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"Formulation Strategies For Cream-Based Topical Drug Delievery System: A Comprehensive Review"

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ABSTRACT:

Topical drug delivery systems (TDDS) have emerged as a promising alternative to oral and parenteral routes, offering localized drug action with minimal systemic side effects. These systems are particularly useful for treating dermatological conditions like, pain, and infections directly at the site of application. The formulation and development of TDDS involve careful selection of drug candidates, excipients, and delivery vehicles such as gels, creams, ointments, or transdermal patches. Advances in nanotechnology, penetration enhancers, and novel carriers like liposomes and niosomes have significantly improved drug permeation through the skin barrier. Key formulation considerations include drug solubility, stability, skin permeability, and patient compliance. This abstract provides an overview of the principles, challenges, and recent advancements in the formulation and development of topical drug delivery systems, emphasizing the importance of skin physiology, formulation strategies, and evaluation techniques in achieving effective and targeted therapy.

Keywords: Penetration enhancers, Dermatological conditions, Penetration enhancers, Liposomes, Niosomes, Nanotechnology.

1. INTRODUCTION

The topical treatments that may be used on the skin are creams. Creams are described as "viscous liquid or semi-solid emulsions of either the oil-in-water or water-in-oil type" dosage forms, the consistency of which depends on the water and oil used.Cosmetic creams are used for purposes like cleaning, beautifying, enhancing looks, protection, or therapy. These topical preparations are utilized for their localized effect. for the purpose of delivering the medication into the mucous membrane or underlying layer of the skin. These products are intended for topical application to the skin in order to facilitate the drug's site-specific delivery into the skin for the treatment of skin conditions**.** Because creams are made utilizing methods created in the pharmaceutical industry, they are regarded as a pharmaceutical item; unmedicated and medicated creams are widely used. Creams, which are ayurvedic, herbal, or allopathic, are used by individuals for the therapy of a variety of skin illnesses or dermatoses, depending on their needs. Creams can be categorized as w/o or o/w. They include one or more medicinal ingredients dissolved or dispersed in a suitable base for treating skin conditions. classification of emulsions according to phases

Topical delivery refers to applying a drug-containing formulation onto the skin to specifically address skin conditions like acne or the skin symptoms of a broader illness like psoriasis, aiming to restrict the drug's pharmacological or other effects to the skin surface or within the skin itself. Semi-solid formulations, in their wide range, primarily dominate the topical delivery system, although foams, sprays, medicated powders, solutions, and even medicated adhesive systems are utilized.A successful topical formulation must

offer a stable chemical environment within an appropriate dispensing container to support various compounds that may possess different, or even conflicting, physicochemical properties. After application, a topical formulation needs to engage with the skin environment, which can impact its effectiveness. Advances in research and technology have led to a deeper understanding of the physics, chemistry, pharmacodynamics, and pharmacokinetics of medications used for acne treatment. This knowledge has paved the way for innovative delivery systems that improve effectiveness, tolerability, and cosmetic appeal of topical products. Topical drug delivery presents several benefits, including simplicity of delivery, a cooperative patient base, and enhanced compliance, while also bypassing first-pass metabolism. When considering the development of a topical dermatological product, it is essential to keep several important factors in mind. You might already be familiar with oral or injectable products; however, the formulation of topical products presents its own set of unique challenges Throughout history, humans have endured many kinds of physiological and psychological issues. However, careful scientific investigation on a global scale has led to significant progress in the prevention, treatment, and elimination of numerous illnesses.In recent decades, there has been remarkable advancement in the therapeutic application of biomolecules, including pharmaceutical compounds, proteins, and other biologically active substances. Initially, their use in clinical settings was restricted due to challenges in delivering drugs in physiologically adverse conditions.

The process of applying a formulation containing medication to the skin to treat skin disorders (like acne) or skin signs of broader illnesses (such as psoriasis) is known as topical drug delivery. The aim is to concentrate the medicinal effect within the skin or on its exterior, although sometimes, injections into the skin may be used. Various pharmaceutical dosage forms are utilized in topical drug delivery, including liquids, powders, sprays, and semisolids, with gels, creams, and ointments being the most commonly used semisolid types. Topical treatments work by directly focusing on the areas that need attention.

Defination: Topical administration is an appealing method for both novel and comprehensive treatment. Applying medications onto the skin is recognized as a successful way to address primary skin conditions. This method can penetrate the skin, allowing for improved absorption.

A topical drug delivery system refers to a way of administering a medication that is placed on a specific area of the body, usually the skin, to address various conditions. There are many common types of topical medications, including creams, gels, patches, and lotions, though they are mostly designed as ointments or creams.

Topical delivery involves two main categories of products:

1. **External topicals**, which are applied or spread over the skin (cutaneous tissues) to treat the affected area.
2. **Internal topicals**, which are administered to mucous membranes—such as oral, vaginal, or anorectal tissues—for localized action.

A topical drug delivery system refers to a method of administering medication directly to a specific area of the body, typically the skin, to address various conditions or provide targeted treatment.

