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## An overview on topical drug delivery system – Updated review

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### ABSTRACT

The paper reviews an overview of a conventional and novel approach in the topical drug delivery system. Drug delivery via the skin is becoming progressively popular due to its convenience and affordability. The skin is the most important mechanical barrier to the penetration of many drug substances and acts as an ideal site to deliver the drug both locally and systemically. The topical route has been a favored route of drug administration over the last decades. Despite conventional topical drug delivery systems limits in poor retention and low bioavailability. This drawback overcomes by extensive research to develop a novel topical drug delivery systems targeting to improve the safety, efficacy and to minimize side effects. The conventional review focuses on dusting powders, poultices, plasters, lotion, liniments, solution, emulsion, suspension, colloidions, tinctures, creams, gels, ointments, pastes, suppositories, transdermal delivery systems, tapes, and gauzes and rubbing alcohol while the novel review focuses on novel gels, aerosol foams, microsponges, muco-adhesive bio-adhesives, novel vesicular carriers, nano-emulsion & nano-emulgel, protein and peptide delivery, polymers, emulsifier-free formulations and fullerenes etc. The key purpose of a topical delivery system is to enhance the skin permeability and to retain in the dermis. This review addresses a basis for further advancement and up-gradation of current techniques and technologies.



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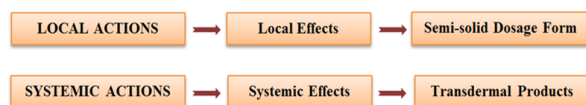
### INTRODUCTION

Dermal products applied topically are categorized based on those applied to produce local effects and systemic effects. These systems are generally used for local skin infections whereas other route of drug

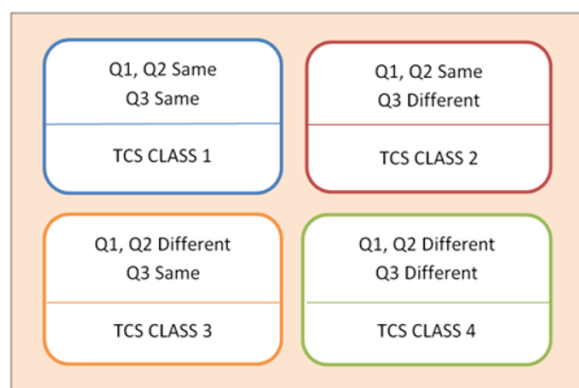
administration fails can be seen in Figure 1, (Asija *et al.*, 2013; Ueda *et al.*, 2010).

Drug molecules with low doses delivered through topical route effectively that are limited to a small area anywhere in the body. Stratum corneum is lipid-rich in nature composed of 40% lipids, 40% protein, and only 20% water. Lipophilic character of the drug is best suited for topical delivery whose transport is aided by dissolution into intercellular lipids around the cells of the stratum corneum. However, hydrophilic drugs are difficult to transport to the stratum corneum layer because of its low water content. These molecules are absorbed into the skin through "pores" or openings of the hair follicles and sebaceous glands that restricts drug absorption. Percutaneous absorption is an ideal factor considered in topical drug delivery systems in order to achieve and maintain a uniform, systemic, therapeutic levels throughout the duration of use.

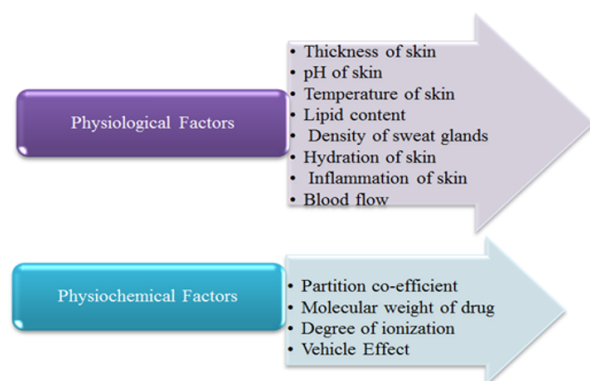
The drug delivered passively via skin should have adequate lipophilicity and a molecular weight of less than 500 Da. Drugs applied via dermally reaches the area in optimum concentration by reducing the side effects and by increasing bioavailability and patient compliance (Kaur *et al.*, 2016).



**Figure 1: Local and Systemic Actions**



**Figure 2: Classification of Topical Drug Products Based on Qualitative & Quantitative Composition**



**Figure 3: Physiological and Physicochemical Factors**

In topical drug delivery, the skin is one of the main and accessible organs on the human body. Stratum corneum forms a major penetration barrier to penetrate the drugs into and through the skin. However, this layer makes selective towards the delivery system. A key aspect of topical drug delivery is to make skin as a target organ for diagnosis and treatment. This review has more concerned with all detailed information regarding the conventional and current advances in topical drug delivery (Bhowmik *et al.*,

2012; Babiuk *et al.*, 2000; Purushottam *et al.*, 2013).

### Topical Drug Delivery

Topical drug delivery systems are localized drug delivery system for local delivery of therapeutic agents via skin to treat the cutaneous disorder. These systems are generally used for local skin infection. The formulations are available in different forms, like from solid through semisolid to liquid. If the drug substance in the solution has a favorable lipid/water partition coefficient and if it is a non-electrolyte, then drug absorption is enhanced via the skin. Dermatological products have various formulation and range in consistency though the most popular derma products are semisolid dosage forms (Hardenia *et al.*, 2014).

### Topical Drug Classification System (TCS)

Based on qualitative & quantitative composition, TCS provides a framework for classifying topical drug products. Topical drug products are classified into 4 classes, as seen in Figure 2, (Shah *et al.*, 2015).

### Rationale for topical preparation

With the purpose to formulate an efficient and effective topical preparation, considerations are mainly concerned with the site of action of the drugs and its effect. Topical preparations may be used produce:

#### Effects on Surface

These effects include,

1. The cleansing effect of removing germs and dirt.
2. Improves cosmetic appearance.
3. Protective action against moisture.
4. Produce an antimicrobial effect.

#### Effects on Stratum Corneum

1. Protectives that penetrate this layer.
2. Keratolytic action.
3. Moisturizing effect.
4. Effects on Viable epidermis and dermis: Anesthetic, anti-inflammatory, antihistamine, antipruritic, etc. are the major classes of drugs that penetrate these layers.
5. Systemic effects: The drugs responsible to produce systemic effects are nitroglycerin, scopolamine, clonidine, and estradiol.
6. Additional effects: These effects include antimicrobial, emollient, antiperspirant, depilatory (Bhowmik *et al.*, 2012).

