the layer (lucid = clear).

Stratum granulosum:

This is a thin layer of flattened rhomboid cells arranged in two to five
rows. Kernetohyaline granules are found in the cytoplasm. The precursor of keratin is the protein keratohyaline.

Stratum spinosum:

Because the cells in this layer have protoplasmic projections that resemble spines, this layer is often referred to as the prickle cell layer. The cells are linked to each other by these projections.

Stratum basale:

Also known as stratum germinativum, is a thick layer composed of columnar or cuboidal epithelial cells in the deeper layers and polygonal cells near the surface. Here, mitotic division is the continual process that creates new cells. The freshly produced cells keep going in the direction of the stratum corneum. Keratinocytes are the name for the stem cells. Certain projections from this layer reach the dermis. These projections serve as both a structural and nourishing element. This layer, which has the pigment melanin, determines the skin's color. [16]

Dermis:

The hydrophilic deposit known as the dermis ranges in thickness from 0.1 to 0.5 cm. The dermis is made up of sweat glands, lymphatic and nerve endings, blood vessels, pilosebaceous units, and a network of elastin and collagen fibers embedded in the mucopolysaccharide matrix. Whereas the elastic tissue offers flexibility, the collagen fibers in the connective tissue offer support. The transfer of chemicals is not significantly inhibited by the dermis (but it could be a major obstacle for medications that are particularly hydrophobic). [17] Substances that penetrate the layers of the epidermis are removed by blood vessels in the dermis domain, maintaining the concentration gradient that encourages penetration between the dermis and skin surface. Furthermore, hair follicles, sweat glands, and sebaceous glands stimulate the dermis region and produce a "shunt" pathway. [18]

Hypodermis:

The skin's hypodermis is its deepest layer. It is the layer that lies between the skin and the body's internal tissues, including the bones and muscles. Although they originate in the dermis, sweat glands, sebaceous glands, and hair follicles are enclosed in the epidermis. A diluted salt solution is released onto the skin's surface via sweat glands. This solution evaporates, cooling the skin, which is beneficial for controlling the body's temperature as well as the skin's temperature. The body is covered in sweat glands. A number of emotional elements, the quantity of heat producing skeletal muscle activity, and the ambient temperature all affect how many dilutions (sweet) are created. Sebaceous glands generate sebum. Sebum is an oily substance that is secreted into hair follicles and then reaches the surface of the skin. Sebum keeps the skin and hair from drying out. [19]

Skin penetration

Drug molecule penetration effectiveness is crucial for TDDS. There are several ways for drugs to enter the skin. The skin can be permeated by macro and micro molecules through three different pathways exist:

a. the transcellular (intracellular) pathway, which passes through corneocytes;
b. the transcellular (intracellular) pathway; an
c. the transappendageal or transfollicular pathway, [20] which passes through hair follicles, sebaceous glands, and sweat glands (Figure 4). The intercellular pathway is the

one that lipophilic molecules most favor. Following topical formulation drug application, molecules come into touch with sebum, bacteria, cellular debris, and other elements at the skin's surface that have no discernible impact on penetration. [21, 22] Drugs travel through the stratum corneum's cells directly via the intracellular pathway, whereas via the intercellular route, they spread throughout the cells in a tortuous manner. [23, 24] The intracellular pathway is preferred by both hydrophilic and lipophilic molecules, depending on their polarity, because it is challenging to travel through because it must first pass through each cell's lipophilic membrane, then the hydrophilic core of the cell, and then back out of the lipophilic membrane. [25] Although the intercellular route is likewise a polar pathway of penetration, the intracellular route also needs some hydrophilic characteristics to pass through the corneocyte. [26] Since the combined surface area occupied by hair follicles and sweat glands is about 0.1%, it is not regarded as a particularly significant passageway for drug permeation. Furthermore, the transfollicular pathway may contribute to the rapid drug diffusion during the first few hours before reaching a steady-state concentration. Nonetheless, it is possible that high molecular weight medications require transportation via this route. The physiological and physicochemical factors that affect drug permeability through the skin is given in figure 5. [27 Up to now, a number of strategies have been used to improve drug transport through the skin, including electrically powered methods, drug-vehicle interaction, vesicles and their analogues, horny layer alteration, and horny layer ablation. Drug-vehicle interaction can be further categorized into approaches like eutectic mixtures, ion pairs, and drug and prodrug selection. Liposomes, ethosomes, niosomes, and transferosomes are the different categories of vesicles and their counterparts. Several kinds of CPEs, including as water, alcohol, terpenes, azone, sulfoxides, surfactants, phospholipids, and urea, are used to modify the horny layer. On the other side, microneedle procedures are used to remove the horny layer. Finally, methods that are powered by electricity comprise photomechanical waves, iontophoresis, electroporation, ultrasound, and magnetophoresis. [18]