2.Anatomy and physiology of skin

The skin is the largest organ in the human body, accounting for approximately 15% of total body weight. It serves several vital functions, including protection against physical, chemical, and biological threats from the external environment. Additionally, it helps prevent excessive water loss and plays a key role in regulating body temperature. The skin is continuous with the mucous membranes that line the body's external openings.

The integumentary system consists of the skin and its associated structures. The skin itself is composed of three primary layers: the **epidermis**, **dermis**, and **subcutaneous tissue**.

- The epidermis, the outermost layer, is made up predominantly of keratinocytes—specialized cells responsible for producing keratin, a fibrous protein that provides structural protection.
- Beneath the epidermis lies the **dermis**, which is mainly composed of collagen, a structural protein that gives the skin its strength and elasticity.
- Below the dermis is the **subcutaneous tissue** (also called the panniculus), which contains small clusters of fat cells known as lipocytes.

The thickness of these layers can vary significantly depending on the location on the body. For example, the skin on the eyelids has the thinnest epidermis, measuring less than 0.1 mm, while the thickest skin is

found on areas like the palms and soles, where the epidermis can be around 1.5 mm thick. In these areas, the dermis can be 30 to 40 times thicker than the overlying epidermis.

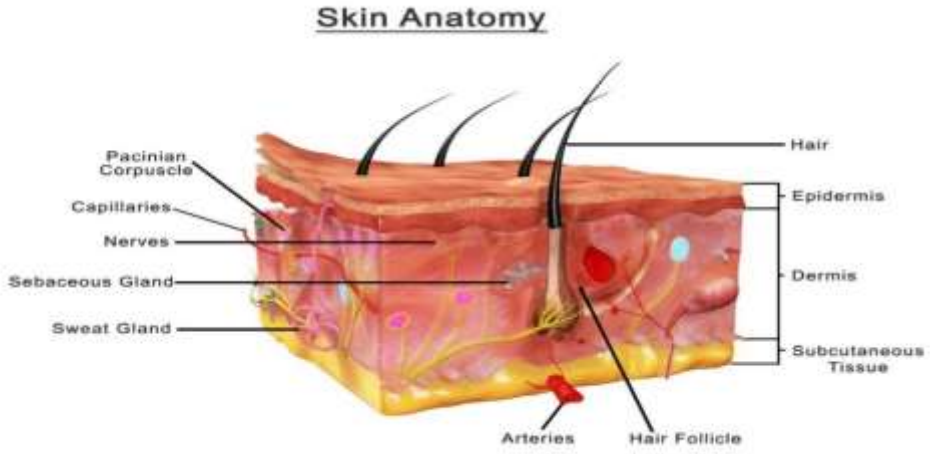

Fig No.1 Structure of the skin

Structurally, the epidermis is organized into four main layers:

- **Stratum basale**
- **Stratum spinosum**
- **stratum granulosum**
- **stratum corneum**

The deepest part of the stratum basale consists of progenitor cells, which are the youngest and least differentiated keratinocytes responsible for the continuous renewal of the epidermis. During differentiation, human keratinocytes take approximately 30–40 days to migrate from the basal layer to the surface of the skin, where they are eventually shed through desquamation. Also located in the basal layer are Merkel cells and melanocytes—the latter being responsible for pigment production.

The orientation of keratinocyte division determines their function: vertical division along the basement membrane contributes to keratin formation through differentiation, while horizontal division supports wound healing via cell proliferation. This layer is separated from the dermis by a specialized structure known as the basal lamina or basement membrane.

Above the stratum basale are the stratum spinosum and stratum granulosum, which together comprise roughly 15 to 20 layers of nucleated keratinocytes. The stratum granulosum, in particular, is rich in granules that support high levels of keratin production. Langerhans cells, a type of immune cell, are present throughout all layers of the epidermis but are most commonly found in the stratum spinosum.

As keratinocytes move upward, their nuclei and organelles gradually break down, allowing keratin to accumulate and form the stratum corneum. This outermost layer consists of dead keratinocytes packed with keratin, creating a strong yet flexible barrier. The stratum corneum typically measures 10–20 μm in thickness and presents a significant obstacle to topical drug delivery due to its dense keratinized structure.

Beneath the epidermis lies the dermis, composed primarily of connective tissue rich in collagen and elastin fibers. Unlike the epidermis, which contains abundant keratinocytes, fibroblasts—the cells responsible for producing these fibers—are sparsely distributed in the dermis. Below the dermis is the hypodermis, which consists mainly of adipose tissue. Like the dermis, the hypodermis originates from the mesoderm, and mesenchymal stem cells found in this fatty layer have the potential to differentiate into fibroblasts.

Blood vessels are primarily located in the dermis and hypodermis, although in certain cases—such as in warts, moles, or skin cancers—they may extend into the epidermis. Effective transdermal drug delivery must overcome the barrier posed by the stratum corneum and enable the drug to diffuse through all layers of the skin to achieve therapeutic effectivenes

The stratum basale, the deepest layer, contains progenitor cells—young, undifferentiated keratinocytes that continuously regenerate the epidermis. As these cells differentiate, they migrate upward toward the surface, a process that takes approximately 30 to 40 days, ending in desquamation**,** or shedding of the outermost cells.