### Advantages of topical drug delivery systems

1. Avoidance of primary pass metabolism.
2. Convenient to use and easy to apply.
3. Easily to terminate the medications.
4. Drug delivered selectively to a specific site.
5. The gastro-intestinal incompatibility will be avoided.
6. Provides drugs utilization with short biological half-life and narrow therapeutic window.
7. Better patient compliance.
8. Self-medication.
9. It provides effectiveness in low doses and by continuous drug input.
10. Avoids fluctuation in drug levels and risks.
11. A large area of application compared to other route.
12. Drug delivery at a specific site ([Sultana et al., 2014](#); [Kute and Saudagar, 2013](#)).

### Disadvantages of topical drug delivery systems

1. Possibility of local skin irritation at the site of application.
2. Contact dermatitis due to some drug may occur.
3. Some drugs with poor permeability are difficult to penetrate via the skin.
4. Drugs with larger particle sizes are difficult to penetrate.
5. Possibility of allergenic reactions.
6. Drugs with a very small plasma concentration can be used for action ([Sultana et al., 2014](#); [Kute and Saudagar, 2013](#)).

### Factors Affecting Topical drug absorption

The physiological and physicochemical factors that affect drug absorption are shown in Figure 3, ([Farage et al., 2006](#); [Vats et al., 2014](#)).

### Challenges for designing topical dosage form

The challenge of developing a successful topical product stems from the several requirements that a formulation must meet all the below criteria

**Table 1: Marketed Organogel Products**

Product Name	Drug
Diltigesic organogel	Diltiazem
Nifecaine organogel	Nifedipine + Lidocaine

**Table 2: Marketed Hydrogel Products**

Product Name	Drug
Galentic hydrogel	Glycerin
Dynarex hydrogel	Glycerin
Neutrogena	Olive extract, glycerin, hyaluronic acid

**Table 3: Marketed Emulgel Products**

Product Name	Drug
Voltaren Emulgel	Diclofenac-diethyl-ammonium
Clinagel	Clindamycin phosphate, allantoin
Avindo gel	Azithromycin
Pernox gel	Benzoyl peroxide

**Table 4: Marketed Aerosol Products**

Product Name	Drug
Minoxidil Topical Aerosol Foam	Minoxidil
Lidayn	Lidocaine
Cutiwash soft TM	Glycolic acid + Aloe-Vera juice

**Table 5: Marketed Microsponges products**

Product name	Drug
Retino-A-Micro	Tretinoin
Cerac cream	Fluorouracil
Ultra Guard	Dimethicone
EpiQuin Micro	Retinol and Hydroquinone
Lactrex TM	Lactic acid

**Table 6: Novel Carriers and their Applications**

Sr. No.	Novel Carriers	Carriers Application
1.	Archaeosomes	Archaeosomes are vesicles derived from a combination of the words archaea and liposomes. It is also referred to as liposomes made up of one or more ether lipids. A carrier for topical delivery of Betamethasone dipropionate (BMD), Molecular shielding, specific targeting ( <a href="#">Chaudhary et al., 2014</a> ).
2.	Aquasomes	Aquasomes are nanoparticulate carrier systems with three-layered (i.e., core, coating, and drug) self-assembled structures. Stable structure is formed through ionic, hydrogen & van der Waals links. It is the best carrier for the therapeutic delivery of proteins and peptides ( <a href="#">Chaudhary, 2018</a> ).
3.	Discomes	The discomes thermo responsive large disc-like niosomes. The addition of non-ionic surfactant leads to solubilization of the vesicles. It has applications in ligand-mediated drug targeting.
4.	Cryptosomes	Cryptosomes was derived from the Greek word Crypto means hidden, and Soma means body or carrier. The Cryptosomes is formed from the mixture of phospholipids like distearoyl-phosphatidylethanolamine-polyethylene glycol (DSPE-PEG) with di-stearoyl phosphatidylcholine. It is having application in ligand-mediated drug targeting ( <a href="#">Immordino et al., 2006</a> ).
5.	Dendrimers	The term dendrimer originates from the Greek word 'Dendron,' meaning a tree. Dendrimers are repetitively hyper-branched Nano-sized three-dimensional molecules. They have a tree-like shape with a central core, branches, and terminal group where the bioactive agents may be either encapsulated or chemically attached or physically adsorbed on the dendrimer surface. Dendrimers are used in transdermal and topical drug delivery systems for nonsteroidal anti-inflammatory drugs (NSAIDs), anti-cancer, anti-viral, anti-microbial, or anti-hypertensive drugs ( <a href="#">Kesharwani et al., 2014</a> ).
6.	Enzymosomes	Enzymosomes is an innovative, currently emerging targeted vesicular drug delivery system. Enzymosomes uses enzymes, which are having a targeted catalytic function for a substrate, which are incorporated within cell-like structures having a high lipid background. It yields newly designed liposomes in which the enzymes are coupled covalently to the surface of lipid molecules. Effective tools for targeted drug delivery ( <a href="#">Shefrin et al., 2017</a> ).
7.	Emulsomes	Emulsomes is a novel lipid-based drug delivery vesicular system consisting of phospholipid bilayer assembly with a polar core. Emulsomes in the form of gel are utilized for topical dermal delivery of drugs ( <a href="#">Ucisik et al., 2015</a> ).
8.	Ethosomes	Ethosomes are noninvasive method of delivering vesicular carrier composed mainly of phospholipids, alcohols, and water. It allows drugs to penetrate the deep layers of skin or systemic circulation ( <a href="#">Tiwari et al., 2010</a> )
9.	Erythrosomes	Erythrosomes are mechanically stable large proteoliposomes. This are cross-linked erythrocyte cytoskeletons, which supports to the coated lipid bilayer. Effective in targeting of macromolecular drugs.

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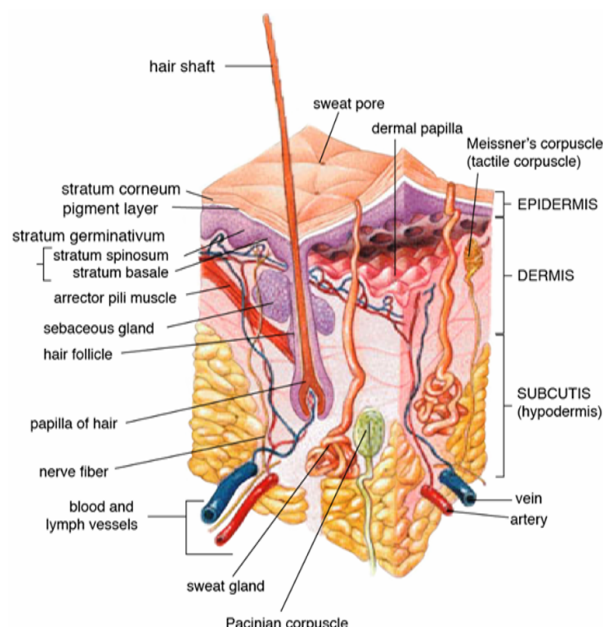
Table 6 continued

