CODEN [USA]: IAJPBB **ISSN: 2349-7750**

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.2978025

Available online at: http://www.iajps.com ***Review Article***

TOPICAL PREPARATION: PAST, PRESENT AND FUTURE PERSPECTIVE – A REVIEW

[1]Vrushali Rajkumar Kale, [2]Dinesh Chhotu Pawar [3]Pradum Pundlikrao Ige
[1]R. C. Patel Institute of Pharmaceutical Education and Research, Shirpur.

Article Received: March 2019 **Accepted:** April 2019 **Published:** May 2019

Abstract:
Topical drug delivery is defined as the application of pharmaceutical dosage form to the skin for direct treatment of cutaneous disorder or the cutaneous manifestation of the general disease, with the intent of limiting the pharmacological or other effect of the drug to the surface of the skin. The skin presents a first line of defence against a wide range of bacterial invaders. The topical route offers several advantages, including the avoidance of systemic toxicity and side effects. Topical dosage forms have been generally classified as liquids, semisolids, and solids. They contain one or more active ingredients dissolved or uniformly dispersed in a suitable base and any suitable excipients such as emulsifiers, viscosity-increasing agents, antimicrobial agents, antioxidants, or stabilizing agents. The most conventional and probably well - known topical dosage forms are creams, gels, and ointments. This review is concern with all detail information regarding approaches to topical formulations, and their permeation.

Keywords: *Topical drug delivery system, semisolid dosage form, skin structure, skin disease, etc*

Corresponding author:
Dr. Pradum Pundlikrao Ige,
Associate Professor, Department of Pharmaceutics,
R. C. Patel Institute of Pharmaceutical Education and Research,
Shirpur, Dist-Dhule, Maharashtra 425405.

QR code

Please cite this article in press Pradum Pundlikrao Ige et al., ***Topical Preparation: Past, Present And Future Perspective – A Review.,*** *Indo Am. J. P. Sci, 2019; 06(05).*

INTRODUCTION:

Topical drug delivery system:

Topical drug product administration is a localized drug delivery technique everywhere in the body via ophthalmic, rectal, vaginal and skin as topical routes. The main route of topical drug administration isskin; is one of the best voluntarily reachable organs on human body for topical drug delivery system [1]. Skin, the most reachable organ of the body, keeps significant barrier properties that inhibit the passive transport of many topically applied product. This barrier is commonly due tothe existence of keratin-rich corneocytes and intercellular lipid arrangements in the toplayer of the skin, the stratum corneum (SC)[2]. The topical dosage form are composed of drug in a appropriate semisolid base which is either hydrophobic or hydrophilic in properties. They consist one or more active ingredients dissolved or consistently dispersed in a proper base and any appropriate additives such as emulsifying agents, viscosity-enhancer, antimicrobial agents, antioxidants, or stabilizing agents. Drug which can topically deliver through skin falls under two types: either by applying for local effect or superficial effect or for systemic effects. Local effect includes action of drug on surface of skin i.e on the epidermal layer the stratum corneum or it will modify the function of epidermis and dermis [3].

Conventional topical dosage forms are classified into three categories: liquid, semi-solid and solid. Liquid topical dosages include low viscosity emulsions (otherwise known as lotions), suspensions, and solutions. Collodions, foams, ointments, pastes, creams and gels are included in semi-solid topical dosage forms. Solid topical dosage forms include powders, patches, gauzes, tapes and sticks. These dosage forms vary widely according to their physical characteristics.The major barrier layer of skin, the stratum corneum, containing an interstitial lipid passage and a proteinaceous cellular section. Drug molecules enter the skin mainlyin the tortuous and continuous intercellularpath. Transport of topical drugs, especially with the aid of solvents and enhancers used in the formulation, may also occur through a transcellular route, the hair follicles, or sweat ducts. Only the drug in the molecular state can penetrate through the skin. Occluded skin, e.g., the application of ointment on the skin, may retain significant amounts of the transepidermal water and facilitate drug transport through the hydrated skin. States with diseased skin, such as atopic dermatitis, psoriasis, and warts, may have effects on the barrier property of skin, which must be considered for the drugs geared toward these skin diseases. From a drug delivery perspective the concentration gradient between the formulation and site of action provides the driving force for penetration of drug through the skin.

Thus saturation of the drug in the vehicle having a thermodynamic activity of unity provides a larger driving force for transporting through the skin than a formulation at a lower fraction of saturation (e.g. highly solubilized system). Super-saturated conditions having a thermodynamic activity greater than unity, can further enhance the drug delivery through skin. However, a drug in a super-saturated solution is in a metastable state and, hence, may convert back to its stable form, thus changing the flux of the drug through skin [4].

Advantages of Topical Dosage Form:

Convenient and easy to apply a topical dosage form
Avoidance of the risk and inconveniences of intravenous therapy and of the varied conditions of absorption, like pH changes, presence of enzymes and gastric emptying time etc.
Avoids fluctuation in drug levels, inter and intra-patient variations.
Ability to easily terminate the medications when needed.
Relative large area of application in comparison with buccal or nasal cavity.
Ability to deliver drug more selective to a specific site.
Avoidance of gastro-intestinal incompatibility.
Providing utilization of drugs with short biological half-life, narrow therapeutic window.
Improved Patient compliance. Suitability for Self – medication [5].

Disadvantages of Topical Dosage Form:

Skin irritation or contact dermatitis may occur due to the drug and/or excipients.
Poor permeability of some drugs through the skin.
Possibility of allergenic reactions due to additives which is allergic.
Can be used only for drugs which require very small plasma concentration for action.
Enzymes in epidermis may denature the drugs.
Drugs of large particle size not easy to absorb through the skin [5].

Anatomy and physiology of skin:

Skin is the largest organ of the body. It is not uniformly thick. Skin is biggest external defence system. Skin covers the outside of the body but has other functions beside the defence mechanism. Temperature of skin varies in a range of 30 to 40 °C degree depending on the environmental conditions [6].

Anatomy of skin:

It consists of three layers. The outer layer is called epidermis, the middle layer is dermis and the inner most layer is hypodermis.

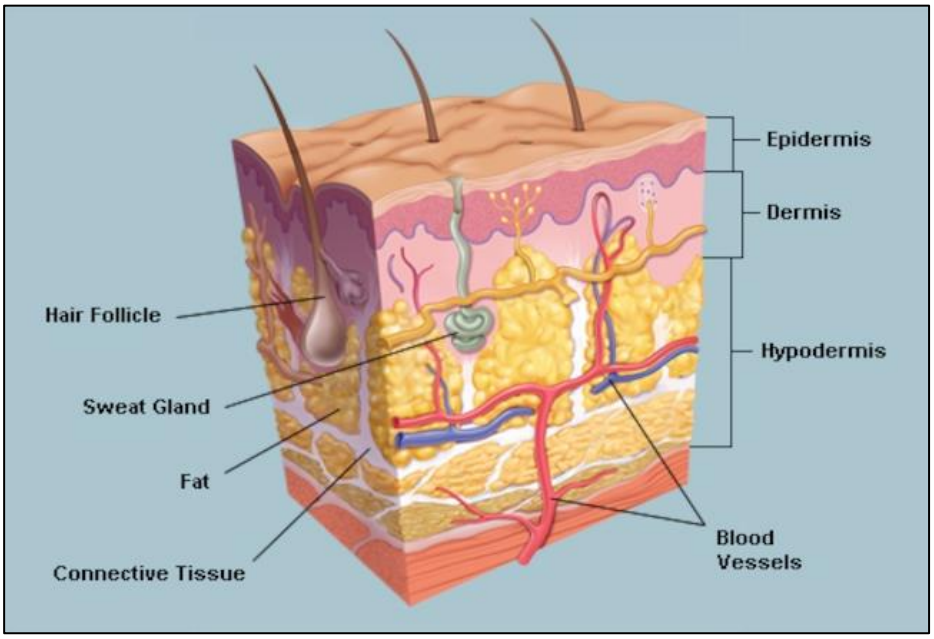

Figure1: Anatomy and physiology of skin

Epidermis:

The epidermis of the skin is formed by stratified epithelium, which is made up of 5 layers:

Stratum corneum, Stratum lucidum, Stratumgranulosum, Stratum spinosum, Stratum germinativum

Stratum corneum: It is also known as horny layer. It is the outer most layer and consists of dead cells which are called corneocytes. These cells lose their nucleus due to pressure and become dead cells. The cytoplasm is flattened with fibrous protein known as keratin. Apart from this, these cells also contain phospholipid and glycogen.