This basal layer also includes Merkel cells (involved in sensory perception) and **melanocytes**, responsible for pigment production**.** Keratinocyte division in this layer is orientation-dependent**:** vertical divisions (relative to the basement membrane) support keratin formation via differentiation, while horizontal divisions

contribute to wound healing through proliferation**.** The basal lamina**,** a type of basement membrane**,** separates the epidermis from the dermis.

The stratum spinosum **and** stratum granulosum**,** together comprising about 15 to 20 layers**,** consist of nucleated keratinocytes. The granulosum is rich in granules that facilitate high levels of keratin synthesis**.** Langerhans cells**,** which are immune cells, are found throughout the epidermis but are especially abundant in the stratum spinosum**.**

As keratinocytes move upward, they lose their nuclei and organelles, while accumulating keratin**,** eventually forming the stratum corneum—a layer of dead keratinocytes that serves as a flexible and durable barrier. This outermost layer is typically 10–20 μm thick and poses a significant barrier to topical drug delivery**.**

Beneath the epidermis lies the dermis, which is primarily composed of connective tissue made up of collagen and elastin fibers**.** These fibers are produced by fibroblasts**,** which are sparsely distributed, unlike the dense keratinocyte population in the epidermis.

The hypodermis**,** or subcutaneous layer, lies beneath the dermis and is made up of **adipose tissue**. Like the dermis, the hypodermis is of mesodermal origin**,** and contains mesenchymal stem cells that can differentiate into fibroblasts.

Blood vessels are primarily found in the dermis and hypodermis, though in certain conditions such as **warts, moles, or** skin cancers they can extend into the epidermis as well.

For transdermal drug delivery to be effective, it must overcome the stratum corneum barrier and achieve sufficient penetration and diffusion through all layers of the skin.

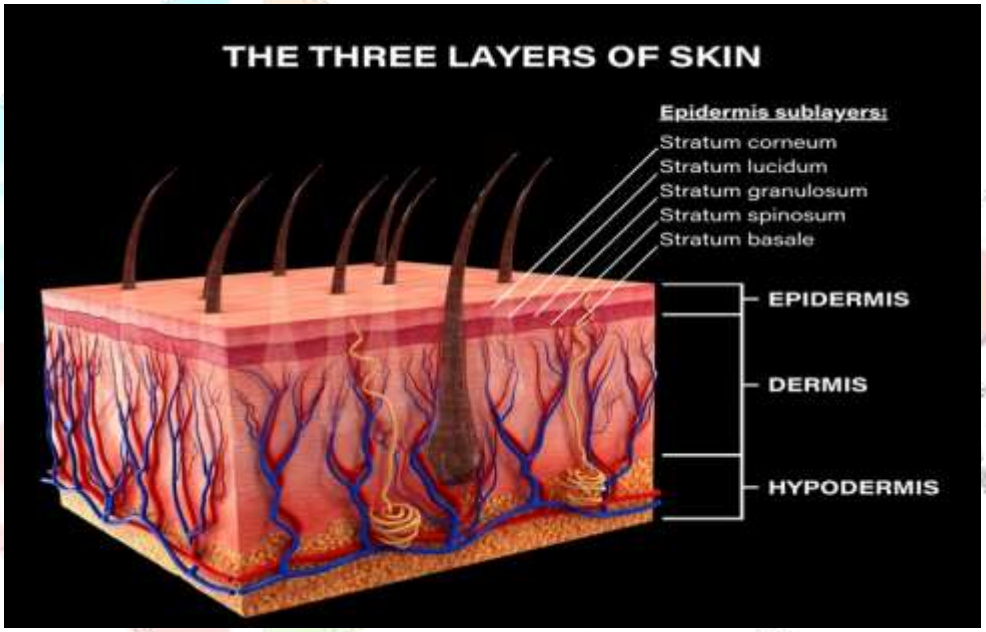

Fig No. 2. Three layers of skin

Skin Accesories

Sweat glands produce sweat with a pH ranging from 4 to 6.8. In addition to regulating body temperature through heat dissipation, they also play roles in absorbing certain medications and secreting proteins, lipids, and antibodies

Hair follicles

Hair follicles are associated with sebaceous glands, which secrete sebum—a mixture that includes glycerides, , cholesterol, and squalene.

Absorption Through skin

Topical drug administration includes transdermal delivery, where substances applied to the skin are absorbed into the body to achieve systemic effects. These drugs are often hydrophobic, such as steroid hormones. Topical medications are applied to treat localized conditions or, in some cases, enter the bloodstream through the skin.

The main goal of a topical drug delivery system is to enhance skin permeability and retain the drug within the dermis. Absorption typically occurs through openings like pores, hair follicles, and sebaceous glands, although these structures can also limit drug penetration.

There are three primary pathways for active compound penetration through the epidermis:

1. **Appendageal (intercellular) route** – via hair follicles or associated glands such as sebaceous and sweat glands.
2. **Transcellular (intracellular) route** – directly through corneocytes.
3. **Intercellular route** – through the lipid matrix between cells.