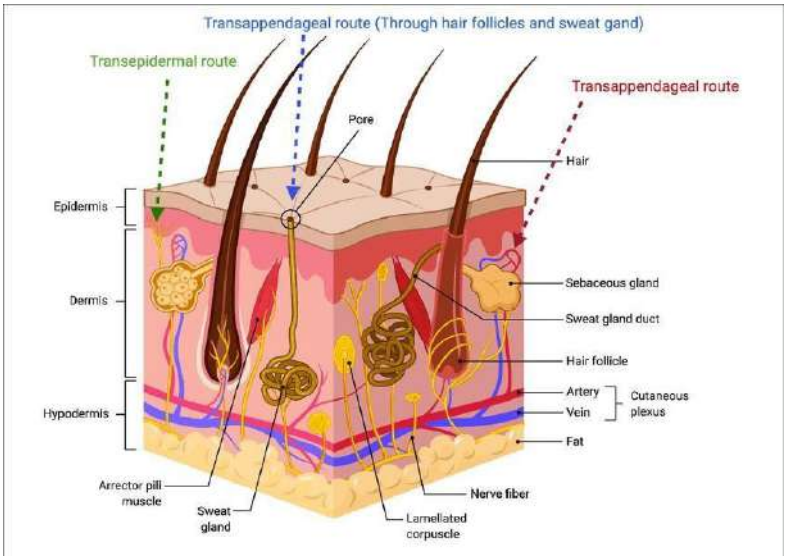


Figure 4: Schematic representation of the permeation process through the skin

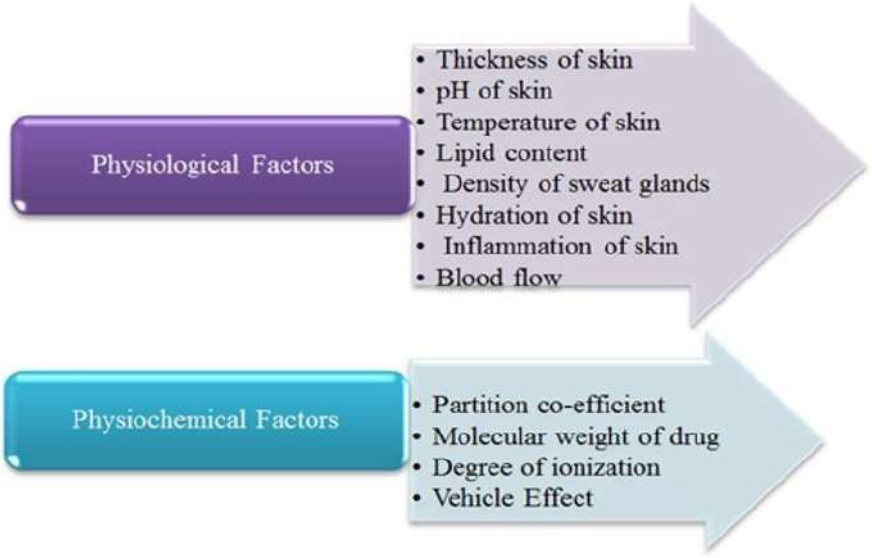


Figure 5: Factors affecting drug permeability through the skin

Function of skin

The largest organ in the body, the skin, has been assigned many roles. The skin serves as a barrier against the environment that shields important organs, a diffusion barrier that reduces the amount of water lost through sweating that could lead to dehydration, and a metabolic barrier that breaks down chemicals to make it easier to expel waste after absorption. Blood arteries dilate to release heat and contract to retain heat when the skin regulates body temperature. While sweating promotes heat loss through evaporation, hair and fur serve as insulation. The skin can function as an effector axis in the immune system by allowing Langerhans cells to process antigens and as an effector axis in the body by initiating an inflammatory response in response to an external assault. Its stroma is fully developed, supporting all other organs. Receptors in the skin use its neurosensory qualities to detect touch, pain, and heat. Furthermore, by producing vitamin D, the skin acts as an endocrine organ. It is also a target for androgens, which control the generation of sebum, and insulin, which controls the metabolism of carbohydrates and fats. Many sebaceous glands in the skin secrete sebum, a complex mixture of lipids that many animals use as a water-repellent barrier or as an antibacterial agent. Sweat secretions from the apocrine and eccrine sweat glands have a fragrance and are used to mark territory. The integument is involved in respiration, the biotransformation of xenobiotics, and the metabolism of keratin, collagen, melanin, lipids, carbohydrates, and vitamin D. [28, 29, 30]

Topical drug delivery

Topical medication delivery systems are specialized methods for delivering therapeutic substances locally through the skin to address cutaneous conditions. Localized skin infections are typically treated with these systems. The formulations come in a variety of forms, including solid, semisolid, and liquid. Drug absorption via the skin is improved if the drug ingredient in the solution has a favorable lipid/water partition coefficient and if it is a non-electrolyte. [31] The medicine in the topical dose form is included in a suitable semisolid base that has either hydrophobic or hydrophilic qualities. They are made up of one or more active substances that have been dissolved or uniformly distributed in a suitable base together with any necessary additions, including stabilizing agents, emulsifying agents, viscosity enhancers, antibacterial agents, or antioxidants. There are two categories of drugs that can be topically applied

through the skin: those that are applied for systemic effects, or for local or superficial effects. The term "local effect" refers to a drug's activity on the skin's surface, specifically the stratum corneum, or how it alters the way the dermis and epidermis operate. [32] The process of creating a topical delivery system is difficult and necessitates careful consideration of both the active ingredient and the delivery method since the obstacles connected to both pathways may restrict the drug's availability at the site of action. When a medicine is applied topically, it avoids the side effects of oral administration, such as fluctuations in plasma levels, pH changes in the stomach, and hepatic first pass metabolism.