Stratum Lucidum: It is made up of flattened epithelial cells. Many cells have degenerated nucleus and, in some cells the nucleus is absent. As these cells exhibit shiny character, the layer looks like a homogenous translucent zone. So, the layer is called stratum lucidum (Lucid = clear).

Stratum Granulosum: This is a thin layer with 2 to 5 rows of flattened rhomboid cells. The cytoplasm contains keratohyaline granules. The protein keratohyaline is the precursor of keratin.

Stratum Spinosum: This layer is also known as prickle cell layer because; the cells of this layer possess some spine like protoplasmic projections. By these projections, the cells are connected to one another.

Stratum Germinativum: This is a thick layer made up of polygonal cells superficially and columnar or cuboidal epithelial cells in the deeper parts. Here new cells are constantly formed by mitotic division. The newly formed cells move continuously towards the stratum corneum. The stem cells are known as keratinocytes. From this layer; some projections extend down up to dermis. These projections provide anchoring and nutritional function. The colour of the skin depends upon this layer which contains the pigment melanin [7].

Dermis:

The Dermis is an integrated system of fibrous, filamentous,and amorphous connective tissue that accommodates stimulus-induced entry by nerve and vascular networks, epidermally derived appendages, fibroblasts macrophages, mast cell.The dermis comprises the bulk of the skin andprovides its pliability, elasticity, and tensile strength. It protects the body from mechanical injury, binds water, aids in thermal regulation, and includes receptors of Sensory stimuli. The dermis interacts with the epidermis in maintaining the properties of both tissues Dermis is positioned under epidermis and is characterized by lots of elastin fibres that provide thestretching ability as well as lots of collagen that provides the strength to the skin. Blood vessels found in dermisprovide nutrients for both dermis and epidermis. Dermis also plays a

major role in temperature regulation.Dermis has a thickness of 3-5mm[8].
Dermis consisting of 2 different layers: Superficial papillary layer and deeper reticular layer.
Superficial papillary layer: This papillary dermis locates into the epidermis. This layer consist of lightly arranged bag of collagen, blood vessels, lymphatic's, nerve and elastic fibres. This layer also containing cells called as chromatophores.

Reticular layer: This layer is made up of reticular and elastic fibres. These fibres are found around the hair bulbs, sweat glands and sebaceous glands. The reticular layer composed of dense collagen fibers, thicker elastic fibers, deep part of epidermal appendages, and vascular and nerve systems[9] .The dermis ranges from2000 to 3000 μm thick, containing a matrix of loose connective tissue composed of collagen, elastin, and reticulum (fibrous proteins) implanted in an amorphous ground material [10].

Hypodermis:
Hypodermis is the deepestlayer of skin. It is the layer between skin and the inner tissuesin body such as muscles and bone. Sweat glands, sebaceous glands and hair follicles enclose in epidermisbut they stem from dermis. Sweat glands discharge a dilute salt solution into the surface of skin. The evaporation ofthis solution makes skin cool and this is important for temperature regulation of both body and skin. Sweetglands are present all over the body. The amount of dilutions (sweet) that gets produced depends onenvironmental temperature, the amount of heat generating skeletal muscle activity and various emotionalfactors. The sebaceous glands produce sebum. Sebum is an oily liquid released into hair follicles and from thereonto the skin surface. Sebum protects both hair and skin from drying out and provides waterproof layer [11].

Function of skin:
Protection-The skin show a moderately waterproof layer, delivered mostly by its keratinised epithelium protecting inner and more delicate arrangements. Provide mechanical barrier against the external environment. Defence against solar UV radiation.
Regulation of body temperature: important function is thermoregulation. The temperature of the body remains fairly constant at about 36.8 $^{\circ}C$ across a wide range of environmental temperature. Formation of Vitamin D by conversion of lipid based substance in skin is7 dehydrocholesteroland ultraviolet light from the sun converts it to vitamin D. This circulates in the blood and is used, with calcium and phosphate, in the formation of maintenance of bone. Absorption: Some drugs, in transdermal patches, e.g. hormone replacement therapy during the menopause, nicotine as an aid to stopping smoking. Excretion: Sodium chloride in sweat; excess sweating may lead to blood sodium levels (hypernatremia) Urea, especially when kidney function is impaired Aromatic substances, e.g. garlic and other spices [12,13, 14].

Skin Penetration:
Once the product is applied on the skin, a complex interaction occurs between the formulation, the active compounds, and the skin itself. Drug molecules in contact with the skin surface can penetrate by the three potential pathways: through the sweat ducts, hair follicles and sebaceous glands (cooperatively called the shunt or appendageal route), or directly across the stratum corneum [15]. The amount of substances that can cross the stratum corneum under passive conditions is abundantly limited, andhence penetration enhancers are in employment to stimulate active penetration.Skin penetration can also be enhanced by physical, mechanical, and electrical approaches. Percutaneous absorption is usually assessed in silico, in vitro, ex vivo, and in vivo in animal models and humans [16].Drug penetration activity can be enhanced by incorporating the suitable penetration enhancer, Penetrationenhancers are used to promote the drug transport across the skin barrier[17].

Classification of topical preparations: - [18].

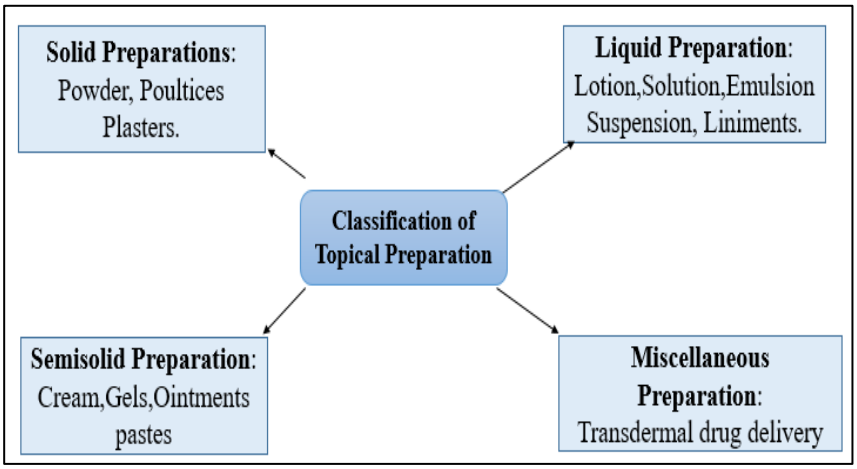

Figure 2: Classification of topical preparation

Powder:
Powders are solids or solid mixture in a dry, finely divided state for external use.Containing ingredients such as zinc oxide, starch, and talc used on wound. Powder vary from liquid topical product in their physical appearance. Which covers enormous surface area of body, due their fine particle size produces the large surface area per unit weight.
Body powders are also known as talcum powder or dusting powder, compact and face powder. Medicated powders are generally applied in condition of prickly heat or avoiding microbial growth on skin [18].