3.Pathways of Drug Absorption Across the Skin

3.1. Transepidermal Route

The transepidermal pathway involves the movement of substances directly across the skin's cellular structure and is divided into two mechanisms: (i) **transcellular** and (ii) **intercellular**.

- **Transcellular absorption** occurs when drugs pass directly through individual skin cells. This route is particularly effective for hydrophobic substances, as the lipid-rich cell membranes readily accommodate such compounds.
- **Intercellular absorption**, on the other hand, involves the diffusion of drugs through the spaces between skin cells, navigating the extracellular (intercellular) matrix. Since this matrix is also highly lipophilic, it further favors the absorption of hydrophobic drugs. This intercellular route is widely considered the dominant pathway for dermal drug delivery.

3.2. Transappendageal Route

The transappendageal route allows drug penetration through skin appendages such as hair follicles and sebaceous glands. This pathway is especially beneficial for the delivery of polar, ionizable drugs and large molecules, which typically struggle to pass through the compact structure of the stratum corneum.By utilizing the natural openings provided by these appendages, this route offers an alternative means for delivering complex or high-molecular-weight compounds, thereby broadening the spectrum of drugs that can be effectively absorbed through the skin.

3.3. Intercellular route

The intracellular space is filled with a lipid-rich, unstructured substance. In the intercellular pathway, the drug diffuses through the continuous lipid matrix located between the cell

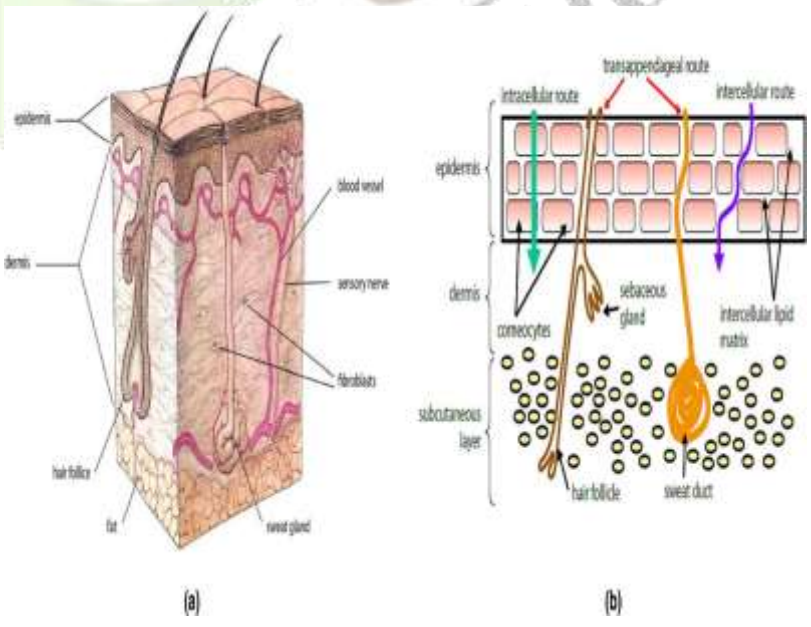

Fig.No.3 [a] interior layers of skin [b] routes of drug absorption

ADVANTAGES OF TDDS

- Ability to easily discontinue drug delivery when needed.
- Provides a relatively larger surface area for absorption compared to buccal or nasal routes.
- Enables more targeted drug delivery to a specific site.
- Avoids gastrointestinal incompatibilities
- Suitable for drugs with a short biological half-life and a narrow therapeutic window.
- Enhances both physiological and pharmacological responses.
- Improves patient compliance and convenience.
- Bypasses first-pass metabolism.
- Easy to access and apply.
- Minimizes fluctuations in drug levels and reduces inter- and intra-patient variability
- Achieves therapeutic effect with a lower total daily dose through continuous drug delivery
- Drugs with large molecular size may have difficulty penetrating the skin.

4.TYPE OF TOPICAL DOSAGE FORM

A. SOLID DOSAGE FORMS
B. SEMI-SOLID DOSAGE FORM
C. LIQUID DOSAGE FORM

A. SOLID DOSAGE FORM
Powders
Aerosols
Plasters

B. LIQUID DOSAGE FORM
Lotion
Liniments
Solutions
Suspensions
Aerosols
Emulsion

C. SEMI-SOLID DOSAGE FORM
Ointment
Gels
Cream
Paste
Jelly

5.CREAM

Creams are topical preparations designed for application on the skin. They are defined as “viscous liquid or semi-solid emulsions of either the oil-in-water (O/W) or water-in-oil (W/O) type,” with their consistency determined by the ratio of oil to water. Creams serve both cosmetic and therapeutic purposes, such as cleansing, enhancing appearance, providing protection, or treating skin conditions.

These topical formulations are intended to deliver drugs locally to the skin or mucous membranes, ensuring targeted action at the site of application. As site-specific delivery systems, creams are widely used for treating various skin disorders.

Classified as pharmaceutical products, creams are prepared using techniques developed in the pharmaceutical industry. They can be either medicated or unmedicated, and are available in allopathic, herbal, or ayurvedic forms, depending on individual needs and treatment preferences.