The following are some additional benefits linked to the topical drug delivery mechanism:

- Patient Acceptability And Compliance,
- Simplicity And Ease Of Application,
- Painless And Noninvasive Approach,
- Increased Drug Bioavailability,
- Improved Physiological And Pharmacological Response,
- Minimal Systemic Toxicity, And
- Medication Exposure To Non-Infectious Tissue/Sites. [33]

The topical drug delivery also has some disadvantages that are mentioned below:

- Potential For Localized Skin Irritation When The Product Is Applied,
- Drug-Induced Contact Dermatitis Is A Possibility,
- Certain Medications That Have Low Permeability Find It Challenging To Pass Through The Skin,
- It Is More Difficult For Drugs With Bigger Particle Sizes To Enter,
- Potential For Allergic Responses, And
- Medication That Has A Very Low Plasma Concentration Is The Only Kind That Works. [34]

Classification of topical preparation

TOPICAL DRUG CLASSIFICATION SYSTEM (TCS):

Based on qualitative (Q1) & quantitative (Q2) composition, semi-solid products (Q3), TCS provides a framework for classifying topical drug products. Topical drug products are classified into 4 classes, as seen in Figure 6. [35]

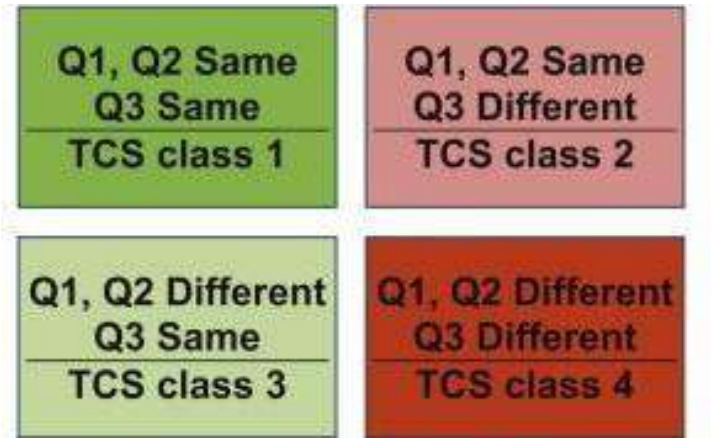


Figure 6: TCS Classification System

CONVENTIONAL TOPICAL DOSAGE FORMS:

Conventional topical dosage forms are classified as following:

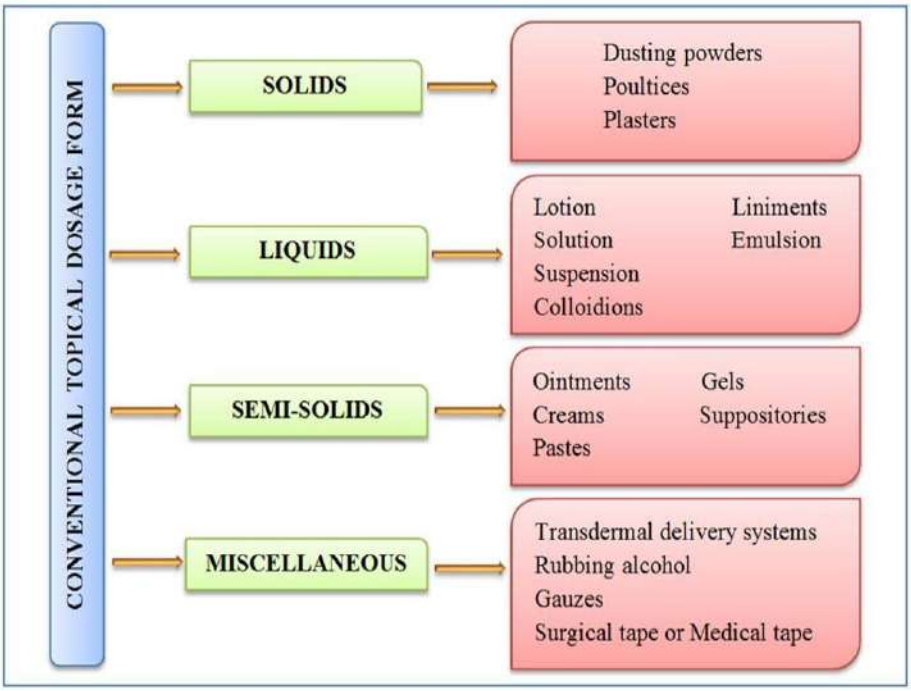
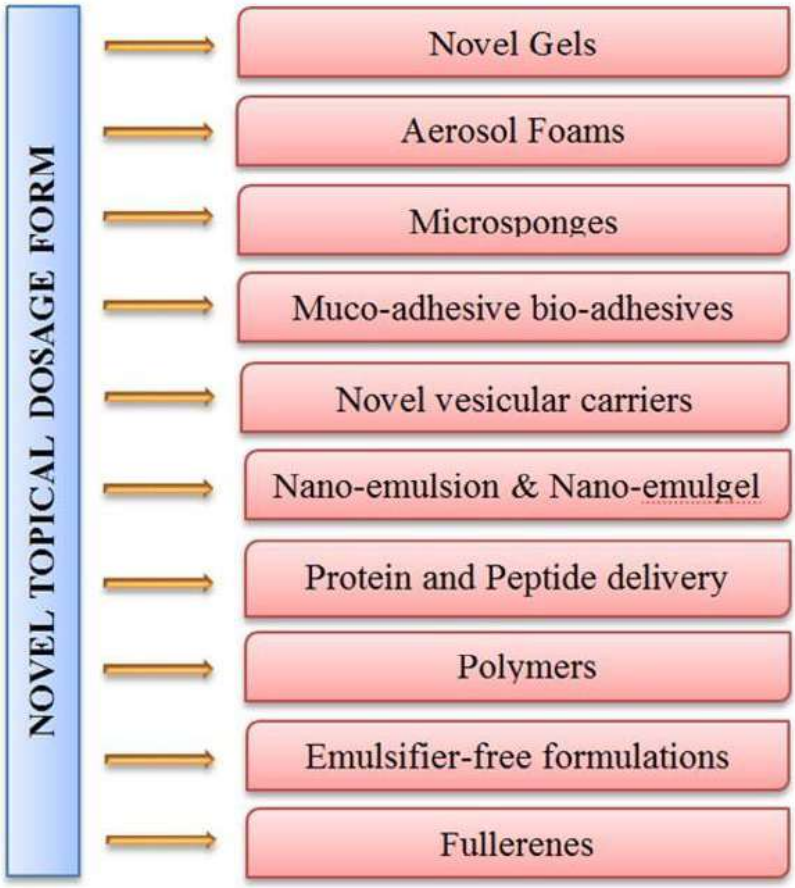