Lotion:
A lotion is a low- to medium- viscosity topical preparation intended for application to unbroken skin. An emulsionliquiddosage form for external application to the skin.Usually contains an aqueous vehicle and more than 50% water and volatilisedOpaque, thin, non-greasy; tends to evaporate rapidly with a cooling sensation when rubbed onto the skin. Exhibits Newtonian or pseudoplastic flow behaviour.

Liniment:
The liniments are liquid or semiliquid preparations meant for application to the skin. Applied to skin with friction and rubbing of the skin. They act as rubefacient, soothing or stimulant. The vehicle may be alcohol, oil or soap based [18].

Gels:
The term gel represents a physical state with properties intermediate between those of solids and liquids. They are semisolid systems in which a liquid phase is constrained within a three dimensional polymeric matrix in which high degree of cross linking has been introduced. The polymers used to prepare pharmaceuticals gel includes the natural gums, tragacanth, pectin, carrageen, agar, alginic acid and synthetic and semisynthetic materials. Such as MC, HEC, CMC etc. and carbopol as synthetic vinyl polymer [19].

Ointment:
Ointment composed of fluid hydrocarbons meshed in a matrix of higher melting solid hydrocarbons. While most of ointments are based on mineral oil and petrolatum. Polyethylene can be incorporated into mineral oil to yield a plastic matrix. Mixture of polyethylene glycol can yield products of consistency that are water soluble. Most ointments are prepared by melting the components together. Drugs or other components are added in fluidized state. If the solids are insoluble and to be suspended, a system is put through a milling process [19].

Creams:
The cream are semisolid emulsion system with opaque appearance, as contrasted with translucent ointments. Their consistency and rheological characteristics depends on weather the emulsion is w/o or o/w types and the nature of solid in internal phase. An emulsion is a two-phase system consisting of at least two immiscible liquids, in which one phase is dispersed throughout a vehicle. There are two types of emulsions: O/W and W/O. These emulsions are mainly formulated for the topical application of water-soluble drugs with a local effect. They are more acceptable to consumers because they provide a pleasant skin feel and are easily washed from skin surfaces. O/W emulsions do not give a greasy texture or 'feel' since they contain the oils in the internal phase, which can increase patient compliance. On the

other hand, the system designated as a W/O emulsion has an aqueous phase dispersed as the internal phase in an oleaginous external phase. They act as an emollient or occlusive by hydration of the upper layers of the stratum corneum [19].

Transdermal drug delivery:
Transdermal drug delivery is the topical drug delivery system, medicament in a self- contained, and patch with discrete dosage form that releases the drug after application to the skin; by the skin portal to systemic circulation at measured or fixed rate over a extended period of time in accordance with high the therapeutic efficacy and side effect of drug will be reduced. Ideal characteristics of TDDS:
Shelf life 2years, Low melting point of drug less than 200˚C, Patch size less than 40cm2. Having an Optimum partition coefficient [20].

Table 1: Various semisolid dosage forms with marketed preparations

Name of preparations	Brand name	Generic name	Company name	Indication
Cream	Aclovate Cream	Aclometasone 0.05%	Glenmark & Taro pharmaceutical	Eczema and psoriasis
	Vanos cream	Fluocinonide 0.1%; crm.	Bausch Health Companies Inc	Corticosteroid-responsive dermatoses
	Aristocort A 0.025% cream	Triamcinolone 0.025%	Perrigo pharmaceuticles	Ulcer , mouth sores
	Cordran SP cream	Flurandrenolide 0.025%	Aqua pharmaceuticals	Anti-inflammatory Agent.
	Cutivate Cream (0.05%)	Fluticasone 0.05%	Glaxosmithkline	Skin lesion.
	Vitaros cream	Alprostadil cream	Apricus Biosciences, Inc	Erectile dysfunctioning
Gel	Temovate	Clobetasol Propionate 0.05%	Hi-tech pharma	Anti-inflammatory
	Voltaren gel	Diclefenac gel	GSK consumer healthcare	Osteoarthritis, pain, inflammation
	Differin gel	Adapalene gel 0.1%	Galderma laboratories	Acne vulgarise
Ointment	DesOwen	Desonide 0.05%	DPT laboratories ltd	eczema, dermatitis,
	Topicort	Desoximetasone 0.25%	Made in Germany	Antipruritic

Skin Disorder:
Psoriasis- Psoriasis is regarded as an autoimmune disease in which genetic and environmental factors have a significant role. The name of the disease is derived from Greek word, psora‟ which means, itch. Psoriasis is a non-contagious, dry, inflammatory and unpleasant skin disorder, which can involve entire system of person [21].

Table 2: Topical preparations in various skin infections**.**

General category	Disorders/diseases	Pathogenic conditions/microorganisms	Ex, of topical drug products
Bacterial infection	Impetigo, forunculosis, cellulitis, folliculitis	Staphyloccocus Aureus, Streptococcus pyogenes	Mupirocin (Bactroban), Polymyxin, Bacitracin zinc, Gentamicin sulfate, Neomycin, Silver sulfadiazine, Sulfanilamide, Nystatin Clotrimazole, Terbinafine, Ketoconazole, Butoconazole Nitrate,Halobetasol Propionate, Terconazole Salicylic acid, Imiquimod (Aldara), Podophyllotoxin, Acyclovir, Docosanol
Fungal/yeast infection	Tinea pedis, cruris, corporis, unguium Candidiasis.	Trichophyton rubrum, Trichophyton mentagrophytes, Trichophyton tonsurans, Candida albicans	
Viral infection	External genital/ perianal warts, cold sores	Molluscam contagiosum virus, Human papillomavirus Herpes Simplex virus	
Inflammatory and pruritic manifestations	Allergic contact dermatitis, atopic dermatitis, seborrhea dermatitis, eczema	The exact cause is unknown, but it is thought to be linked to an overactive response by the Body's immune system to external and/or internal triggers.	Triamcinolone 0.1% (Triamcinolone), Fluocinonide (Lidex), Clobetasol (Temovate), Tacrolimus (Protopic), Pimecrolimus (Elidel), Mometasone furoate, Desoximetasone, Prednicarbate, Diflorasone Diacetate Amcinonide
Acne, Rosacea	Acne, Rosacea	Acne is caused by the stimulated sebaceous glands at the time of puberty, leading to the inflammation of skin surface.	Metronidazole, Isoretinol, Benzoyl peroxide, Dapsone, Azelaic acid, Clindamycin, Erythomycin, Sodium, sulfacetamide, Adapalene, Tretinoin
Psoriasis	Psoriasis vulgaris	The exact cause remains unknown. There may be a combination of factors, including genetic predisposition and environmental factors Triggering cell proliferation out of control.	Hydrocortisone, Calcipotriene , Anthralin, Lactic acid, Tacrolimus (Protopic), Pimecrolimus
Loss of hair	Androgenic alopecia, Cicatricial alopecia Alopecia areata	Due to hormonal changes, inflammation damages/scars, autoimmune disease, and other reasons, hair follicles may have a shorter growth period and produce thinner And shorter hair shafts.	Minoxidil, Anthralin, Cyclosporine

Types of psoriasis:

Plaque psoriasis: The commonest form of psoriasis is plaque psoriasis in which patients may have sharply circumscribed, round-oval, or nummular (coin-sized) plaques. The lesions may initially begin as erythematous macules (flat and ,1 cm) or papules, extend peripherally, and coalesce to form plaques of one to several centimetres in diameter.

Guttate psoriasis:Guttate psoriasis, from the Greek word gutta meaning a droplet, describes the acute onset of a myriad of small, 2–10 mm diameter lesions of psoriasis. These are usually distributed in a centripetal fashion although guttate lesions can also involve the head and limbs. Guttate psoriasis accounts for 2% of the total cases of psoriasis.