Creams consist of one or more active substances dissolved or dispersed in a suitable base. Based on the nature of the emulsion, they are categorized as either oil-in-water (e.g., vanishing cream) or water-in-oil (e.g., cold cream) types. The term "cream" has traditionally referred to these semi-solid emulsified formulations used for dermatological purposes.

6.TYPES OF SKIN CREAMS

Skin creams are generally classified into two main types based on the nature of their emulsions:

1. Oil-in-Water (O/W) Creams:

These are emulsions in which small amounts of oil are dispersed as droplets within a continuous water phase. In other words, oil-in-water creams have oil distributed throughout an aqueous base. They are typically lighter, non-greasy, and easily absorbed, making them suitable for daytime use or oily skin.

2. Water-in-Oil (W/O) Creams:

These creams consist of small amounts of water dispersed within a continuous oil phase. That means water droplets are embedded in an oily base. Water-in-oil creams are thicker, more moisturizing, and form a protective barrier on the skin, making them ideal for dry or sensitive skin.

7. CLASSIFICATION OF CREAMS

Creams can be classified based on various criteria:

- **Based on Function:**
- Cleansing creams
- Foundation creams
- Massage creams
- Protective creams

- **Based on Characteristic Properties**
- Cold creams
- Moisturizing creams
- Night creams

- **Based on Type of Emulsion**:
- Oil-in-Water (O/W) Emulsions
  - Vanishing creams
  - Foundation creams
- Water-in-Oil (W/O) Emulsions
  - Cleansing milk
  - Facial cleansers
  - Cleansing lotions

8.Common Ingredients Used in Skin Creams:

The raw materials used in the formulation and production of skin creams include the following:

1. Water:

Water is the most essential and widely used raw material in cream formulations. It is inexpensive, readily available, and serves as a solvent, helping to dissolve other ingredients. Water also plays a vital role in forming emulsions. Depending on the proportions of the oil and water phases, creams can be classified as either oil-in-water (O/W) or water-in-oil (W/O) emulsions.

2. Oils, Fats, and Waxes:

These components form a significant portion of most creams and each has specific functions:

- **Oils:**

Oils can be of two main types — mineral oils and glyceride (vegetable) oils.

Mineral Oils:

Derived from petroleum, mineral oils are clear, odorless, and highly refined. They are lightweight, inexpensive, and widely used in cosmetics to reduce water loss and keep the skin moisturized. Common examples include:

Light liquid paraffin,Heavy liquid paraffin, Liquid petroleum, Almond oil, Castor oil, Coconut oil, Olive oil, Arachis (peanut) oil, Avocado oil, Sunflower oil,Wheat germ

- **Fats:**

Fats used in creams can come from animal, plant, or mineral sources. They are composed of higher fatty

acids and glycerin. Upon saponification, they produce either soap or a mixture of fatty acids and glycerin. Common fatty acids include:
- Lauric acid
- Margaric acid
- Palmitic acid
- Stearic acid (saturated)
- Oleic acid (unsaturated, and most widely used)

Common fat sources include:
- Cocoa butter

- **Waxes:**

Waxes serve to stabilize emulsions by preventing the separation of oil and water. They also increase the thickness of the cream and provide a protective layer on the skin. Common waxes used include:
- Beeswax
- Carnauba wax
- Ceresin
- Spermaceti

3. Lanolin:
Lanolin is a waxy substance obtained from sheep's wool. It acts as a lubricant, giving the skin a soft and smooth appearance. It also assists in forming emulsions and blends well with other cosmetic ingredients. Lanolin is available in two types:
- **Hydrous lanolin** (contains 25%–30% water)
- **Anhydrous lanolin** (melting point: 38°C–42°C, has a mild odor)

4. Colors:
Traditionally, natural sources such as turmeric, saffron, and indigo were used to color creams. Today, synthetic and plant-based colors are also used to enhance appearance without relying solely on wild-harvested plants.

5. Emollients:
Also known as moisturizers, emollients soften the skin and are especially helpful for treating dryness. Most emollients are oil- or grease-based, such as:
- Mineral oil
- Squalene
- Lanolin

6. Humectants:
Humectants are hygroscopic organic compounds that attract and retain moisture from the environment, helping to hydrate the skin. They are vital multifunctional ingredients in skincare formulations. These ingredients offer several benefits, including moisturization, exfoliation, and more. Examples of humectants commonly used in skincare products include glycerin, hydroxyethyl urea, betaine, sodium PCA, and sodium L-lactate.

7. Perfumes: Perfume is a substance that adds a scent to products, often providing a sweet and pleasant aroma. Natural fragrances commonly used in creams include White Blossoms, Rosy Dreams, and Orange Blossom.

8. Vitamins: Vitamins play a vital role in maintaining the body's overall physiological functions, including skin health. Vitamins A, B, C, and E are frequently incorporated into cream formulations for their beneficial effects.

9. Preservatives: Preservatives are essential in cosmetic formulations to prevent microbial growth and contamination during manufacturing, shipping, storage, and use. Antioxidants are also added to protect the product from oxidative damage caused by exposure to air. When used at low concentrations, synthetic preservatives can effectively maintain the product's stability and safety.