Figure 7: Classification of topical dosage forms

NOVEL TOPICAL DRUG DELIVERY SYSTEM: Novel topical drug delivery system consists of the following novel dosage forms:



Challenges for designing topical dosage form

The difficulty in creating a topical product lies in the numerous conditions that a formulation must satisfy, including all of the following needs:

Skin Penetration

The main obstacle to delivering bioactive agents into the skin via skin penetration is Fick's first law of diffusion, which describes the solute transfer rate as a function of the concentration of the different ingredients, the area that has to be treated, and the skin's permeability. The relationship between percutaneous absorption and molecular weight, which influences the coefficient of diffusion. Furthermore, some of the excipients included in the formulation, which have moisturizing, drying, or occluding actions, can also alter permeability, which in turn changes the drug release at the treatment site. [36]

$$J = -D.\{dC/dx\}$$

where, J is flux

D is the diffusion coefficient of the drug.

dC/dx is the concentration gradient

Skin pH

It is very difficult for drugs to permeate the stratum corneum if their molecular size is greater than 500 Daltons. Both high and low pH formulations can be harmful to the skin. For topical distribution, a moderate pH value is therefore appropriate. Additionally, the level of ionization at a specific pH is significant. [37]

Choice of Container

Stability

It offers database studies during the development stage to help with formulation, excipient, and container closure system selection; to determine shelf life and storage conditions; and to confirm that no modifications to the manufacturing process or formulation will negatively impact the stability of the product. [38]

Acceptability

Patients are currently looking for topical medications that are easy to use, safe, effective, and acceptable from a cosmetic standpoint. Routines for acne improve convenience and little disrupt the skin, which raises the topical system's effectiveness and compliance level.

Skin delivery past

Since hundreds of years ago, the skin has been routinely employed all over the world to deliver medications that are poorly soluble and low bioavailability when taken orally. In 4000 BC, Africans used minerals, phytochemicals, and cosmetics including henna, kohl, and red ochers to cure skin conditions. [39] In 3000 BC, animal, mineral, or plant extracts were frequently used to make ointments and potions in Egyptian and Babylonian medicine. [40] A Sumerian clay tablet, for instance, from 2100 BC describes a skin condition remedy that included ground snake and bat excrement mixed with an aqueous paste of plant extracts and earths. The Ebers Papyrus, dated to 1550 BC, provides information on topical treatments that were anointed, wrapped, rubbed, or applied to the skin to cure skin disorders in ancient Egypt. [41] The compounding of herbal remedies was first introduced to Western medicine by the Greek physician Claudius Galenus (often known as Galen; 129–199 AD). Galen's Cerate, a formula for a cold cream, was created and is still in use today. In his book The Canon of Medicine, the Persian physician Ibn Sina (better known as Avicenna, 980–1037 AD) postulated that topical medications had two spirits or states: a soft component that permeates the skin and a hard part that does not. Thus, Avicenna offered the earliest known mechanistic method that serves as the foundation for our present understanding of pharmaceutical development in topical and