Flexural psoriasis: Psoriasis affecting the flexures, particularly inframammary, perineal, and axillary, is distinct morphologically from traditional plaques elsewhere on the trunk and limbs. Flexural lesions are devoid of scale and appear as red, shiny, well demarcated plaques occasionally confused with candidal, intertrigo, and dermatophyte infections.

Palmoplantar pustulosis: Palmoplantar pustulosis presents as sterile, yellow pustules on a background of erythema and scaling affecting the palms and soles.The pustules are tender and fade to form dark brown coloration with adherent scale/crust. Palmoplantar pustulosis is frequently associated with psoriatic nail involvement [22].

Causes of psoriasis:
Scans of the human genome reveal at least nine differentloci with susceptibility to psoriasis (PSORS1-9).Causes is not understood fully but it have its genetic component. Psoriasis is immune mediated state which is initiated by defective signs in the bodys immune system.It is supposed that psoriasis cultivates when the immune system expresses the body to over-react and accelerate the growth of skin cells.These cause inflammation and increased proliferation of skin cells leading to the characteristic clinical features of scaling and redness [23].

Treatment for psoriasis:
Corticosteroids and Salicylic acid -It benefits to remove scales and keratolytic. In a concentration of 2-10%, it is usually combined with coal tar, steroids and dithranol. Corticosteroids like amcinonide, clobetasole propionate, fluticasone propionate.

Topical vitamin D3 analogs:Calcipotriol, a synthetic Vita-D3 analog, is both safe and effective. It blocks epidermal proliferation, enhances maturity of cells, and has anti-inflammatory effects .
Tazarotene:Tazarotene is a synthetic retinoid with properties similar to that of Vita-A. Tazarotene is available as a gel. In the treatment of psoriasis, it may be used as a single agent or in combination with a corticosteriod cream or ointment, calcipotriol or phototherapy[24, 25].

Atopic dermatitis:
Atopic dermatitis is a common, chronic, relapsing, inflammatory skin disease that primarily affects young children. Atopy is defined as an inherited tendency to produce immunoglobulin E (IgE) antibodies in response to minute amounts of common environmental proteins such as pollen, house dust mites, and food allergens. Dermatitis derives from the Greek “derma,” which means skin, and “itis,” which means inflammation.Dermatitis and eczema are often used synonymously, although the term eczema is sometimes reserved for the acute manifestation of the disease.

Causes: cause due to allergens, such as food allergens, house dust mites, or pets, whereas those with late-onset atopic dermatitis are less often sensitized, first hypothesis concerns an imbalance of the adaptive immune system; the second hypothesis concerns a defective skin barrier the second hypothesis concerns a defective skin barrier [26].

Treatment: Clobetasol propionate 0.05(cream, ointment), betamethasone dipropionate0.05,Halobetasol propionate 0.05(cream, ointment),Triamcinolone diacetate 0.5 (Cream)[27].

Acne: Acne vulgaris is the most common condition understood by a dermatologist, affecting about approximately 85% of adolescents in some form [28]. Acne is a disease ofthe pilosebaceous unit that causes non-inflammatory lesions (open and closed pimples), inflammatory lesion (pustules, nodules and papules) [29].

Cause : Acne is produced mainly by both external and internal causes. Though, the original cause sebum production is increased and irregular desquamation of epithelial cells. One of the primary procedure in the development of acne lesions is the enlargement of the microcomedo, or obstruction of the follicular canal. Improved cohesiveness ofcorneocytes and hyperkeratosis of the follicular lining cause keratin and sebum to accumulate in the follicle. This creates a plug (comedo) above the sebaceous gland duct [30].

Treatment: Topical retinoid medication (adapalene, tretinoin, trazarotene)Topical retinoids perform on abnormalkeratinisation and are also anti-infl ammatory, so they work for both comedonal and inflammatory acne. Topical antibiotic medication (clindamycin, erythromycin) and benzoyl peroxide [31].

Method of preparation of semisolid dosage form:-

Gel:
A Gel is defined as asemisolid preparation, which displays an external solvent phase, isHydrophobic or hydrophilic in nature, and is immobilized within the spaces available of a three-dimensional network structure with the help of gelling agents.Gels are

exceptional substances which are stiff and flexible in nature[32] andhave a wide range of applications in medicine, biomaterials, cosmetics and food technologies[33].Gel may be polar or nonpolar or maybe clear or opaque.Gels are formulated by eithera fusion process or a superiormethodneeded by the gelling properties of the gallant [34].

Gel forming substances: Polymers which are help to give the structural linkage, which is necessary for the productions of gels. Followings are the Gel forming polymerase classified as[35]:

Natural polymer:
Proteins (Collagen, Gelatin,) Polysaccharides (Agar, Alginic acid, Sodium or Potassium carrageenan, Tragacanth, Pectin, Guar Gum, Cassia tora, Xanthin, Gellum Gum.)

Semisynthetic polymers: Cellulose derivatives (Carboxymethyl cellulose, Methylcellulose, Hydroxypropyl cellulose, Hydroxypropyl methyl cellulose, Hydroxyethyl cellulose,)

Synthetic polymers:
Carbomer Carbopol -940, Carbopol -934, Carbopol -941, Poloxamer , Polyacrylamide , Polyvinyl alcohol , Polyethylene and its co-polymers.

Inorganic substances:
Inorganic substances consist of Aluminium hydroxide , Bentonite.

Surfactants:
Surfactants includes Cetostearyl alcohol , Brij – 96.

PREPARATION OF GELS:
Gels can be prepared by following methods:
Thermal changes
Flocculation
Chemical reaction

Thermal changes:
Solvated polymers (lipophilic colloids) when subjected to thermal changes causes gelatin. Many hydrogen formers are more soluble in hot than cold water. If the temperature is reducing, the degree of hydration is reduced and gelatin occurs. (Cooling of a concentrated hot solution will produce a gel). E.g. Gelatin, agar sodium oleate, guar gummed and cellulose derivatives etc. In contrast to this, some materials like cellulose ether have their water solubility to hydrogen bonding with the water. Raising the temperature of these solutions will disrupt the hydrogen bonding and reduced solubility, which will cause gelation. Hence this method cannot be adopted to prepare gels as a general method.

Flocculation:
Here gelation is produced by adding just sufficient quantity of salt to precipitate to produce age state but insufficient to bring about complete precipitation. It is necessary to ensure rapid mixing to avoid local high concentration of precipitant. E.g. Solution of ethyl cellulose, polystyrene in benzene can be gelled by rapid mixing with suitable amounts of a non-solvent such as petroleum ether. The addition of salts to hydrophobic solution brings about coagulation and gelation is rarely observed. The gels formed by flocculation method are Thixotropic in behavior. Hydrophilic colloids such as gelatin, proteins and acacia are only affected by high concentration of electrolytes, when the effect is to “salt out”, the colloidal and gelation doesn’t occur.

Chemical reaction:
In this method gel is produced by chemical inter action between the solute and solventE.g.aluminium hydroxide gel can be prepared by interaction in aqueous solution of an aluminium salt and sodium carbonate an increased concentration of reactants will produce a gel structure. Few other examples that involve chemical reaction between PVA, cyanoacrylates with Glycidol ether (Glycidol), toluene diisocyanates (TDI), methane diphenyl Isocyanine (MDI) that cross-links the polymeric chain [36].

Cream:
Definition : Creams areviscous, homogeneous, semisolid preparationswith one or more drug substances dissolved or dispersed in a suitable base, usually oil in- water emulsion or aqueous microcrystalline dispersion of long-chain fatty acids or alcohols that are waterwashable and are cosmetically and aesthetically acceptable for application on the skin or mucous membrane [37].

Method of preparation:
Product design and development:
Drug substance : The physicochemical parameter and biological properties of drug haveimportant effect on drug product performance and manufacturability.while preformulation studies, melting point,drug characteristics like solubility, partition coefficient, particle size, pKa, permeability, and molecular weight essential to be analysed since their role on percutaneous permeation [38].