10. Antimicrobial agent: An antimicrobial agent is a substance that kills or inhibits the growth of bacteria. To treat infectious disorders, conventional antimicrobial therapy involves the use of chemotherapeutic drugs or antibiotics. Since the commercialization of the first antibiotic penicillin in the late 1940s, antimicrobial medicines have been used to treat infectious disorders ranging from topical ointments to intravenously administered solutions. Infectious illnesses, whether intracellular, extracellular, or biofilm-mediated, have always been a global issue, claiming millions of lives each year

9. METHOD OF PREPARATION:

1. Preparation of Oil-in-Water (o/w) Emulsion Cream

To prepare an o/w emulsion cream:

- The oil-soluble components and emulsifier are placed in one beaker and melted using a water bath at 75°C.
- In a separate beaker, water, preservatives, and water-soluble ingredients are combined and also heated to 75°C.
- Once both phases reach the desired temperature, the oil phase is transferred to a mortar.
- The water phase is then gradually added to the oil phase while triturating continuously until a clicking sound is heard, indicating emulsification.
- After the mixture cools down, perfuming agents and/or any remaining preservatives are added.
- In this type of cream, the water content is higher than the oil content.

2. Preparation of Water-in-Oil (w/o) Emulsion Cream

To prepare a w/o emulsion cream:

- The oil-soluble ingredients and emulsifier are melted together in one beaker at 75°C.
- Simultaneously, water and water-soluble substances are heated in another beaker to 75°C.
- Once melted, the water phase is placed in a mortar.
- The oil phase is then gradually added to the water phase while triturating until a clicking sound is heard, indicating the formation of the emulsion.
- After cooling, perfuming agents are added to the cream.
- In this formulation, the oil content is higher than the water content

Preparation of oil in water phase cream

The oil-in-water (o/w) cream is formulated by dispersing oil droplets within a continuous water phase. This type of cream is widely used in both cosmetology and medical applications. Below is a basic procedure for preparing an o/w cream:

Ingredients:

1. Oil Phase
- 20% emulsifying agents (e.g., polysorbate 60 and cetearyl alcohol)
- 10% oils (such as almond oil, sunflower oil, or jojoba oil)
- 5% fatty alcohols (e.g., cetyl alcohol)
- 2% stearic acid (optional, serves as a thickening agent)
- 1% glycerin (optional, for added moisturization)

2. Aqueous Phase
- 57% distilled water or aqueous herbal infusion
- 1% preservative (to inhibit microbial growth)

3. Cooling Phase
- 3% propylene glycol (to enhance moisture retention)
- 1% fragrance or essential oil (for scent)

Preparation of Water-in-Oil (w/o) Creams

Water-in-oil (w/o) creams are formulated by dispersing water droplets within a continuous oil phase. These creams are commonly used in both cosmetology and medical treatments. Below is a simple method for preparing a w/o cream:

Ingredients:

1. Oil Phase
- 20% emulsifying wax (e.g., beeswax, cetyl alcohol)
- 50% oils (such as mineral oil, sweet almond oil, or jojoba oil)
- 5% fatty alcohol (such as cetearyl alcohol)

- 1% vitamin E oil (optional, acts as an antioxidant)

2. Water Phase
- 25% distilled water or herbal water infusion
- 3% glycerin (optional, for added moisturization)

3. Cooling Phase
- 1% preservative (to prevent microbial contamination)
- Fragrance or essential oils (optional, for fragrance)

10.Evaluation parameters of cream

- **pH Value:**

Calibrate the pH meter with a standard buffer. Dissolve 0.5g of cream in 50ml distilled water and measure the pH.

- **Viscosity:**

Measure viscosity using a Brookfield viscometer at 100 rpm with spindle No. 7.

- **Dye Test:**

Mix scarlet red dye with the cream, place a drop on a slide, cover, and observe under a microscope. Red disperse globules on a colorless background indicate an oil-in-water (o/w) cream; colorless globules on a red background indicate water-in-oil (w/o).

- **Homogeneity:**

Assess homogeneity by visual inspection and touch.

- **Appearance:**

Evaluate cream's color, pearlescence, and texture by grading its visual and tactile qualities

- **After Feel:**

Evaluate emolliency, slipperiness, and the amount of residue left after applying a fixed amount of cream.

- **Type of Smear:**

Assess the type of film or smear formed on the skin after cream application.

- **Removal:**

Check how easily the cream can be removed by washing the applied area with tap water.

- **Acid Value:**

Dissolve 10g of the sample in 50ml of an equal mixture of alcohol and ether, reflux until fully dissolved. Add 1ml phenolphthalein and titrate with 0.1N NaOH until a faint pink color persists for 30 seconds.
Formula:
Acid value = (n × 5.61) / w
Where,
n = ml of NaOH used
w = weight of sample (g)

- **Saponification Value:**

Reflux about 2g of the sample with 25ml of 0.5N alcoholic KOH for 30 minutes. Add 1ml phenolphthalein and titrate immediately with 0.5N HCl.
Formula:
Saponification value = ((b − a) × 28.05) / w
Where,
a = volume of HCl used for sample
b = volume of HCl used for blank
w = weight of sample (g)
Where:
a = volume (ml) of titrant used for the sample
b = volume (ml) of titrant used for the blank
w = weight (g) of the substance

- **Irritancy Test:**

Mark a 1 sq.cm area on the dorsal surface of the left hand. Apply the adhesive to this area and note the time. Monitor and record any itching, redness, or swelling for up to 24 hours.