transdermal delivery. [42] Years later, in 1880, a German chemist created "gutta-percha plaster gauze" to treat skin conditions. [43] In 2000 BCE, plasters with medicinal properties were utilized in China. These plasters included various herbs and medications, such as castor oil, sesame seed, and moringa, which were employed as astringents, diaphoretics, and protectors. Plasters have been used extensively historically to treat skin conditions. [44] Still, when phenol skin poisoning from broken off from plasters was investigated in the 20th century, researchers became interested in medication distribution through transdermal and topical channels. [45] A German dermatologist who published histology of skin illnesses in 1896 highlighted the significance of topical treatment for skin conditions and thought of the skin as an organ for the administration of dermatological therapies. [46] Due to ignorance of the medicinal agent's safety profile, a number of minerals, plant extracts, and colors that demonstrated therapeutic action but had harmful side effects were administered topically during the middle ages and ancient times. These goods include silver metallic mercury (quicksilver), orange to red mercuric chloride (cinnabar), and blue-gray lead sulfide (Kohl), which has been used for antibacterial properties since the time of the Egyptians. Originally, Arab nations employed quicksilver ointment to treat skin conditions. Following that, in the European Renaissance, the Swiss physician and alchemist Paracelsus supplemented the quicksilver ointment with calomel, sublimate, and a few additional oxides or metallic salts to treat syphilis. Arachelus, who is credited with founding modern toxicology, initially employed a topical mercury ointment to address the toxicity of the mercury ointment when taken orally. Penicillin was eventually used in place of topical mercury ointment for skin conditions later in the 20th century. [47] Rein's comprehensive in vitro experiments from the 1920s investigated the discovery that skin was relatively permeable to lipid-soluble compounds but not to water and electrolytes. [41, 48] Moore et al. demonstrated that applying testosterone, testosterone propionate, or estradiol to animal skin improved a range of hormonal reactions. [49] Zondek reported the effective treatment of urogenital infections after topical administration of an ointment containing the disinfectant chloroxylenol in the early 1940s, as well as the 1938 cutaneous application of follicular hormone for amenorrhea. [50, 51] Using nitroglycerin's ability to infiltrate and widen cutaneous blood capillaries, an ointment was successfully used to treat Raynaud's illness in 1948. [52, 53] Systematic research revealed that drug solubility, partition coefficient, and thermodynamic activity, drug vehicle-skin interactions and skin temperature were significant determinants of skin permeability. [54-59] In the early 1970s, the Alza Corporation, through their founder Alejandro Zaffaroni, filed the first US patents describing transdermal delivery systems for scopolamine, nitroglycerin and nicotine. These delivery systems offered advantages including: (i) overcoming the drawbacks of oral delivery, such as vomiting and low bioavailability (due to a high liver and gut wall first-pass); (ii) offering an alternative to parenteral administration, which can be invasive, painful, and risky for bruising and infection; (iii) serving as a practical, non-invasive way to achieve relatively constant and reliable blood levels over the course of 24 to 72 hours, with the flexibility to stop the delivery at any time by removing the patch. [60]

Current status of topical drug delivery

In the present, topical drug delivery systems involve the use of conventional and novel topical dosage forms and physical methods for enhancing topical drug delivery.

Conventional topical dosage forms:

- **Powder:**

It is an insoluble powder that has been finely divided and contains chemicals like talc, zinc oxide, or starch. These ingredients are applied topically to the skin or wounds, particularly to reduce irritation or absorb moisture. Some of the constituents also have lubricating characteristics. [61]

- **Poultices:**

It is soft, viscous, pasty preparation for external use. They are applied to skin while they are hot. Poultice must retain heat for a considerable time because they are intended to supply warmth to inflamed parts of body. [62]

- **Plasters:**

Plasters attach to the skin when spread on a backing of cotton felt or muslin. They can be solid or semisolid. These skin-friendly medical bandages provide protection for minor cuts, wounds, burns, abrasions, scars, scratches, and grazes. It provides mechanical support and a macerating action, bringing medication into contact with the skin. [97]

- **Creams:**

Creams are dosage forms that are semisolid and comprise one or more medication ingredients that have been dissolved or spread in an appropriate base. Traditionally, semisolids with an oil-in-water or water-in-oil emulsion formulation and a somewhat soft, spreadable consistency have been referred to by this word. [63] When compared to ointments, water-in-oil (w/o) emulsion type creams are less greasy and have better spreadability, but oil-in water (o/w) emulsion creams are easily rubbed into the skin and are known as disappearing creams easily eliminated by water.

- **Gels:**

Gels are semisolid system comprised of a dispersion of big organic molecules or small inorganic particles surrounded and pierced by liquid. Gels are made up of two phase systems: the continuous phase contains big organic particles that are dissolved and randomly coiled in the flexible chains, while the inorganic particles are simply scattered throughout the phase. [64]

- **Ointments:**

The word ointment derived from the Latin ungere meaning anoints with oil. [34] Semisolids called ointments are applied externally to the skin or mucous membranes. Typically, they have a vehicle composition of greater than 50% hydrocarbons, waxes, or polyols and fewer than 20% water and volatiles. [63] Due to the fact that they often include few chemicals other than base oil or fat, they are suitable for dry skin, have moisturizing properties, and a low risk of sensitivity and irritation. [65]

- **Pastes:**

Pastes are semisolid, stiff formulations with a high concentration of finely powdered substance. Zinc oxide, titanium dioxide, starch, kaolin, or talc powders are highly concentrated in a lipophilic, oily carrier. A clinically distinguishing property of pastes is their ability to absorb exudates due to the nature of the powder or other absorptive components. They are less greasy, less penetrating, less macerating, less heating, and more stiffer than ointments. [98]

- **Suppositories:**

Suppositories are medicated solid dose forms designed for insertion into bodily orifices such as rectum, urethra, and vagina, where they dissolve or melt or soften to release the drugs and exert local or systemic effects. The phrase suppositories originate in Latin and meaning "to place under". [99]

- **Lotion:**

Lotions typically consist of an aqueous base suspended or dispersed with a finely split insoluble medication. They have a non-greasy texture, are thin, and are opaque. Lotions are the least effective topical vehicle since they are easily applied and only marginally occlusive. [66] Generally speaking, they are less hydrating than creams.

Lotions have a cooling effect on the skin as the aqueous phase quickly evaporates, making them particularly helpful in the treatment of exudative dermatoses. [67]

- **Liniment:**

Topical liquid or semiliquid treatments are known as liners. These are oily or alcoholic non-aqueous liquids applied topically under friction. Alcohols accelerate the anti-irritant effect and the skin's absorption of medication. Analgesic, rubefacient, calming, and counter-irritating or stimulating drugs are added to liniments. They may cause extreme irritation, thus they shouldn't be used to skin that has been broken or injured. [68]

- **Solutions:**

Topical solutions are less viscous liquid preparations often use water, alcohol, and sometimes oil intended for topical application.