Selection of excipients:
Oily excipients:

Saturated and unsaturated fatty acids/fatty acid esters,hydrocarbons, and polyols can constitute the oily phase, also functioning as penetration enhancers, and consistency
or viscosity modifiers.

Thickners:
Thickeners are important excipients with impact on cream viscosity and, consequently, on skin retention of the topical dosage form and on drug penetration. For ex: Gelatin, Polyethylene oxide, Alginic acid, Methyl cellulose, Sodium carboxyl methylcellulose, Colloidal silicon dioxide, Guar gum, etc.

Emulsifying agent:
During manufacturing of cream formulation, Emulsifying agents are important for process of emulsification.To ensure emulsion physical stability during the product shelf life. In o/w emulsion ionic surfactants are used whereas nonionic surfactants can be used in both o/w and w/o formulations. Ex :Polysorbate 20, Polysorbate 80, Polysorbate 60, Poloxamer,
Emulsifying wax, Sorbitan monostearate, Sorbitan monooleate, Sodium lauryl sulfate, Propylene glycol monostearate, etc.

Table :3 HLB scale

HLB range	Application
4-6	W/O emulsifier
7-9	Wetting agent
8-18	O/W emulsifier
13-15	Detergents

Table 4: Emulsifying agents

Anionic	Nonionic	Cationic
Alkyl sulphate	Glyceryl fatty acid esters	
Sulfosuccinates	Polyoxyethylene sorbitan esters	Quaternary ammonium compounds
silicones	Sorbitan fatty acid esters	Alkoxyalkylamines
Phosphate ester	Sucrose fatty acid esters	
Dodecyl benzene sulfonate	Polyoxyethylene fatty acid ester	

Preservatives :
Emulsion containing aqueous continuous phase are more liable to microbial contamination.
Hence , it is essential to addition of antimicrobial agents(preservative) so as to reduces the microbial growth. Ex: Benzoic acid, Propyl paraben, Methyl paraben, Imidurea,
Sorbic acid, Potassium sorbate, Benzalkonium chloride, etc.

Antioxidants :
Susceptibility of oxidation by atmospheric oxidation or action of microorganism are due to addition of oil and fats in emulsion formulation. Therefore, degradation of products occurs due toAtmospheric oxidation, Offers unpleasant cream properties. By addition of excipients having antioxidant properties may prevent resulting instability. Ex: Butylated hydroxyanisole, Butylated hydroxytoluene, etc.

Buffer agents: Maintain proper pH for dosage form.To ensure physical compatibility and to provide chemical stability; it is required to include buffering agents. Ex: Citric acid, Phosphoric acid, Sodium hydroxide, Monobasicsodium Phosphate, etc [39,40].

Manufacturing Process:
In cream formulation, mechanical process is done by mixing the both the phases; oil phase and aqueous phase by adding continuous phase to aqueous phase or aqueous phase to continuous phase. There are two type of emulsion cream base viz; o/w emulsion and w/o emulsion .
Preparation of oil phase
Preparation of aqueous phase
Different excipients are dissolved in phase in which they are soluble, primary temperature of mixing the aqueous and oil phase must be high enough to ensure close liquid mixing and
avoid early solidification of the oily phase by the cool water. Aqueous phase should be warmed to temperature considerably higher than oil phase.

Active pharmaceutical ingredients can be dissolved at high temperature and recrystallized during the cooling stage.
Further step is homogenization stage in cream manufacturing. Agitators, mechanical mixers, rotor stators, homogenizers, or ultrasonic devices might be working to ensure uniform excipientdispersion and droplet size reduction.Homogenization time and vacuum pressure aresignificant process variables that can affect physical stability (e.g. Coalescence of droplets, phase separation) and homogeneity. During cream manufacturing mechanical stirrer,time, temperature are high risk parameters of the homogenization tools that must be controlled to make desired consistent quality. Further, cooling rate takes part in final product quality, variable cooling rates after melting, mixing, and homogenization step should be invented as process variables [41].

Ointment:
An ointments are homogeneous, viscous semisolid dosage form, they are usually greasy, oily (Oil-80%, Water-20%) with high viscosity that is proposed for external application to skin or mucous membranes.They are soft hydrocarbon based semisolid preparation, composed of fluid hydrocarbon meshed in a matrix of higher melting solid hydrocarbon petrolatum being a tasteless, odorless, unctuous material with a melting range. Principle ingredients forming the system hydrocarbon and silicon oil are generally poor solvent for most drugs, seemingly setting a low limit on the drug delivery capabilities of the system [42].

Selection of Ointment Base:
It should be physically and chemically stable.
Rate and extent of topical or percutaneous drug absorption.
It should be smooth and free from grittiness.
Stability of the drug in the ointment base.
Aesthetically appealing, easy to apply, and nongreasy.
Easy removal of base on washing.
Characteristic of the surface to which it is applied [42, 43].

Classification of ointment bases:
Oleaginous bases.
Absorption bases.
Water soluble bases.
Water removable bases.

Oleaginous base -
Water insoluble, Not water washableEmollient, Occlusive, Greasy uses : protectant , emollient, vehicle for drug prone to hydrolysis.
Ex.: petrolatum, yellow ointment, mineral oil.

Absorption base-
These bases categorize into two groups:
a. Permit the incorporation of aqueous solution with the formation of water in oil type of bases.
Ex: Hydrophilic petrolatum, Lanolin
b.These are already w/o type of bases and permit the additional amount of aqueous solution.
Ex: Anhydrous lanolin

Water soluble base –
Water soluble vehicles are prepared from mixtures of high and low molecular weight polyethylene glycol. These are water soluble because of the presence of many polar groups and their linkages. The “water soluble” bases are also known as greaseless ointment bases.
Ex: polyethylene glycol ointment .

Water removable base-
Water removable bases are oil-in-water emulsions that are capable of being washed from skin or clothing with water. Also known as water washable bases. Ex: hydrophilic ointments [44, 45]

Preparation of ointments:
Ointment can be made either by mechanical incorporation or by fusion methods.
In manufacturing of ointments, the following common characteristics must be considered:
If insoluble materials are to be incorporated in the ointment base then they should be in
Imperceptible powder form.

Incorporation method :
This can be achieved by the use ofMortar and pestle,Ointment slab and spatula, andAn ointment mill.In this finely subdivided insoluble medicaments are evenly distributed by grinding with a small amount of the base followed by dilution with gradually increasing amounts of the base

Fusion method :
In this method the ingredients are melted together in descending order of their melting points and stirred to ensure homogeneity. Many medicated ointments and ointment bases containing components such as beeswax, paraffin, stearyl alcohol, polyethylene glycol are mostly prepared by fusion method. Ingredients having highest melting point are melted first. And other components are added to this hot liquid, all of the components will be subjected to this high temperature,

irrespective to their own individual melting points. And generally a temperature higher than necessary will have to be employed to achieved fusion [45].

Evaluation of semisolid dosage forms:-
Evaluations of semisolid dosage forms are organoleptic characteristics, pH, drug content, viscosity, spreadability, Extrudability study, skin irritation study, in-vitro release, in vivo release study, stability study, etc[46].

Organoleptic characteristics:
All formulation does not contained active ingredients (blank formulations) and active formulations were tested for physical appearance, texture, colour, phase separation, and homogeneity.These parameter were evaluated by visual observation.Texture andhomogeneityremainedtested by pressing a small quantity of the formulated cream and gels between the index finger and thumb. Immediate skin feel (containingoleaginousness, stiffness, grittiness,) was also estimated.

pH measurement:
pH was measured by digital pH meter. 1g of sample was dissolved in 100ml of distilled water. Measurement of pH were made in triplicate. Average value are calculated.The pH meter was calibrated with standard buffer solutions (pH 4, 7, and 10) [47].