- **Rapid Stability Test:**

Conduct the rapid stability test on the two most stable formulations (Formulations 4 and 5). Store them at room temperature and at 40°C ± 1°C for 20 days. Evaluate the formulations on days 0, 5, 10, 15, and 20 following the preparation process

11.Active Methods for Enhancing Topical Delivery to the Skin:

Active methods involve applying external energy to drive drug molecules into the skin or to reduce the skin's barrier properties, thereby improving drug permeation. Recent advancements in bioengineering, computing, chemical engineering, and material sciences have led to the development of innovative devices that enhance skin drug delivery, helping to achieve the desired therapeutic outcomes. The following are examples of active methods or devices used for topical drug delivery

1. Ultrasound (Sonophoresis or Phonophoresis):

Ultrasound uses ultrasonic energy to enhance transdermal drug delivery, either during treatment or as a pre-treatment. This technique, known as sonophoresis or phonophoresis, increases skin permeability by creating gaseous cavities within the intercellular lipids, which disrupt the subcutaneous skin layer. Ultrasound significantly boosts the absorption of topical compounds into the epidermis, dermis, and skin appendages. The ultrasound waves generate microvibrations in the skin, increasing the kinetic energy of the drug molecules and facilitating deeper penetration. Sonophoresis is commonly used in clinical settings for effective drug delivery through the skin.

2. Laser Radiation and Photomechanical Waves:

Lasers have been used in clinical therapies for many years, and their effects on biological membranes are well understood. They are commonly employed to treat dermatological conditions like acne and for facial rejuvenation. Laser radiation targets and destroys specific cells in a very short time (~300 nanoseconds). This precise and controlled exposure ablates the stratum corneum (SC) without causing significant damage to the underlying epidermis. The removal of the subcutaneous layer by this method enhances skin permeability.This method has been shown to enhance the delivery of both lipophilic and hydrophilic drugs.

4. Electroporation:

Electroporation uses short, intense electric pulses to temporarily increase the permeability of cell membranes, allowing drugs or genes to enter cells that otherwise wouldn't pass through. When delivering chemotherapeutic agents, this process is called electrochemotherapy, and when transferring DNA, it's known as gene electrotransfer. However, more clinical data on its safety and effectiveness is needed to determine its commercial viability.

5. Iontophoresis:

Iontophoresis enhances drug penetration through the skin by applying a mild electric current. The drug is placed under an electrode with the same charge, while a return electrode of opposite charge is positioned elsewhere on the body. The electric current drives the movement of ions across the skin based on the principle that like charges repel and opposite charges attract.

6. Magnetophoresis:

Magnetophoresis enhances drug permeation across biological barriers by applying a magnetic field. Both in vitro and in vivo studies have shown that magnetophoresis improves transdermal drug delivery. The main mechanisms involved are magnetokinesis and increased partitioning of the drug into the stratum corneum

7. Skin Puncture and Perforation Devices:
These devices use microfabrication technology similar to microneedles, featuring blade- or needle-like structures that create tiny holes by cutting through the skin barrier. Once the skin is disrupted, various delivery methods such as solutions, patches, gels, ointments, or techniques like iontophoresis and electroporation can be applied.

8. Non-Needle Injections:
This painless drug delivery method administers drugs by propelling liquid or solid particles at supersonic speeds using a controlled energy source, such as the Medijector device, enabling effective transdermal delivery without needles.

9. Skin Stretching Devices:
These devices apply tension to the skin in multiple directions, which increases skin permeability. As a result, the drug formulation or device can more easily penetrate and deliver the drug into the skin.

12.Advances of topical drug delievery system
Aerosol foams have become an increasingly popular form of topical formulation for treating various skin conditions, including acne vulgaris. These foams can have a liquid or semi-solid consistency and share similar physicochemical properties with traditional vehicles like gels, lotions, and creams. However, they offer additional benefits such as moisturizing effects, faster drying, and enhanced drug bioavailability. Dispensed from gas-pressurized cans, the foam is released in a controlled manner. Key product characteristics—such as thickness, viscosity, texture, bubble size, density, stability, persistence, and spreadability—depend on both the formulation and the design of the dispensing container.

. Liposomes:
Artificially created vesicles known as liposomes consist of a lipid bilayer and are often utilized in pharmaceuticals and cosmetics to deliver drugs in a controlled way to specific areas of the skin or its layers. These vesicles are spherical in shape, and their membranes are made from amphiphilic lipids, which possess hydrophilic properties on one side and lipophilic characteristics on the other, giving them dual traits that surround an aqueous core, similar to the bilayer membranes found in living cells. Due to their amphiphilic nature, liposomes can encapsulate hydrophilic materials within their aqueous core and lipophilic materials in their lipid bilayer. This remarkable ability to release both types of substances allows for the delivery of two different materials upon application to the skin, each affecting skin permeability in unique ways.which could improve the intended therapeutic effect.