- **Emulsions:**

Emulsions are thermodynamically unstable biphasic liquid dosage forms with one phase (dispersed or internal) evenly dispersed in the other (continuous or external phase). An emulsifying agent is required to stabilize the mixture. Types of emulsions include, 1) Simple emulsions (Macro emulsions): Oil-in water (O/W), Water- in-oil (W/O) 2) Multiple emulsions 3) Micro emulsions (transparent emulsion) 4) Double emulsion: O/W/O and W/O/W emulsion. [100]

- **Suspensions:**

Suspensions are coarse dispersion, heterogeneous mixture, two-phased systems in which finely divided solid particles are dispersed in a liquid medium. These are heterogeneous systems that consist of two phases, the continuous phase (external phase/suspending medium) which is usually a liquid or semisolid and the dispersed phase (internal phase) which is made up of insoluble solid particles having a size range 0.5 to 5 microns. [101]

- **Collodions:**

Collodions are clear or slightly opalescent liquids that can be applied externally to the skin. They use nitrocellulose (pyroxylin) as the film-forming material and volatile solvents such alcohol, ether, and acetone. After applying collodion, it shrinks as the volatile solvent evaporates, leaving a thin, flexible, transparent protective film on the affected area. They are used to close tiny wounds, abrasions, and cuts. secure surgical dressings and keep medications in contact with the skin.

- **Transdermal delivery system:**

Transdermal medication delivery is characterized by discrete, self-contained dosage forms that, when applied to undamaged skin, allow the drug to enter the systemic circulation at a controlled rate through the skin. [69] Numerous benefits are available with them, including less adverse effects, enhanced patient adherence, continuous medication administration, and the removal of first-pass metabolism. [102]

- **Rubbing alcohol:**

Rubbing alcohol, ethanol-based solutions, or surgical spirit are generally employed as topical antiseptics. These are both volatile and lamable. It effectively kills or prevents bacteria growth on skin. It acts as a topical rub to alleviate minor muscle soreness. [103]

- **Gauzes:**

Gauze is a natural, woven bandage with a permeable barrier that effectively treats wounds. It varies in breadth and length. It prevents wound adhesion and holds dressings securely in place. [104]

- **Surgical tapes:**

Surgical tape, often known as medical tape, is a pressure-sensitive, hypoallergenic adhesive tape. They are constructed of 3M Micro-pore material, which typically incorporates zinc oxide to prevent infections. The tapes allow air to reach the skin. In first aid, dressing bandages are securely fastened to the wound and can be readily removed without causing skin damage.

Novel topical dosage forms

- **Foam:**

Colloids known as foams are "composed of two or three distinct phases: a gaseous dispersion phase distributed throughout a hydrophilic liquid continuous phase with a foaming agent; there may also be a third hydrophobic dispersed phase." The kind and quantity of foaming agent used will affect the foam's density and stability. The benefit of foam delivery is that it covers a lot of surface area with ease and doesn't leave the skin feeling sticky, greasy, or oily after application. [70]

- **Liposomes:**

Liposomes are minuscule vesicles consisting of one or more lipid bilayers wrapped around an equal number of aqueous compartments in a circular pattern. Drug molecules can be intercalated into the lipid bilayer or encapsulated in the aqueous space; the precise location of a drug within a liposome is determined by its physicochemical properties as well as the makeup of the lipids. [71]

- **Aquasomes:**

Aquasomes are self-assembled nanoparticles with three layers: core, coating, and medication. Stable structures are formed through ionic, hydrogen, and van der Waals linkages. It is the most effective carrier for delivering therapeutic proteins and peptides. [105]

- **Nanoemulsions:**

With the aid of an appropriate surfactant to stabilize the system, oil or water droplets are finely dispersed in the opposing phase of an emulsion system known as a nanoemulsion, with droplet sizes measured in nanometers. Typically, droplet sizes fall between the range of 0.1 to 500 nm. Additionally referred to as miniemulsions, fine-dispersed emulsions, submicron emulsions, etc., nanoemulsions can be W/O (water in oil) or O/W (oil in water) emulsions.[72] They are made up of two immiscible liquid phases that are joined to form a single phase by an interfacial layer made of co-surfactant and sensible surfactant. [73]

- **Niosomes:**

A nonionic liposome based on surfactants is called a niosome. Cholesterol is incorporated as an excipient in the majority of niosome formations. You can utilize different excipients as well. Niosomes are more able to penetrate than earlier emulsion formulations. Although they have a bilayer and are structurally similar to liposomes, niosomes are more stable due to the materials employed in their creation, which gives them many additional benefits over liposomes. Niosomes range in size from microscopic to nanometric. Particle sizes vary from 10 nm to 100 nm. [74]

- **Micelles:**

Micelles encapsulate hydrophilic medicines, leading to increased therapeutic efficacy and reduced side effects. Polymeric micelles improve drug delivery to specified skin areas in both normal and dermatological conditions, including psoriasis and acne. [106]

- **Microsponges:**

Microsponges are a type of porous microsphere with a large number of interconnected voids that range in size from 5 to 300 µm. These microsponges are employed as a topical carrier system and are capable of encasing a broad variety of active compounds, including sunscreens, essential oils, emollients, and anti-infectives. They are made of non-collapsible structures with porous surfaces that allow for the regulated release of active substances. [75]

- **Solid Lipid Nanoparticles:**

With sizes ranging from 50 nm to 1000 nm, colloidal drug carriers known as SLNs are quickly becoming popular. [76] SLNs typically have a diameter of 50–1000 nm and a spherical shape. Lipids, which are solid at room temperature, emulsifiers or occasionally a combination of the two active pharmaceutical ingredients (APIs), and

a suitable solvent system are the main components of SLN formulations. [77]

- **Hydrogels:**

Hydrogels are polymeric materials that do not dissolve in water but can expand and trap a significant amount of water in their network structure. The drug should be incorporated with a suitable hydrophilic polymer and solvent so that the polymer degrades slowly to release the drug present in the core.