Viscosity measurement :
Measurement of viscosity of formulation were carried out by Brookfield viscometer.
A Brookfield viscometer DV-I (Brookfield Engineering Laboratories,Middleboro,MA) was used with a concentric cylinder spindle #29 to determine the viscosity of the different topical formulations. The tests were carried out at room temperature. The spindle was rotated at 0, 0.5, 1, 2, 2.5,4, 5, 10, 20, 50, and 100 rpm values. All measurements were made in triplicate[47].

Spreadability:
Spreading value is detected by measuring the spreading diameter of 1g of sample
Between two glass plate after 5min. The standard weight is applied on glass plate is 100g.Each preparation detected for triplicate. Spreading ability was done to determined extent of area to which formulation is spread evenly on application to skin or affected area.Spreading value indicates the therapeutic effectiveness of preparation [48].

$S = m * l / t$

Where,

m = weight tide to upper slide

l = length moved on the glass slide

t = time taken.

Extrudability study:
Extrudability was detected by, using an extrudabilityapparatus. A closed collapsible tube containing formulation was pressed firmly at the crimped end. When the cap was removed, formulation extruded until the pressure dissipated. Weight in grams required to extrude a 0.5-cm ribbon of the formulation in 10 seconds was determined. The average extrusion pressure in grams was reported [48].

The skin irritation study:
In general no ointment should possess irritant effect on the skin or the skin or mucous
membranes. The tests for irritancy can be carried out on the skin and eyes of rabbits or the skin in rats. Reactions are noted at intervals of 24, 48, 72 and 96 hours. Lesions on cornea, iris, conjunctiva, are used for judging the irritancy to the eyes. Presence of patches on the skin within 2 weeks indicate irritancy to skin [49].

In vitro release study:
In vitro release test can be carried out to describe and optimized the formulation release performance. The Franz diffusion cell is most widely used apparatus for topical formulation release performance. Artificial membrane have been invented to study in vitro release profile of topical formulation to show batch to batch consistency. (For example; polycarbonate, silicone, cellulose.) These synthetic membrane shows the same properties as that of physiological and anatomical characteristics of skin.In 1970, Thomas J. Franz established their first work in this field. A *in vitro* release method fortopical dosage forms is based on an open chamber diffusion cell system such as a Franz cell system, fitted usually with a synthetic membrane.The test sample is placed at upper side of semipermeable membrane in donor chamber where the drug released need to permeate.Semipermeable membrane.Receiver chamber ; sampling fluid can be collected for drug analysis by HPLC method for drug content.

From topical formulation diffusion of drug through the membrane is examined from receptor fluid by assay of serially collected sample. At regular time interval, the component of receptor chamber is stirred by small magnetic stirrer and sample is withdrawn from receiver chamber replaced with fresh receptor medium and analyzed it.Modified Franz diffusion cell is also known as vertical diffusion cell. This equipment has

been used to demonstrate various preparations such as cream, gel, ointment and patches [50, 51].

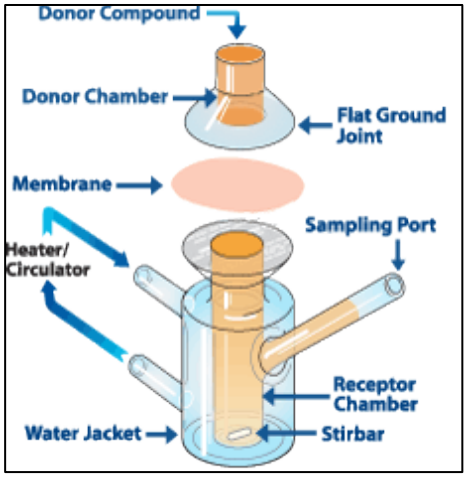

Figure 3: Vertical *in vitro* Franz diffusion cell

In vivo method:

The *in vivo* skin percutaneous absorption is carried out by performing pharmacokinetic study or with the help of cutaneous microdialysis. In both these process they using animal model or human volunteers and previously ethical committee approved for such protocol.

Animal models:

Animal models are largely applied because they are easily accessible, and less issues related to ethical committee, fewer variations between subjects, and large numbers of data might be evaluated related to percutaneous penetration, toxicokinetic and toxicodynamic studies. Most animals alterconsiderably from man in structure that affect percutaneous absorption; the nature and thickness of stratum corneum, hair follicles density and sweat glands, and the papillary blood supply and biochemical aspects. Few methodsyield animal disease similar to human disorders. Hence animal models are valuable for studying the anatomy, physiology and biochemistry of skin, for selection of topical agents, for identifying possible hazards, and for biopharmaceutical studies.The most common animal species used for evaluating transdermal drug delivery system are mouse, hairless rat, hairless dog, hairless rhesus monkey, rabbit, guinea pig etc.

Human models:

Clinical trials are then conducted to assess the efficacy, risk involved, side effects, patient compliance etc. Phase I clinical trials are conducted to determine mainly safety in volunteers and phase II clinical trials determine short term safety and mainly effectiveness in patients. Phase III trials indicate the safety and effectiveness in large number of patient population and phase IV trials at post marketing surveillance are done for marketed patches to detect adverse drug reactions. Though human studies require considerable resources but they are the best to assess the performance of the drug [49, 52].

Preclinical pharmacokinetic evaluations:

Preclinical pharmacokinetic estimations with the help of animal models lead clinical trials with human volunteers. Plasma concentration of drug use in pharmacokinetic studies. At different time interval, blood sample can be withdrawn after administration of formulation.By using centrifugation technique, plasma is separated and the drug is take out and analysed by suitable analytical method, like HPLC or gas chromatography.The pharmacokinetic parameters are determined from a plot of drug plasma concentrations versus time. Rhesusmonkey is one of the most reliable models for *in vivo* evaluation of transdermal drug delivery in man.Before application of formulation on animal model;hair must be removed at the site of administration, using clipper and depilatory cream.Pharmacokinetic evaluations of a topical delivery system are necessary to conclude the in vivoperformance of the drug administered by the skin route since in vitrostudies does not mimic the difficulty of biological systems, such as metabolism, distribution, and elimination.

Cutaneous microdialysis:

By using cutaneous microdialysis assessment of in vivo skin permeation of drug from topical route has been described. Cutaneous microdialysis is classified as a semi-invasive technique in which a

semipermeable microdialysis probe is inserted into defined skin layers (epidermis or dermis), directly under the formulation . The physiological solution (saline or Ringer's solution) is slowly perfused by using a pump (1–10 µL/min). The compounds in the tissue interstitial fluid diffuse into the dialysate in the probe. Cutaneous microdialysis shows better results for recovery of hydrophilic compounds. cutaneous microdialysis evaluates drug absorption in the depth layers of the skin. In these cases, cutaneous microdialysis enables characterization of skin absorption and clearance of drugs from topical formulations [53, 54].

Stability study:

The ICH stability testing is carried out for prediction of product performance. To analysed the product performance over its shelf life. There are three stability conditions; short term, intermediate term, long term (Accelerated stability study.) at 25°C/60% RH, 30°C/65% RH, and 40°C/75% RH (ICH Q1A(R2)).such study can performed over a period at time t =0, 1, 3, 6, 9, 12, 18, and 24 months. There are some parameters that must be determined,
such as macroscopic and microscopy appearance, odor, assay, active substance crystallization, uniformity, oil droplet size, impurities, preservative content, antioxidant content, pH, rheology, viscosity, microbial quality or microbial limit test, and preservative efficacy test [55].