10.	Genosomes	Genosomes is a macromolecular complex of lipid and DNA used to deliver the genes. Due to its high biodegradability and stability, cationic lipids are preferred. Effective in cell-specific gene transfer.
11.	Liposome (Liposomal gel)	Liposomes are microscopic concentric bilayered vesicles in which aqueous compartments is entirely enclosed by lipid bilayer mainly comprised of natural or synthetic phospholipids. Effective in cosmetics (gels or creams) and in topical treatments of diseases in dermatology ( <a href="#">Schmid and Korting, 1996</a> ).
12.	Micelle	Micelles have to encapsulate hydrophilic drugs, which increases therapeutic efficacy and reduces the side effects of the drugs. Polymeric micelles enhance the drug deposition in targeted sites of the skin both in normal and dermatological diseases (psoriasis and acne) ( <a href="#">Makhmalzade and Chavoshy, 2018</a> ).
13.	Niosome (Proniosome gel)	Niosomes are non-ionic surfactant vesicles in which aqueous media is enclosed by a bilayer membrane consisting of cholesterol and a non-ionic surfactant. Topical niosomes may serve as a local depot for sustained release of active compounds via the dermal route ( <a href="#">Shatalebi et al., 2010</a> ).
14.	Novasomes	Novasomes are the modified form of liposomes (0.1-1.0 micron in diameter) containing 2-7 bilayer membranes consisting of unstructured space, which occupies the large amorphous core of hydrophilic and hydrophobic drug substances. It increases absorption rate via topical delivery of pharmaceuticals and cosmetics products ( <a href="#">Waghmare et al., 2016</a> ).
15.	Photosomes	Photosomes constituted of photolyase in liposomes, which is derived from photosynthetic plankton, called <i>Anacystis nidulans</i> that release the contents by photo-triggered changes in membrane permeability characteristics. They are incorporated in sun care products and in the cosmetic treatment system.
16.	Proteosomes	Proteosomes are high molecular weight large protein complexes involved in breaking down intracellular proteins by proteolysis. They are effective as an adjuvant and a protein carrier ( <a href="#">Tanaka, 2009</a> ).
17.	Solid-lipid nanoparticles (SLN)	Solid lipid nanoparticles are sub-micron colloidal carriers (50-1000 nm), which are composed of lipid dispersed in aqueous surfactant. Effective in the topical delivery of anti-inflammatory and anti-arthritis drugs ( <a href="#">Dasgupta et al., 2012</a> ).
18.	Transferosomes	Transferosomes are novel, elastic liposomes or deformable vesicle carriers composed of a phospholipid, surfactant, and water, which enhance drug delivery across the deeper skin layers. Enhances transdermal drug delivery ( <a href="#">Pawar et al., 2016</a> ).
19.	Vesosomes	Vesosome is a multi-layered, aggregated structure where large lipid bilayer encloses smaller liposomes. It is effective in active targeting ( <a href="#">González-Rodríguez et al., 2016</a> ).
20.	Virosomes	Virosomes are a class of unilamellar proteoliposomes vesicle incorporating virus-derived proteins in order to allow fusing with the target cell. These are target-oriented, having applications as immunological adjuvants ( <a href="#">Bhattacharya and Mazumder, 2011</a> ).

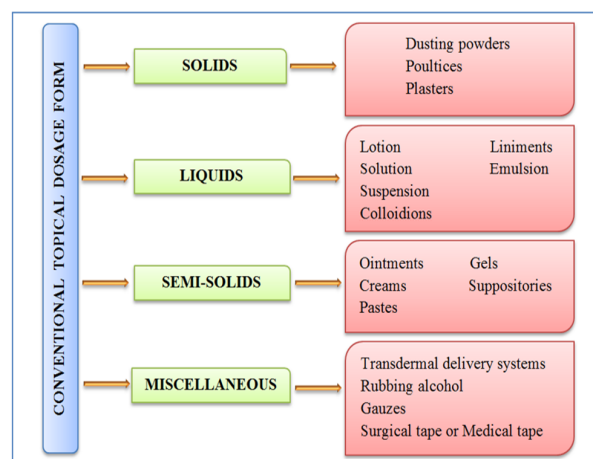
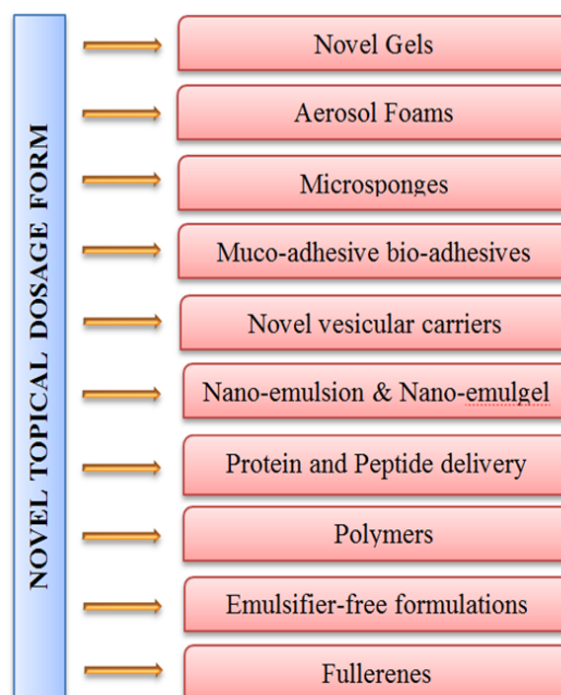


**Table 7: Strategies used to ease the peptide delivery through transdermal route**

Mode	Advantages
Passive diffusion	1. No modification of skin physical properties
Prodrugs	1. Drug protection 2. Increases permeability
Chemical enhancers	1. Increases permeability
Iontophoresis	1. Enhances penetration of the drug. 2. Noninvasive technique and painless procedure. 3. Permeation lag time is shortened.
Electroporation	1. Noninvasive technique 2. High degree of improvement
Ultrasound	1. Painless and noninvasive delivery

**Figure 4: Structure of Human Skin****Skin Penetration**

Skin penetration is the primary challenge to deliver the bioactive agents into the skin that follows Fick's first law of diffusion, which states the transfer rate of solutes as a function of the concentration of the various ingredients, the size of the surface area to be treated and the permeability of the skin. Percutaneous absorption is inversely proportional to molec-

**Figure 5: Classification of Conventional Topical Dosage Form****Figure 6: Novel Topical Drug Delivery System**

ular weight, which affects the diffusion coefficient. Further, permeability can also be affected by some of the factors such as the moisturizing, drying, or occluding effects of the excipients used in the formulation, which in turn modifies the drug release at the treatment site (Sultana *et al.*, 2014).