- **Emulgel:**

Emulgel is a combination of gel and emulsion, as the name suggests. Different medications are delivered to the skin using emulsions that are either water-in-oil or oil-in- water in composition. An emulgel is created when a gelling agent is included in the water phase of a traditional emulsion5. Thixotropic, greaseless, easily spreadable, readily removable, emollient, non-staining, water soluble, longer shelf life, biocompatible, clear, and aesthetically pleasant are just a few of the advantageous qualities of emulgel for dermatological application. [78]

- **Ethosomes:**

A combination of phospholipids and a high ethanol concentration forms ethosomes. This carrier's ability to profoundly penetrate the skin improves blood circulation and drug delivery into the skin's deeper layers. For the comfort of patients, these formulations are helpful for topical alkaloids delivery in the form of gel and cream. Because they cause the skin's lipid domain to become more fluid, they exhibit an increase in permeability through the skin. The delivery of ethosomes in tropical regions is limited by their unstable nature and low skin penetration. [79]

- **Film-forming sprays:**

Typically, FFS is made up of polymers, enhancers, and active ingredients dissolved in organic solvents. In contrast to other traditional topical preparations, a thin, non-sticky film can form that can prolong the drug's contact duration and permeability, resulting in continuous drug release. It can also prevent crystallization, increasing the amount of medication available to give therapeutic benefits. The sprayability of FFS is greatly influenced by the kind of nozzle, the size of the aperture, the applied spray pressure, and the type of liquid. [80]

- **Dendrimers:**

The Greek word "dendron" (meaning tree, meros, or branch) is where the name "dendrimer" originates. [81] Their nanosizes range, ability to exhibit various surface groups for targeting, and their ease of production and functionalization make them appealing drug delivery vehicles. [82] These macromolecular structures are globular and frequently branching, with a high density of surface functional groups. Medications can be complexed to the functional groups on the surface through covalent conjugations or electrostatic interactions, or they can be contained in the dendrimer core. Dendrimers offer controlled drug release in addition to enhancing the absorption of weakly permeable molecules like hydrophilic chemicals. The surface functional groups, charge, size, and production of dendrimers determine their physicochemical and biological characteristics, which affect the kind of drug-skin contact. [83]

- **Fullerenes:**

Fullerenes are an allotrope of the carbon family of nanomaterials, popularly known as Buckminster fullerenes or Buckyballs. The structure of fullerenes is made up of sp2carbons, which have special chemical and physical properties, and a highly symmetric cage with various sizes (C60, C76, etc.). C60 is the fullerene that is most prevalent in the synthetic composition. The remarkable nanomaterial known as fullerenes has the potential to be used in cosmetic and transdermal administration due to its antioxidant activity and interactions with epidermal keratinocytes. [84]

Physical enhancement methods for topical drug delivery

- **Ultrasound/Sonophoresis/ Phonophoresis:**

Sonophoresis is a physical treatment that employs ultrasound (US) to stimulate transdermal absorption. It has several advantages, including its noninvasive nature, little skin injury, ease of use, wide applicability, and appropriateness for practically all medications. Sonophoresis requires an ultrasonic coupling agent, which is typically hydrogels, to transport US. As a result, active chemical agents might be added to the ultrasonic coupling agent, allowing for simultaneous physical therapy and transdermal medicine administration. According to current research, the mechanism of enhanced transdermal distribution using sonophoresis consists mostly of a cavitation effect, a heat effect, and a mechanical effect. [85] The most common process is cavitation, which is defined as the acoustically stimulated activity of gaseous cavities. Cavitation is split into two types: steady and inertial cavitation. Stable cavitation is defined as the sustained oscillation of bubbles in response to low acoustic pressure, resulting in acoustic streaming, a circulatory flow of fluid, and hydrodynamic shear stresses on the skin surface. Second, inertial cavitation refers to the rapid rise and collapse of bubbles over a few cycles, which can result in shock waves in the liquid or micro-jets at the skin surface. These cavitation-induced secondary effects appear to disrupt the SC lipid bilayer and produce temporary channels, allowing for the transport of different chemicals through these watery channels. [86]

- **Laser radiation and photomechanical waves:**

Lasers have been employed in therapeutic therapies for decades, therefore their impact on biological membranes is well- known. Lasers can heal dermatological disorders like acne and provide "facial rejuvenation" by destroying target cells in a short period of time (about 300 ns). Exposing the skin to laser radiation in a regulated manner allows for ablation of the SC without causing major damage to the epidermis. Using this approach to remove the SC improves medication distribution for both lipophilic and hydrophilic medicines. Laser radiation's barrier disruption depends on characteristics such as wavelength, pulse length, energy, pulse number, and repetition rate. [87]