Table 5: Stability conditions

Storage condition	Stability test method	ICH test temp and humidity (period in months)	WHO test temp and humidity (period in months)
Room temp	Long term	25±2˚C/60±5%RH(12)	25±2˚C/60±5%RH
			30±2˚C/65±5%RH
			30±2˚C/75±5%RH(12)
	Intermediate	30±2˚C/65±5%RH (6)	30±2˚C/65±5%RH (6)
	Accelerated	40±2˚C/75±5%RH (6)	40±2˚C/75±5%RH (6)
Refrigerated	Long term	5˚C/ambient (12)	5±3˚C
	Accelerated	25±2˚C/60±5%RH(6)	25±2˚C/60±5%RH or 30±2˚C/65±5%RH
Freezer	Long term	-20˚C/ambient (12)	-20˚C±5˚C

DISCUSSION:

Based on literature survey, it is reported that, Topical preparations are used for the localized effects at the site of their application by virtue of drug permeation into the underlying layers of skin or mucous membranes. Varieties of medicated or non-medicated treatments are provided by the topical route proven as effective. There are many different dosage form, from which topical delivery of drug is successfully explored Such as cream, gel, ointment, paste, lotion, liniments, powder, solution and suspension. Topical dosage form are effective in fungal, microbial, and bacterial infection which is affected to the skin. Here skin comprises the largest organ of body. It is made up of three primary layers like epidermis, dermis, and hypodermis. Skin protect from various microorganism. Formulation excipients and skin condition affects on rate and extent of drug absorption. Excipients are inactive ingredients in dosage form. Various excipients play a vital role in the manufacturing of the topical dosage forms such as emulsifying agents, emollients, humectant, gelling agents, thickening agent, preservative, permeation enhancer, chelating agents, antioxidant agents, vehicle/ solvents.

Gels are moderately easier to formulate as compared toemulsion-type creams and lotions.
In general, a selected gelling agent, such as Carbomers and xanthan gum, can be distributed in purified water or hydro alcoholic medium to form uniform lump-free dispersion and consequently, Medicated gel can be prepared by adding an active and preservative phase to the gel phase. Gel can be manufactured by 3 methods like thermal changes, flocculation, and Chemical reactions. Various applications of gel such as gel are directly apply on skin surface or mucus membrane to deliverlocal action.Gel preparations consisting anti-inflammatory steroids are used to treat infections of scalp because this is an area of the body where creams and ointments are too oleaginous for patient acceptance.

Cream are biphasic delivery of drug, containing dispersed phase and uniformly distributed in Continues phase, According to the internal phase environment, it is promising to obtainawater-in-oil

cream (w/o) or oil-in-water cream (o/w).Cream is made up of mechanical mixing of aqueous phase into oil phase or oil phase to aqueous phase. The additives are dissolved in the phase in which they are soluble. Homogenization, agitator, mechanical mixturecan be employed to confirm the uniform dissolution. In cream formulation, different Process variables need to considered and to develop a robust manufacturing process, protect cream quality attributes.Applications of cream dosage form in drug delivery are cetirizine hydrochloride cream in treatment of pruritus related with atopic dermatitis. Retinoic acid decreases RA-induced skin infection without reducing effectiveness. But take part in innovative way/ treatment for Acne vulgaris with RA.

Ointments are semisolid preparation prepared by ointment bases as vehicles or their physical appearance. Ointment base consisting of oleaginous base (hydrocarbon base), absorption base, water removable base, water soluble bases. Ointments are behaves like a viscoelastic material when force is applied. Ointment can be prepared by mainly 2 methods vise; Incorporation method and Fusion method. Applications of ointments: -Acyclovir ointment for skin lesions, diclofenac in serious painful inflammation. Pastes are semisolid dosage forms that contain a high percentage (often _ 50%) of finely dispersed solids with a stiff consistency intended for topical application. Although the term lotion may be applied to a solution, lotions usually are fluid, somewhat viscid emulsion dosage forms for external application to the skin. Lotions share many characteristics with creams. Topical solutions are liquid preparations, that usually are aqueous but often contain other solvents such as alcohol and polyols that contain one or more dissolved chemical substances intended for topical application to the skin, or, as in the case of Lidocaine Oral Topical Solution USP, to the oral mucosal surface.

CONCLUSION:

There are different physical forms that can effectively deliver a drug topically. Topical dosage from designed to exert local activity when applied to the skin or mucous membranes. Dermatological factors are absorption penetration, skin condition, compatibility and emollient properties. Pharmaceutical factors are stability, solvent properties, emulsifying property. In addition, patient acceptability is much better than other route of drug delivery due to their noninvasiveness. Various topical preparations like cream, gel, ointment, solution, suspension, emulsion, paste, powder, etc. play a vital role in variety of skin infections. Development approaches may implement to prepare a robust semi solid dosage form and manufacturing process to achieve product quality.

REFERENCES:

1. Bhowmik, D., Gopinath, H., Kumar, B.P., Duraivel, S. and Kumar, K.S., 2012. Recent advances in novel topical drug delivery system. *The Pharm Innov*, *1*(9, Part A), p.12.
2. Ramezanli, T., Zhang, Z. and Michniak-Kohn, B.B., 2017. Development and characterization of polymeric nanoparticle-based formulation of adapalene for topical acne therapy. *NANOMED-NBM 13*(1), pp.143-152.
3. Mishra, A., Panola, R., Vyas, B., Marothia, D. and Kansara, H., 2014. Topical antibiotics and semisolid dosage forms. *Int J Pharm Erudition*, *4*, pp.33-54.
4. Chang, R.K., Raw, A., Lionberger, R. and Yu, L., 2013. Generic development of topical dermatologic products: formulation development, process development, and testing of topical dermatologic products. *The AAPS journal*, *15*(1), pp.41-52.
5. Singla, V., Saini, S., Joshi, B. and Rana, A.C., 2012. Emulgel: A new platform for topical drug delivery. *Int J Pharma Bio* Sci. , *3*(1), pp.485-498.
6. Verma, A., Singh, S., Kaur, R. and Jain, U.K., 2013. Topical gels as drug delivery systems: A review. *Int. J. Pharm. Sci. Rev. Res*, *23*(2), pp.374-382.
7. Bangarwa, S., Garg, S. and Aseri, A., 2014. A review on antifungal gels: as a topical drug delivery system. *Int. J. Pharm. Technol. Biotechnol*, *1*, pp.48-55.
8. Kolarsick, P.A., Kolarsick, M.A. and Goodwin, C., 2011. Anatomy and physiology of the skin. *J Dermatol Nurses Assoc.*, *3*(4), pp.203-213.
9. Khavkin, J. and Ellis, D.A., 2011. Aging skin: histology, physiology, and pathology. *Arch Facial Plast Surg19*(2), pp.229-234.
10. Kanikkannan, N., Kandimalla, K., Lamba, S.S. and Singh, M., 2000. Structure-activity relationship of chemical penetration enhan-cers in transdermal drug delivery. *Curr Med Chem*, *7*(6), pp.593-608.
11. Roberts, M.S. and Cross, S.E., 1999. Percutaneous absorption of topically applied NSAIDS and other compounds: role of solute properties, skin physiology and delivery systems. *Inflammopharmacology*, *7*(4), p.339.
12. Waugh, A. and Grant, A., 2014. *Ross & Wilson Anatomy and physiology in health and illness E-book*. Elsevier Health Sciences.