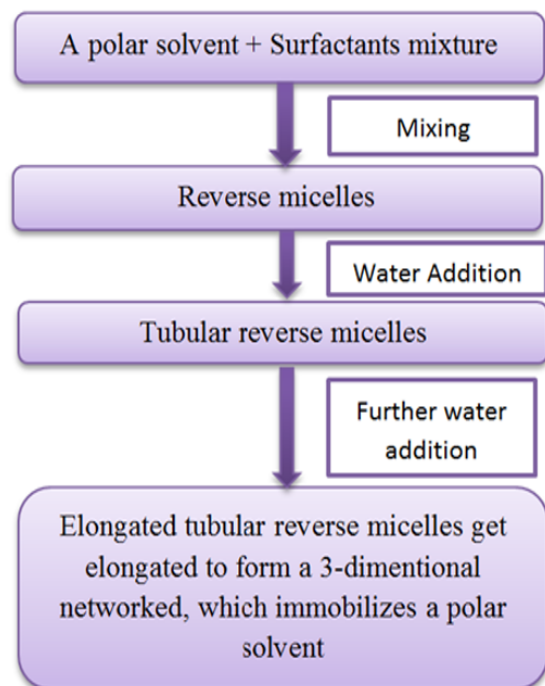
$$J = -D \cdot \{dC/dx\}$$

Where,

J is flux

D is the diffusion coefficient of the drug.

dC/dx is the concentration gradient



**Figure 7: Method of Preparation of Organogel**

### Skin pH

Drugs with molecular size larger than 500 Daltons are very difficult to penetrate stratum corneum. Formulation with high or low pH can harm the skin. Therefore moderate pH value is suitable for topical delivery. The degree of ionization at a particular pH also plays an important role (Bos and Meinardi, 2000).

### Stability

It provides a database studies at the stage of development to benefit the selection of formulation, excipients and container closure systems, to determine shelf life and storage conditions and to confirm that no changes in the formulation or process of manufacturing that adversely affect the product stability (Bajaj *et al.*, 2012).

### Acceptability

In the current scenario, the patients are eyeing for the topical products that are safe, effective, easy to apply, and cosmetically acceptable. In the case of acne, routines increase convenience and are disruptive minimally that increase compliance level and efficacy of the topical system.

### Container Selection

Container selection such as can, jar, tube, etc. provides a stable environment that depends on drug and excipients physicochemical properties, which protect from chemical degradation. The state of the

formulated product depends on API characteristics.

### Physiology of Human Skin

The skin is the largest accessible organ, accounting 15% of the whole adult body weight. The penetration of molecules in the skin mainly occurs through three routes, i.e., through intact stratum corneum, sebaceous follicle, and sweat ducts.

### Important functions of Skin

1. Prevention of excessive loss of water from the body.
2. Vital role in thermo-regulation.
3. An enzyme in epidermis can denature the drugs.

### Taxonomical classification

The skin is divided taxonomically into three scales:

1. Micro scale: It comprises of cells and layers of skin.
2. Meso scale: It comprises of skin features, hair, freckles, moles pores, skin surface, and wrinkles.
3. Macro scale: It comprises of body regions and body parts.

### Histological classification

1. Histologically, the skin is divided into epidermis, dermis, and hypodermis, as mentioned in Figure 4 in which collectively form a cover against external agents and loss of water from the body.
2. Histological classification: The skin is divided histologically into the epidermis, the dermis, and the hypodermis, which collectively forms a cover against an external agent and loss of water from the body.

### Epidermis

Epidermis consists of the non-viable epidermis (Stratum corneum) and viable epidermis. It is a stratified squamous epithelium layer, which is composed primarily of two types of cells: dendritic and keratinocytes cells. The epidermis layer harbor a number of other cells such as melanocytes, Merkel cells, and Langerhans cells. However, the keratinocytes cells type comprises the majority of the cells by far (Andrews *et al.*, 2013).

The layers of epithelium are,

**Stratum basale** (basal cell layer or stratum germinosum): It is the deepest basal sublayer composed of a single layer of basal cells. It is composed of merkel cells, melanocytes, keratinocytes, and stem cells. Stratum basale forms the boundary to the dermis that holds approximately 8% of the water in the epidermis. With aging, this layer becomes thinner and loses the ability to retain water.

**Stratum spinosum** (prickle cell layer): It lies between stratum granulosum and stratum basale. It is composed of 8-10 layers of cells that contain desmosomes. Their spiny appearance is due to shrinkage of the microfilaments between desmosomes.

**Stratum granulosum** (granular cell layer): It is consist of dying flattened granular cell in 3-5 layers. The thickness of this layer is 3  $\mu\text{m}$ . In this layer, keratinization of keratinocytes starts. Cell organelles like nuclei and mitochondria resolve. Cells become increasingly filled with keratin fibers and contain less moisture. The shape of these cells becomes much flatter during this process.

**Stratum lucidum** (clear layer): It is a thick skin that can only found in soles and palms that is composed of 3-5 rows of clear, flat, and more densely packed dead cells.

**Stratum corneum** (horny layer): Stratum corneum (non-viable epidermis) is the outermost layer of skin that is responsible for the barrier function of the skin. It is composed of dead, flattened corneocytes surrounded by an extracellular matrix of lipid, and its thickness various from 10-15  $\mu\text{m}$ . Epidermal keratinocytes, upon mortal differentiation, produce corneocytes. It conceals different enzymes, which help in the maintenance of health. It also helps to regulate the exchange of moisture and oxygen with the external environment. The chief route of permeation is around the corneocytes. The size of corneocytes depends upon the site of the body. Larger the size of corneocyte, longer will be the route of permeation. The cells are joined together by desmosomes, which maintains the cohesiveness of the layer. The stratum corneum is mainly composed of 40% protein and 40% water, along with the lipid components. The lipid classes in human stratum corneum involve ceramides, cholesterol, and saturated long-chain fatty acids. The water present in stratum corneum acts as a plasticizer prevents cracking and provides flexibility (Bouwstra and Gooris, 2010).

## Dermis

Once a drug molecule passes the stratum corneum, it passes the deeper epidermal tissues and enters

into the dermis. It is mainly made of fibrous tissues and is 1-2 mm thick. The dermis has a rich supply of blood vessels from where the drug gets absorbed into the general circulation. Sebaceous glands, sweat glands, and hair follicles rises to the surface of the skin from the dermis and subcutaneous layer where they originates. The skin surface of human is recognized to contain an average of 10-70 hair follicles and 200-250 sweat glands on every centimeter square of the skin area (Ali et al., 2015).