- **Electroporation:**

Electroporation is the application of brief, high-voltage pulses to the skin. Electroporation creates microscopic pores in the barrier, facilitating the delivery of bigger molecules. Electroporation has been used to transport larger macromolecules like as vaccines, insulin, oligonucleotides, and microparticles. [88] The benefits of electroporation are numerous: (1) The pace and amount of transdermal penetration can be controlled by adjusting the electroporation settings. (2) The pores formed following the high-pressure pulse are reversible, and the harm is minimal. (3) Most medications that can permeate the skin might be improved, such as macromolecules, fat-soluble or water- soluble pharmaceuticals, or charged molecules. [89]

- **Iontophoresis:**

Iontophoresis technique, which uses a tiny current to promote drug absorption through the skin, is one of the most successful ways to bypass the stratum corneum.[90] The drug is pushed into the skin through electrostatic repulsion using an electrode with the same polarity as the drug's charge. [91] This strategy offers a more efficient, noninvasive, and patient-friendly means of medication delivery.[90] This technique's potential has been used for transdermal distribution of several medications with low penetration qualities, such as

high molecular weight electrolytes like proteins, peptides, and oligonucleotides, which are generally difficult to provide except by parenteral route. It also has a high potential for delivering charged peptides used as medicines. [91]

- **Magnetophoresis:**

Magnetic energy has been used to heal for thousands of years. Magnetophoresis is the motion caused by a magnetic field on a particle of magnetic or magnetizable substance. Magnetophoresis is also used to describe the deployment of a magnetic field to enhance medication absorption over a biological barrier. Small molecule enhancement has been proven employing several magnetic methods, including static magnets and pulsed electromagnetic fields. Magnetic arrays, whether static or dynamic, provide advantages in the manufacturing of electronics. These can be included into a transdermal patch or used to apply topical creams or gels. [92]

- **Radio-frequency:**

Radio frequency uses high-frequency alternating current (~100 kHz) to create heat-induced microchannels in the epidermal membrane, similar to laser radiation. The device's drug delivery rate is determined by the number and depth of its microchannels, which are influenced by the microelectrodes' characteristics. [93]

FUTURE PROSPECTS OF TOPICAL DELIVERY

TDD is a non-invasive delivery approach that is generally regarded as being easy to administer even in more vulnerable age groups, such as pediatric and geriatric patients, whilst circumventing some bioavailability concerns that arise from oral drug delivery due to poor absorbability and metabolism concerns. The huge surface area and accessibility of the skin make it a convenient and patient-friendly drug delivery target. Elimination of first-pass metabolism, stable delivery, improved patient compliance, reduced systemic drug interactions, sustained drug release, and generally greater therapeutic efficacy are all key advantages of transdermal delivery. [94]

Despite progress, numerous problems are yet to be solved, particularly in the enhancement techniques commonly employed for effective TDDS. To completely understand the penetration mechanism, it is essential to investigate it at the molecular level. In the meantime, barriers related to the cellular level need to be examined to increase retention time and improve delivery efficiency. Moreover, to hasten the translation from bench to bedside, the safety features of the formulation must be assessed methodically at an early stage of the development process. [95] Concerning the future of TDDS, it is expected that techniques such as transdermal patches and gels will be continuously used to deliver drugs with some specific properties effectively in comparison to oral and parenteral routes. Approaches such as nano-formulations and CPEs will be continuously employed to enhance the transdermal delivery of various drugs. [18] Born out of the inherent restrictions of chemical TDD methods, physical methods have evolved into promising systems for physical drug delivery via the skin. The majorities of these physical approaches is still in clinical trials and are intended to administer a wide range of drugs, especially hydrophilic drugs and macromolecules. To date, over 1000 clinical trials investigating transdermal drug delivery are indexed in the United States National Library of Medicine (NLM; clinicaltrials.gov). Another approach that is currently being investigated to improve TDD is the hybridization of chemical approaches with physical approaches, though the investigation is still in its early stages. [96] However, despite having made enormous advancements, successful proof-of-principle studies, and their feasibility in humans, these techniques do not ensure the effective development and commercialization of a new

product. Developing more "cost-effective or delivery-efficient" formulations could be an approach to persuade the distrustful but "off-the-shelf" solutions, primarily developed for "conventional" molecules, which are being used more often nowadays. Little work has been carried out on some drugs by utilizing novel drug-designing approaches and formulation optimization techniques. However, currently, they have gained more attention towards drug delivery via the transdermal route. Formulation development could be a key to the successful exploration of these new technologies in many ways; firstly, it preserves the stability and therapeutic activity of the drug, for example, biotechnology derived drugs; furthermore, it enables drug partitioning through the skin; and lastly, it provides an efficient drug delivery system that offers targeted delivery of the drug with minimal side-effects. Hence, more efforts need to be focused on the formulation design and development approach so that the potential of novel delivery technologies can be utilized efficiently. [94-96]

CONCLUSION

The above review focuses on the historical, current, and topical aspects of topical medication delivery systems. Over the last few decades, the topical drug delivery technique has gained popularity. The skin is an important region for local and systemic medication delivery. It has the rare property of being both easily accessible and somewhat impenetrable. This permits treatments with a variety of compositions to be applied to the skin and then removed as needed. Products for skin application have progressed from simple solutions and ointments to multiphase, nanotechnology, and aided technologies. However, conventional topical medication administration has significant limitations. In comparison, novel formulations outperform in terms of patient compliance, safety, efficacy, practicality, and shelf life. Extensive research is conducted to advance new topical medication delivery. As a result, it is possible to conclude that changing conventional formulations to novel formulations via carriers necessitates substantial research, which offers new hope for illness mitigation. In the future, these carriers associated delivery will be a milestone for hydrophilic drug delivery via the skin.

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