. Microsponges:
This innovative technology allows for the controlled release of topical substances and is made up of microporous beads, usually ranging from 10 to 25 microns in size, which contain an active agent. Once applied to the skin, the MDS gradually dispenses its active component based on time, as well as in reaction to various stimuli such as friction, temperature, pH, and so on. MDS technology finds applications in cosmetics, over-the-counter skincare products, sunscreens, and prescription treatments. These particles are biologically inactive and are crafted from synthetic polymers capable of holding a quantity of active agent that can match their own weight. Additionally, the particles help to safeguard the Entrapped active substances are protected from environmental and physical damage. The microsponge technology can be incorporated into different formulations, although it is often produced as gels. After being applied to the skin, microsponges gradually release the active ingredients

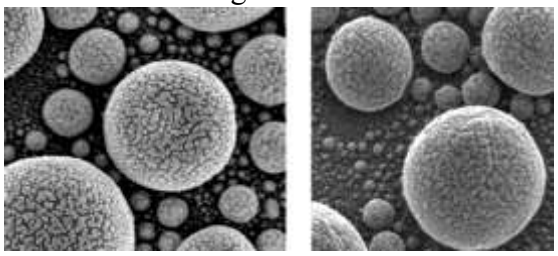

Fig No. 4. Surface Electron Microscopic (SEM) image of Microsponges

Microneedles

The combination of a needle and syringe has become the primary method for delivering drugs and vaccines that are considered ineffective when administered through other means and It is not unexpected that the needle architecture we are familiar with is central to the initial microdevice for drug delivery: "Microneedles. " These microneedles are crafted to be pain-free while addressing the skin's natural barrier. Microneedle therapy provides a method to enhance the skin's appearance without harming the epidermis. Techniques for creating these microneedle devices involve micromolding, microfabrication, microshaping, and various combinations of these. Microneedles offer numerous potential advantages for patients, healthcare providers, and the pharmaceutical sector in comparison to other delivery methods. Many individuals, especially children, experience fear of needles. Additionally, some patients, like diabetics, rely on multiple daily injections. Other medical conditions also necessitate the delivery of therapeutic substances to the skin, and in the event of a pandemic, widespread vaccinations would be required. The advancement of microneedles presents a solution to the challenges associated with conventional needle injections. This innovation aims to facilitate the creation of devices that are smaller, more affordable, painless, and user-friendly, with a variety of biomedical and other uses.

13.FUTURE SCOPE:

The future of cream-based topical drug delivery lies in the integration of advanced formulation strategies that enhance therapeutic efficacy, patient compliance, and safety. Nano-enabled formulations, including liposomes, niosomes, solid lipid nanoparticles, and polymeric nanoparticles, are increasingly being explored to improve drug solubility, stability, controlled release, and skin penetration . Smart and stimuli-responsive creams that release drugs in response to local temperature, pH, or enzymatic activity offer the potential for on-demand and site-specific therapy, particularly relevant for inflamed or diseased skin. Bioadhesive and penetration-enhanced formulations can prolong skin residence time and facilitate deeper drug delivery, especially when combined with microneedle-assisted or iontophoretic systems. The use of natural and biodegradable polymers, such as chitosan, alginate, and hyaluronic acid, aligns with patient-centric and eco-friendly approaches, while also providing additional therapeutic benefits like hydration and wound healing . Personalized and precision creams, supported by AI-driven design and 3D printing technologies, enable tailoring of drug dose and release profiles based on individual patient characteristics, including skin type, age, and disease state. Furthermore, combination creams delivering multiple active agents simultaneously, along with multifunctional formulations integrating antioxidant, antimicrobial, and anti-inflammatory agents, can simplify therapy for chronic and complex conditions. Finally, integration with wearable and digital devices offers real-time monitoring of drug release and skin responses, opening new avenues for Internet of Medical Things (IoMT)-enabled topical therapies. Collectively, these innovations suggest a future in which cream-based topical drug delivery systems are not only more effective and patient-friendly but also adaptable, responsive, and personalized for a wide range of dermatological and systemic applications

14. CONCLUSION:

Cream-based topical drug delivery systems continue to be a cornerstone in dermatological and localized therapy due to their ease of application, versatility, and patient compliance. The future of these formulations lies in leveraging advanced strategies such as nano-enabled carriers, stimuli-responsive polymers, bioadhesive bases, and natural biodegradable excipients to enhance penetration, stability, and therapeutic efficacy. Personalized and precision creams, 3D-printed formulations, multifunctional combination systems, and integration with digital or wearable technologies offer opportunities for targeted, adaptive, and patient-centric therapy. Advances in packaging and regulatory frameworks will further ensure safety, quality, and clinical translation. Collectively, these innovations signal a shift toward more effective, responsive, and sustainable cream formulations that meet the evolving needs of both patients and healthcare providers, making topical drug delivery a dynamic and promising field for future research and development

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