The dermis consists of the following sublayers,

### Papillary layer

Upper dermal sub-layer composed of loosely connected tissue and a large amount of nerve fibers, capillaries, fibroblasts cells, and water. In this sub-layer, collagen fibers form a fine network.

### Reticular layer

Lower dermal sub-layer, which is a denser and thicker network, composed of fewer nerve fibers and capillaries. In this sub-layer, collagen fibers are aggregated into thick bundles that are aligned parallel to the skin surface.

### Subcutaneous tissue (Hypodermis/Connective Tissue)

Subcutis is the third layer present underneath the dermis composed of a large number of fat cells, mainly acts as a shock absorber for blood vessels and nerve endings. An average thickness of this layer is 4 to 9 mm.

## Classification of Topical Drug Delivery Systems

### Conventional Topical Dosage Form

Conventional topical dosage forms meant to produce local or systemic effects can be classified, as shown in Figure 5, (Singla et al., 2012).

### Solid Topical Dosage Form

#### Dusting powders

Topical dusting powder (Desiccant) is a finely divided insoluble powder designed to deliver the drug to the target site. It is generally dusted on the broken or unbroken skin that reduces bacterial growth and skin infection. The chemical composition of dusting powder includes talc, zinc oxide, or starch. Due to its easy flow ability and spreadability, powder adheres easily to the skin by giving good covering and absorptivity. These are generally prepared by mixing two or more ingredients. One of the ingredients must be starch, talc, or kaolin in the formulation (Garg et al., 2015).

#### Poultice

The word poultice originated from the Latin Puls or Pulte is meaning "porridge". Poultices (Cataplasma)



are a soft, moist mass of solid substances spread on cloth over the skin in order to reduce inflamed or painful part of the body. They are often heated first then used as a medication on the skin while they are hot in order to supply warmth to inflamed or achy parts of the body.

E.g., Kaolin Poultice BP ([Kaur et al., 2016](#)).

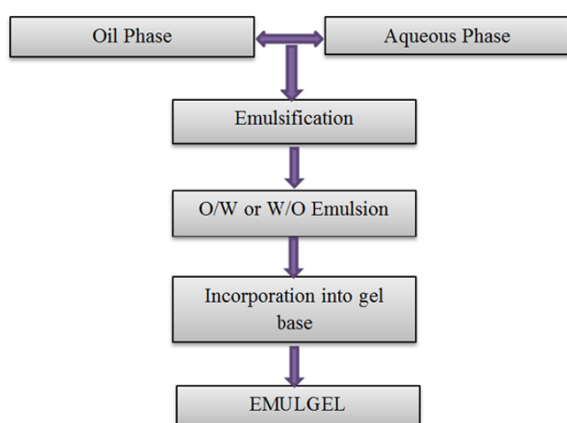
### Plasters

Plasters are solid or semisolid masses when spread upon cotton felt line or muslin as a backing material adhere to the skin. These are skin-friendly medical dressings generally used as a protective covering to cover all types of minor cuts, small wounds, burns, abrasions, scars, scratches & grazes, etc. It gives mechanical support and macerating action that brings medication in contact with the skin ([Boddupalli et al., 2010](#)).

### Liquid Topical Dosage Form

#### Lotions

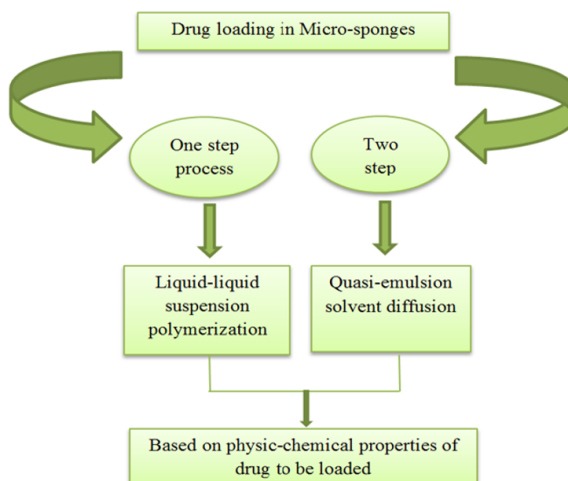
A skin lotion is a pseudo-stable mixture of water and oil, which has a greater percentage of water, and less viscous in nature intended for application on the skin. These lotions keep your skin smooth, nourished, moisturized, protected, and hydrated. On application, it spreads easily, absorbs quickly, and feels very light on the skin. Occlusive agents in the lotion retard the water loss by restoring moisture in the surface. This additional moisture alleviates the problems associated with dry skin. Types of lotions include hand lotions, face lotions, body lotions, after shave lotions, and antiperspirants ([Bhowmik et al., 2012](#)).



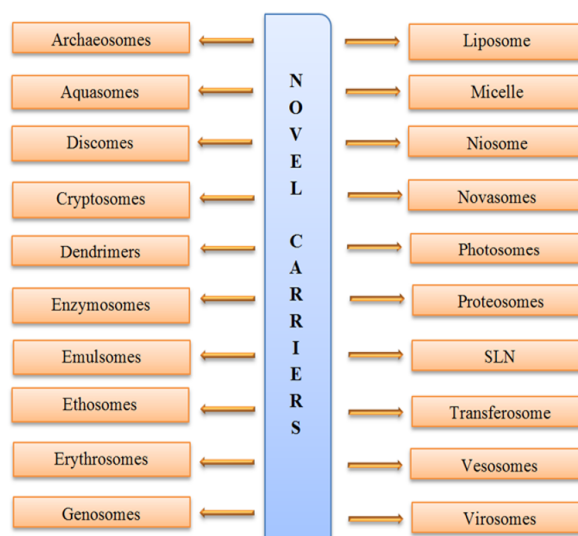
**Figure 8: Method of Preparation of Emulgel**

#### Liniments

Liniments are alcoholic or oleaginous liquid or semiliquid preparations of solutions or emulsion with suitable antimicrobial preservatives. They are less viscous than lotions and are usually rubbed on



**Figure 9: Method of Preparation of Microsponges**



**Figure 10: Emerging Novel Carriers for Topical Drug Delivery**



**Figure 11: Molecular Structure of C<sub>60</sub> Fullerene**

the skin to create friction. Generally used as antipruritic, astringents, emollients, analgesics, rubefacient, counterirritant. Types of liniment include alcoholic liniment and oleaginous liniment. Liniments are intended for external application and should be labeled as "external use only" ([Garg et al., 2015](#)).