13. Biniek, K., Levi, K. and Dauskardt, R.H., 2012. Solar UV radiation reduces the barrier function of human skin. *Proc Natl Acad Sci*, *109*(42), pp.17111-17116.
14. McGrath, J.A. and Uitto, J., 2008. The filaggrin story: novel insights into skin-barrier function and disease. *Trends Mol Med.*, *14*(1), pp.20-27.
15. Mathur, V., Satrawala, Y. and Rajput, M.S., 2014. Physical and chemical penetration enhancers in transdermal drug delivery system. *Asian J Pharm: Free full text articles from Asian J Pharm*, *4*(3).
16. Godin, B. and Touitou, E., 2007. Transdermal skin delivery: predictions for humans from in vivo, ex vivo and animal models. *Adv Drug Deliv Rev*, *59*(11), pp.1152-1161.
17. Saikumar, Y., Saikishore, V., Pavani, K., Sairam, D.T. and Sindhura, A., 2012. Role of Penetration Enhancers in Transdermal Drug Delivery System. *RJPDFT4*(6), p.II.
18. Garg, T., Rath, G. and Goyal, A.K., 2015. Comprehensive review on additives of topical dosage forms for drug delivery. *Drug delivery*, *22*(8), pp.969-987.
19. Lachman, L., Lieberman, H., Kanig, J., 2012. *The theory and practice of industrial pharmacy*. Third edition., pp.534
20. Bala, P., Jathar, S., Kale, S. and Pal, K., 2014. Transdermal Drug Delivery System (TDDS)-A Multifaceted Approach For Drug Delivery. *Journal of Pharmacy Research*, *8*(12), pp.1805-1835.
21. Kuchekar, A.B., Pujari, R.R., Kuchekar, S.B., Dhole, S.N. and Mule, P.M., 2011. Psoriasis: A comprehensive review. *Int J Biol Pharm Allied Sci.*, *2*(6).
22. Langley, R.G.B., Krueger, G.G. and Griffiths, C.E.M., 2005. Psoriasis: epidemiology, clinical features, and quality of life. *Ann Rheum Dis*, *64*(suppl 2), pp.ii18-ii23.
23. Smith, C.H. and Barker, J.N.W.N., 2006. Psoriasis and its management. *Bmj*, *333*(7564), pp.380-384.
24. Mason, J., Mason, A.R. and Cork, M.J., 2002. Topical preparations for the treatment of psoriasis: a systematic review. *Br J Dermatol 146*(3), pp.351-364.
25. 25.Tan, X., Feldman, S.R., Chang, J. and Balkrishnan, R., 2012. Topical drug delivery systems in dermatology: a review of patient adherence issues. *Expert Opin Drug Deliv.*, *9*(10), pp.1263-1271.
26. homsen, S.F., 2014. Atopic dermatitis: natural history, diagnosis, and treatment. *ISRN allergy*, *2014*.
27. Simpson, E.L., 2010. Atopic dermatitis: a review of topical treatment options. *Curr Med Res Opin 26*(3), pp.633-640.
28. McHugh, R.C., Rice, A., Sangha, N.D., McCarty, M.A., Utterback, R., Rohrback, J.M., Osborne, B.E., Fleischer Jr, A.B. and Feldman, S.R., 2004. A topical azithromycin preparation for the treatment of acne vulgaris and rosacea. *J Dermatolog Treat.*, *15*(5), pp.295-302.
29. Tan, A.U., Schlosser, B.J. and Paller, A.S., 2018. A review of diagnosis and treatment of acne in adult female patients. *Int J Womens Dermatol.* , *4*(2), pp.56-71.
30. Well, D., 2013. Acne vulgaris: A review of causes and treatment options. *NP 38*(10), pp.22-31.
31. Williams, H.C., Dellavalle, R.P. and Garner, S., 2012. Acne vulgaris. *The Lancet*, *379*(9813), pp.361-372.
32. Rehman, K. and Zulfakar, M.H., 2014. Recent advances in gel technologies for topical and transdermal drug delivery. *Drug Dev Ind Pharm.* , *40*(4), pp.433-440.
33. Kirilov, P.L.A.M.E.N., Le Cong, A.K., Denis, A.L.I.C.E., Rabehi, H.A.L.I.M.A., Rum, S.I.L.V.I.A., Villa, C.A.R.L.A., HAFTEK, M. and PIROT, F., 2015. Organogels for cosmetic and dermocosmetic applications. *evaluation*, *6*, pp.30-6.
34. Sandhu, P., Bilandi, A., Kumar, S., Rathore, D. and Bhardwaj, S., 2012. Additives in topical dosage forms. *IJPCBS*, *2*(1), pp.78-96.
35. Supraja, R., 2016. AN OVERALL REVIEW ON TOPICAL PREPARATION-GEL. *Innovat International Journal Of Medical & Pharmaceutical Sciences*, *1*(1).
36. Kaur, L.P., 2013. Topical gel: a recent approach for novel drug delivery. *Asian journal of biomedical and Pharmaceutical Sciences*, *3*(17), p.1.
37. Nwoko, V.E., 2014. Semi solid dosage forms manufacturing: tools, critical process parameters, strategies, optimization and validation. *Sch Acad J Pharm*, *3*(2), pp.153-161.
38. Lawrence, X.Y., 2008. Pharmaceutical quality by design: product and process development, understanding, and control. *Pharm res*, *25*(4), pp.781-791.
39. Patel, H., Parmar, S. and Patel, B., 2013. A comprehensive review on Quality by Design (QbD) in pharmaceuticals. *development*, *4*, p.5.
40. Chen, M.X., 2014. *Formulation of topical products with antiviral and antibacterial activity* (Doctoral dissertation, University of Toledo).

41. Simões, A., Veiga, F., Vitorino, C. and Figueiras, A., 2018. A Tutorial for Developing a Topical Cream Formulation Based on the Quality by Design Approach. *J Pharm Sci 107*(10), pp.2653-2662.
42. Bhaskar, R., Ola, M., Patil, P.H. and Nawandar, K.S., 2016. A REVIEW ON: OINTMENT AND OINTMENT BASES.de Villiers, M., Ointment Bases.
43. Shelke U. and Mahajan A., 2015. A REVIEW ON: AN OINTMENT.
44. Ansel H., Popovich N. and Allen L., Sixth edition. *Pharmaceutical dosage form and drug delivery systems* .
45. Chen, M.X., Alexander, K.S. and Baki, G., 2016. Formulation and evaluation of antibacterial creams and gels containing metal ions for topical application. *Journal of pharmaceutics, 2016*.
46. Bhalani, U. and Shah, K., 2015. Preparation and evaluation of topical gel of Nigella sativa (KALONJI). *International Journal of Research and Development in Pharmacy & Life Sciences*, *4*(4), pp.1669-1672.
47. Saad, A.H., Ahmed, S.N. and Mohamed, E.B., 2013. Formulation and evaluation of herbal cream from Ziziphus spina leaves extract. *Int Res J Pharm*, *4*, pp.44-8.
48. Bhowmik, D., Gopinath, H., Kumar, B.P., Duraivel, S. and Kumar, K.S., 2012. Recent advances in novel topical drug delivery system. *The Pharma Innov*, *1*(9, Part A), p.12.
49. Ruela, A.L.M., Perissinato, A.G., Lino, M.E.D.S., Mudrik, P.S. and Pereira, G.R., 2016. Evaluation of skin absorption of drugs from topical and transdermal formulations. *Braz. J. Pharm. Sci 52*(3), pp.527-544.
50. Rafiee-Tehrani, M. and Mehramizi, A., 2000. In vitro release studies of piroxicam from oil-in-water creams and hydroalcoholic gel topical formulations. *Drug Dev Ind Pharm 26*(4), pp.409-414.
51. Ashara, K.C. and Shah, K.V., 2016. Elementary of animal model for percutaneous and ocular penetration. *Asian Pac J Trop Dis*, *6*(12), pp.1007-1010.
52. Suthakaran, C., Bioavailability of Topical Dosage Forms.
53. Nair, A., Jacob, S., Al-Dhubiab, B., Attimarad, M. and Harsha, S., 2013. Basic considerations in the dermatokinetics of topical formulations. *Braz. J. Pharm. Sci*, *49*(3), pp.423-434.
54. Brown, M.B., Turner, R. and Lim, S.T., 2012. Topical product formulation development. *Transdermal and topical drug delivery: principles and practice. Hoboken: Wiley*, pp.255-84.