Examples: Compound calamine liniment; Efficacent oil; White liniment.

### Solutions

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

Examples: Aluminum acetate topical solution; Povidone iodine topical solution.

### Emulsions

Emulsions are thermodynamically unstable biphasic liquid dosage form in which one phase (dispersed phase or internal phase) is finely dispersed in other phase (continuous or external phase). It must be stabilized by the addition of an emulsifying agent.

Types of emulsions,

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

Theory of emulsion,

1. Surface tension theory
2. Surface adsorption theory
3. Oriented-wedge theory
4. Plastic film theory (Interfacial film theory)

Preparation of Emulsion,

1. Dry gum method (Continental Method)
2. Wet gum method (English or American method)
3. Bottle Method or Forbes Bottle Method

Stability of Emulsion,

1. Creaming or Sedimentation

2. Aggregation and co-alescence (Creaking or Breaking of emulsion)
3. Phase Inversion
4. Microbial Growth ([Khan, 2011](#)).

### 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 consists of two phases.

1. The continuous phase (external phase/suspending medium) is usually a liquid or semisolid
2. The dispersed phase (internal phase) is made up of insoluble solid particles having a size range 0.5 to 5 microns.

Example: Calamine lotion ([Nutan and Reddy, 2010](#)).

### Collodion

Collodions are clear or slightly opalescent liquid preparations meant for external application on the skin. They consist of film-forming substance, nitrocellulose (pyroxylin) in volatile solvents like alcohol, ether, and acetone. After the application of collodion, it shrinks as the volatile solvent evaporates and leaves a thin, flexible transparent protective covering film on the affected part.

Uses,

1. To close the small wounds, abrasions, and cuts.
2. To hold the surgical dressings in place and to keep medicaments in contact with skin.

Examples: Flexible Collodion-B.P, Salicylic acid Collodion-B.P.C ([Venkateswarlu and Devanna, 2014](#)). A textbook of general and dispensing pharmacy: Edition 1: Pharmamedix India Publication Pvt. Ltd.).

### Tincture

These are liquid extracts, which are alcoholic or hydro-alcoholic solutions of non-volatile drug of vegetable and chemical origin, which causes a stinging sensation on application to abraded or broken skin. It contains 1 part of the drug in 5 parts of the solvent. Alcohol content may vary from 25- 60% (US proof)

To qualify as an alcoholic tincture,

1. Ethanol percentage of the extract must be of at least 25- 60% (50-120 US proof).
2. Herbal medicines with various ethanol concentrations of 25%.
3. Sometimes alcohol concentration as high as 90% (180 US proof) is used in tinctures.

### Method of preparation

#### By Extraction Method

1. Maceration
2. Percolation

#### By simple solution

Examples,

Compound Benzoin Tincture

Iodine Tincture

Thimerosal ([Richmond and Stevenson, 2017](#)).

### Semi-solid Topical Dosage Form

#### Ointments

The word ointment derived from the Latin ungere meaning anoints with oil. Ointments are semi-solid preparations meant for topical application to the skin or mucous membrane used to provide a protective and emollient effect. Upon shear stress, it behaves as viscoelastic materials. They generally contain medicament or medicaments dissolved, suspended, or emulsified in an ointment base (vehicles).

Ointments classification based on penetration of skin,

These ointments are applied topically on the external skin. These are of three types,

1. Epidermic ointments
2. Endodermic ointments
3. Diadermic ointments

Ointment bases: They act as a carrier for the medication.

1. Oleaginous (hydrocarbon) bases
2. Absorption (Emulsifiable) bases
3. Emulsion bases (water removable bases)
4. Water-soluble (Greaseless) bases.

#### Preparation of ointments,

Following methods are used in the ointment preparation,

1. By Trituration method
2. By Fusion method
3. By Chemical reaction method
4. By Emulsification method.

#### Creams

Pharmaceutical creams are semi-solid emulsions of oil and water containing one or more drug substances dissolved or dispersed in a suitable base. They possess a relatively soft, spreadable consistency than ointments.

Types of creams,

1. Oil- in- water cream: E.g. Vanishing cream
2. Water -in- oil cream: E.g. Cold cream

Advantages of Cream,

1. Quick, Convenient, pain-free, affordable, and easy to apply.
2. Avoidance first pass metabolism of risk.
3. Non-irritating, less greasy
4. Avoid fluctuation of drug levels

Method of Preparation:

1. Preparation of the oil phase
2. Preparation of the aqueous phase
3. Forming the emulsions (O/W OR W/O)
4. Dispersion of the active ingredients ([Sahu et al., 2016](#)).

#### Pastes

Pastes are semisolid preparations containing a mixture of insoluble particulate solids and ointment intended for application to the skin. Types of paste include fatty Paste and non-greasy paste. The method of preparation of pastes includes the trituration method and fusion method. They are less penetrating, less macerating, and less heating than the ointment. They are less greasy, less penetrating, less macerating, less heating, and more stiffer than ointments. They make particularly good protective barriers when placed on the skin for. In addition, it acts as a good protective barrier by forming an unbroken

film. It contains a solid, which absorb and neutralize certain noxious chemicals before they penetrate into the skin. Like ointments, paste forms an unbroken relatively water-impermeable film, unlike gels.

E.g., Zinc oxide paste; Anthralin paste.

### Gels (Jellies)

Pharmaceutical Gels are semisolid preparations consisting of dispersions of small or large molecules in an aqueous liquid vehicle rendered jelly-like through the addition of a gelling agent. The vehicles may be aqueous/ hydro alcoholic/ alcohol-based/ non-aqueous type.

Types of gels,

1. On the basis of the continuous phase
2. Organogels
3. Hydrogels
4. Xerogels

Based on the nature of the bond involved in the 3-dimensional solid network.

1. Dispersed solids
2. Hydrophilic polymers: Type I & Type II
3. Method of preparation
4. Fusion method
5. Cold method
6. Dispersion method.

### Suppositories

Suppositories are the solid medical preparations meant to be inserted into rectum, urethra, and vagina, where they dissolve or melt or soften to release the drugs and exert local or systemic effects. They are prepared by molding by hand, compression, pour molding, and compression in a tableting machine. Commonly used bases are glycerol-gelatin, theobroma oil, cocoa butter, and polyethylene glycol.

### Miscellaneous

#### Transdermal drug delivery system

TDDS are self-contained discrete dosage forms, which deliver the drug at a controlled rate to the systemic circulation when applied to the intact skin. They offers many advantages such as reduced side effects, improved patient compliance, sustained drug delivery, and elimination of the first-pass metabolism.

Basic components of Transdermal drug delivery

1. Polymer matrix or matrices
2. The drug
3. The permeation enhancers
4. Other excipients

Formulation Approaches used in the development of TDDS

1. Membrane permeation – controlled systems.
2. Adhesive dispersion – type systems.
3. Matrix diffusion-controlled systems.
4. Micro reservoir type or Micro sealed dissolution – controlled systems
5. Poroplastic – type systems.
6. Transdermal delivery of Macromolecules ([Tanwar and Sachdeva, 2016](#))

### Liquid cleaner

This medication is used as a cleansing product to treat acne and other skin conditions like seborrheic dermatitis, rosacea, etc. It is also used to remove dust, dirt, stains, bad smells, and clutter on surfaces. This product contains an antibacterial agent and drying agent, which promotes the shedding of the top layer of skin (keratolysis).

### Rubbing alcohol

Rubbing alcohol or ethanol-based liquids or surgical spirit used primarily as a topical antiseptic. These are volatile and flammable. It kills or prevents the growth of bacteria on the skin. It is used as a topical rub to help relieve minor muscle pain

### Gauzes

Gauze is a bandage, which is a simple natural fiber woven strip of material with a permeable barrier effective in wound dressing. It varies in widths and lengths. It helps to prevent adherence to wounds and to hold a dressing in place.

### Surgical tape or Medical tape

Surgical tape or Medical tape is a type of pressure-sensitive adhesive tape, usually hypoallergenic adhesives. They are made up of micro porous material (3M Micro-pore), usually contains zinc oxide, which helps to mitigate infections. These tapes allow air to reach the skin. They are used in first aid to hold the dressing bandage on the wound, which are designed to hold firmly on the skin and can be easily removed without damaging the skin.

## Novel topical drug delivery systems

The following are the emerging advances in the topical drug delivery system, as shown in Figure 6.

### Novel Gels

Novel gel preparations include,

#### Organogels

Organogels are class of gel based on liquid organic phase useful to deliver lipophilic drugs topically. Organogel exerts both local and systemic effects through percutaneous absorption enhanced by the presence of a penetration enhancers.

Advantages of organogels

1. It acts as a template vehicle
2. Process benefits
3. Structural/physical stability
4. Chemical stability
5. Topical delivery potential-
6. Safety cost-effective.
7. Both hydrophobic and hydrophilic drugs can be incorporated.
8. Enhances skin penetration ([Sreedevi et al., 2012](#)).

Method of Preparation of Organogel

Organogel preparation is shown in Figure 7.

The marketed organogel products are listed in Table 1.

### Hydrogels

Hydrogels are the polymeric material that will not dissolve in water but has the ability to swell and trap a large fraction of water in the 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.

Advantages

1. Degree of flexibility very similar to natural tissue.
2. Release of medicines or nutrients timely.
3. Biocompatible and biodegradable.
4. They have the ability to sense changes of pH, temperature, or the concentration of metabolite and release their load as a result of such a change.

5. They possess good transport properties and easy to modification ([Ahmed, 2015](#)).

### Method of Preparation

Based on the methods of preparation, hydrogels are classified as

1. Homo-polymer
2. Copolymer
3. Semi interpenetrating
4. Interpenetrating network.

The list of Hydrogel products are listed in Table 2.

### Emulgels

Emulgels are a combination of emulsion and gel. Favorable properties of emulgel include transparent, pleasing appearance, emollient, easily spreadable and removable, thixotropic, greaseless, non-staining, long shelf life, and bio-friendly. They require the factors that increase percutaneous absorption.

Types of emulgel

1. Macro-emulsion gel
2. Nano-emulgel
3. Micro-emulgel

Advantages

1. Incorporation of hydrophobic drugs
2. Better loading capacity
3. Better stability
4. Production feasibility
5. Control release, less cost.
6. No rigorous sonication required

The flow chart of the method of preparation of emulgel (Figure 8), ([Panwar et al., 2011](#))

### Marketed Preparations

The marketed products of emulgel are listed in Table 3.

### Aerosol Foams

Aerosol foams are pressurized dosage forms, which contain one or more active ingredients; upon valve actuation, they emit a fine dispersion of liquid and/or solid materials in a gaseous medium.



The category of drugs in aerosol foams includes antiseptics, antifungal agents, anti-inflammatory drugs, local anesthetics, skin emollients, and protectants (Zhao *et al.*, 2010). Foam formulations are advantageous, i.e., easier to apply, less dense, and good spreadability. Excipients include active agents, propellant, surface-active agents, solvents, co-solvents, and viscosity-modifying agents.

Types,

#### Water containing foams

1. Hydrophilic emulsion foam
2. Lipophilic emulsion foam
3. Nano-emulsion foam
4. Aqueous foam
5. Hydroethanolic foam
6. Potent solvent foam
7. Suspension foam

#### Water-free foams

1. Ointment foam
2. Hydrophilic ointment foam
3. Oil foam
4. Saccharide foam

#### Aerosol foams can be prepared by various methods,

1. Whipping, i.e., mechanical agitation of a liquid or a solution,
2. Bubbling, i.e., injecting a stream of gas or liquid or the mixture into a liquid, and
3. Rapid pressure reduction, i.e., sudden actuating the valve of pressurized systems (a solution or emulsion or suspension) (Purdon *et al.*, 2003)

The inclusion of foam excipients in the pressurized canister usually employs a method called 'pressure-fill'.

Engineering foam vehicles to enhance topical drug delivery can also be combined with other skin delivery enhancement strategies. Dynamic topical foams have already been a useful addition to conventional topical formulation approaches, as can be seen from the growing number of topical foam products on the market and the increasing number of foam patents

filed in recent years (Purewal, 1998). The marketed products of aerosol are listed in Table 4.

#### Microsponges

Microsponges are microscopic, uniform, tiny sponge-like spherical, large porous polymeric microspheres that entrap active material. Typically, they are 5-25  $\mu\text{m}$ . This unique technology consists of micro porous beads of size 10-25 microns in diameter, loaded with an active agent.

Advantages,

1. Enhanced product performance.
2. Site-specific action and extended drug release.
3. Reduces skin irritation and improves patient compliance.
4. Elegancy, flexibility, bioavailability, thermal, physical, and chemical stability can be improved.
5. Non-mutagenic, non-irritating, non-allergenic and non-toxic.
6. Immiscible products can be incorporated (Pentewar *et al.*, 2014)

#### Method of Preparation

1. Liquid-liquid suspension polymerization
2. Quasi-emulsion solvent diffusion (Figure 9)

The marketed microsphere products are listed in Table 5.

#### Muco-adhesive bio-adhesives

Bioadhesion is defined as the state in which two materials, at least one biological in nature, are held together for an extended period by interfacial forces.

In biological systems, bioadhesion can be classified into 3 types,

Type 1: Adhesion occurs between two biological phases

Type 2: Adhesion of a biological phase to an artificial substrate.

Type 3: Adhesion of an artificial material to a biological substrate.

#### Advantages

1. Better patient compliance, ease of drug administration, and rapid onset of action.
2. Avoid the first-pass metabolism.
3. Expands the residence time of the dosage form at the site of absorption.

4. Therapeutic efficacy of the drug will be high.
5. Good accessibility and rapid absorption.
6. Drug bioavailability increases.
7. Drug degradation is protected from an acidic GIT environment.

### Theories Of Mucoadhesion

Various theories exist during the bio adhesion process. They are,

1. Wettability theory
2. Electronic theory
3. Fracture theory
4. Adsorption theory
5. Diffusion theory ([Phanindra et al., 2013](#))

### Novel vesicular carriers

Extensive research is required for an effective development to deliver the drug. Many skin diseases are found to be deeply located in dermal layers of the skin, such as acne, alopecia, and psoriasis. Conventional dosage forms are seemed unable to be effective in treating these conditions because of poor retention in the skin. Therefore, there has been a need to explore a new system for the management of such topical diseases. For the drug to deliver topically, vesicular are considered as a carriers or penetration enhancer. These carriers are the most recognized methods in which bioactive agents are encapsulated in the vesicle prepared by using phospholipids and non-ionic surfactants that transport drugs across the skin. Vesicles are the water-filled colloidal particles whose walls are made up of amphiphilic molecules in a bilayer. These vesicles in the presence of water form unilamellar or multilamellar concentric bilayer vesicles<sup>73</sup>. Vesicular carriers are advantageous as they reduce the cost of therapy, improves the bioavailability of poorly water-soluble drugs. Hydrophilic drugs are enclosed within an internal aqueous region, while lipophilic drugs are enclosed within the vesicular bilayer. Many skincare cosmetics like sun screening agents, humectants, and tanning agents are delivered by enclosing them in vesicles. A number of emerging novel vesicular carriers are developed for further improvement in topical drug delivery via the skin as shown in Figure 10 and Table 6, ([Arora et al., 2014](#); [Chiranjeevi et al., 2013](#))

### Nanoemulsion and Nanoemulgel

Nanoemulsions are Nano-scale size (droplet size of diameter 20-200 nm) that are stable emulsions and necessitates emulsifying agents to target poorly soluble drugs in order to increase penetration, increase absorption, better retention time and minimizes the side effects. Due to its Nano-sized particles, a larger amount of drug can be incorporated into the formulation, which enhances thermodynamics towards the skin. Moreover, the drug affinity for partitioning increases permeation into the skin. Nanoemulgel is defined as the nanoparticle composed of nano-emulsion and hydrogel matrix formed by the addition of the nano-emulsion system intergraded into the hydrogel matrix, which influences a better skin penetration. Nanoemulgel acts as a drug reservoir. On intact with the skin, they release the oily droplets from the gel network. The oil droplets then penetrate into the stratum corneum of the skin and directly deliver the drug molecules without a transfer via hydrophilic phase of nanoemulsions

### Advantages of Nanoemulgel

1. Good adhesion property
2. Delivery of lipophilic drugs can be improved.
3. Gelling capability gives a stable formulation
4. Permeation enhancement
5. Better patient compliance
6. Controls the drug release by prolonging the drug with a shorter half-life ([Sutradhar and Amin, 2013](#)).

### Protein and Peptide delivery

In order to avoid protein and peptide degradation via the gastrointestinal tract, protein and peptides are delivered through the transdermal route. Delivery can be disturbed by removing the device. Its prime problem is that the skin acts as an excellent barrier to large, polar hydrophilic drugs ([Amsden and Goosen, 1995](#)). Strategies used in the delivery of peptide is shown in Table 7.

### Polymers

Polymers play an important role in designing topical formulation, which serves as a building block. These are huge molecules composed of repeated monomeric units that are connected chemically by a covalent bond. Synthetic polymers have played milestone functioning within the pharmaceutical sector. In dermatology, an acrylic acid polymer in the presence of water forms a gel by water entrapment microcells. Hydrophilic molecules remain in a solution inside aqueous

microcells, whereas hydrophobic compounds are dispersed in suspension that results in a stable gel, which upon application releases the active compound. The synthetic polymers such as polyesters, polyamides, polyurethanes, poly anhydrides, and poly(orthoesters) show advantages of reproducibility, a range of material properties, and biodegradability, while the natural polymers including polysaccharides, proteins, and lipids have been widely exploited because of the range of materials and properties available, particularly biocompatibility (Tadwee *et al.*, 2012).

Example: BenzaClin® (Clindamycin 1% + Benzoyl peroxide 5%).

### Emulsifier-free formulations

A new formulation developed for both dermatologic and cosmetic products are Emulsifier-free formulations. These formulations are easy to process and suitable for O/W and W/O emulsions. They offer a melting texture with non-tacky skin feel and ease of distribution. Most of the dermatological products are an emulsion. When the mixtures of two or more material are not miscible with each other, they are inherently unstable. Therefore, they require emulsifiers (surfactants) to stabilize it. These emulsifiers on application emulsify and remove natural lipids present on the epidermis. Therefore, the pharmaceutical industry has been developing surfactant-free emulsions by using stabilizers in order to produce stable products with a pleasant appearance (Tadwee *et al.*, 2012).

### Fullerenes

It is a C<sub>60</sub> molecule (an allotrope of carbon) containing a hollow molecular sphere that are highly conjugated by 30 carbon double bonds (Figure 11).

Fullerenes acts as a strong anti-oxidant that effectively quenches radical oxygen species (ROS) that are widely used as an active compound in the formulation of skincare products. On application, they entrap active compounds and release them to the epidermis. Therefore these are promising agents in dermatologic and cosmetic products. An anti-inflammatory role has also been identified for fullerenes so fullerene in the gel form is used in the treatment of acne vulgaris (Lens, 2011; Rouse *et al.*, 2007).

### CONCLUSIONS

The current review focuses on conventional and novel advances in topical drug delivery. Over the last few decades, the topical drug delivery system is gaining attention. However, conventional topical

drug delivery suffers from major drawbacks. Comparatively, novel formulation proves to be better in terms of patient compliance, safety, efficacy, feasibility, and shelf life. Extensive research is made to progress in novel topical drug delivery. So, it can be concluded that converting conventional formulation to novel formulation by using carriers requires extensive research, which provides new hope to mitigate several diseases. In the future, these carriers associated delivery become a milestone for hydrophilic drug delivery via the skin.

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### Conflicts of interest

The author confirms that this article content has no conflicts of interest.

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