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Topical Drug Delivery: A Review

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Abstract: The delivery of drugs to the human body is carried out through various routes of administration. One of these is the topical drug delivery route, which involves delivering drugs to the skin. The skin consists of three layers: the epidermis, dermis, and subcutaneous tissue. The stratum corneum, part of the epidermis, is a major barrier to topical drug delivery. Delivery of drugs across the stratum corneum is facilitated by different systems. Conventional systems include ointments, creams, gels, pastes, emulsions, shampoos, lotions, solutions, and suspensions. These systems are used to deliver the drug to the required site of action.

In recent years, the focus has shifted towards novel drug delivery approaches in search of safer and more effective therapies. This includes the development of nanocarriers for efficient drug delivery. Novel carriers such as liposomes, transferosomes, ethosomes, niosomes, nanoemulsions, solid lipid nanoparticles, and nanostructured lipid carriers are being used in drug delivery systems. Nanosystems are employed in the treatment of viral, bacterial, parasitic, and fungal diseases. Additionally, the potential of these systems has been explored in the treatment of skin-related cancer therapies.

1. Introduction

There are various routes of administration of drug to the human body. Namely oral, sublingual, rectal, parental, topical, inhalation etc. Topical drug delivery system is the localized administration which offer advantages of ease of delivery, high patient compliance as well as the avoidance of first-pass metabolism [1,2]. The specific challenge in designing a topical therapeutic system is lack, or reduced rate of absorption to achieve an optimal concentration of a certain drug at its site of action. One of the drawbacks is lack of cosmetic consideration for an appropriate duration [2,4]. Skin is readily accessible organs of human body for topical administration and it is main route of topical drug delivery system [3]. Topical products, widely used to manage skin conditions [5]. The effectiveness and toxicity of topical products are influenced by percutaneous absorption of drugs or other chemicals from a product and the application conditions used. Skin physiology and the skin physiology and perception by the patient and consumers [5]. A topical formulation which satisfies the target product profile physically and chemically, have an adequate shelf life and can be manufactured with a process that is scalable to commercial levels considered as successful formulation [2,6]. The success of topical therapy is also depend on the local and directed delivery of system [6].

2. Skin

Skin is the largest organ of the human body, which represents the outermost complex barrier between the body and the surrounding environment [6]. It performs many physical, chemical and biological functions [7,8]. Skin varies in thickness according to function and area of the body [9]. Tur E., discussed that skin is a mirror reflecting the many internal characteristics of the body, and it is readily available for visual evaluation. The skin consists of three layers, the epidermis, dermis and subcutaneous tissue. The

subcutaneous layer is found beneath the dermis and is not considered part of the skin [9]. Epidermis act as a main barrier for topical drug delivery. Epidermis consists of keratinocytes layers in the following order: stratum basale (basal cell layer), stratum spinosum, stratum granulosum, and stratum corneum. Keratinocytes are protein-rich cells composed mostly of keratin and keratohyalin. Keratin provides structure and tensile strength by forming bundles of elastic fibrils that stretch across the cell [10,11]. keratinocytes from the stratum basale proliferate and move through the layers of the skin to eventually become anucleate, flattened cells called corneocytes, which are terminally differentiated cells in the stratum corneum [12]. The epidermal lipids act as a cement between cells of the stratum corneum that holds together the building blocks, corneocytes. The cornified envelope proteins and the covalently bound lipid envelope are important for the chemical resistance of the corneocytes [13]. This analogues to brick and morter structure. Menon G. et. al. provides an overview on the factors affecting ceramide-enriched barrier lipids of the SC. They are affected by essential fatty acid deficiency (EFA), enzyme inhibitors, genetic defects resulting in enzyme deficiencies, topically applied agents, environmental factors, and hydration status of the SC. Such perturbations are often reflected in the morphology of SC bilayer organization. Anatomy, hydration of the stratum corneum, and damage to the stratum corneum can also change the barrier functioning of epidermis. Hydration of the stratum corneum plays an important role, hence transepidermal water loss severe as an important factor for the skin conditions [14]. The lower epidermal layers are also significant in barrier function, so that after the stratum corneum, they represent a second-line epidermal barrier [13]. The next outer layer, stratum granulosum, is the last layer that contains living cells [15]. Stratum spinosum is also known as prickle cell layer. Squamous cell layer is formed by a variety of cells, which differ in shape, structure, and subcellular properties [15]. There are desmosomes and tonofibrils are present in the intercellular spaces between the spinous cells [16]. Caputo R. et. al. demonstrated the presence of desmosomes, gap junctions and tight junctions by freeze fracture microscopy. Stratum germinativum or basal cell layer is consists of column shaped cell having oval nucleus. It is a dynamic system involves continuous physiological renewal of this tissues as well as regeneration [17,18]. Venus M. et. al. discussed the anatomy and the physiological functions of the skin in terms of protection, sensation, circulation, and biomechanics. Hendriks F. M. et.al. discussed mechanical behaviour of the epidermis is an important consideration in a number of cosmetic and clinical applications. Distinctive microarchitecture arises from epidermal rete ridges within the papillary dermis are dermal epidermal junctions [19]. They improves dermal-epidermal connectivity, biomolecular movement and enhances the interface strength. Rete ridges enlarge and trigger proliferation of basal precursors resulting in the basal layer's growth, which helps skin to overcome resistance against stresses and pressures [20]. The basement membrane at the dermal-epidermal junction keeps the epidermis attached to the dermis. This anatomical barrier is made up of extracellular matrix proteins: collagen IV, laminin, nidogen and perlecan [21]. They hold together the cells and tissues and maintain the structural integrity and the plasticity of the body. Provide positional information to adjacent cells and control their behaviour – including adhesion, polarisation, differentiation, migration and survival as well as expression of specific genes [22]. Two intracellular proteins in the epidermis are keratins and plakins they participate in the formation of structural scaffolds within keratinocytes and dermal epidermal junctions. Keratins are major components of the intermediate filament system of epithelial cells, forming a network which connect perinuclear region to desmosomes at the apicolateral cell membranes and to hemidesmosomes at the cell [23]. Plakins serve two roles: they anchor the keratin intermediate filaments to the nuclear and plasma membranes, and they connect intermediate filaments, microtubules and microfilaments together [24]. Skin appendages are all derivatives of the embryonic ectoderm. Reciprocating ectodermal mesenchymal interactions determine the fate of skin and appendage formation [25]. Hair Follicle development initiates from a specific thickening of the epidermis called the hair placode. Sebaceous glands pilosebaceous gland attached to hair follicle, which secrete an oily substance called sebum through the hair canal onto the skin surface for lubrication and waterproofing [26]. The signalling pathways between the dermis and epidermis is required for appendageal development [27]. Coiled tubular structures regulates human body temperature are sweat glands. Humans have three different types of sweat glands: eccrine, apocrine, and apoeccrine. Eccrine sweat glands are abundantly distributed all over the skin and mainly secrete water and electrolytes. Apocrine glands secrete oily substances containing lipids, proteins, and steroids through hair canals and are found only in skin containing hairs. They are also responsible for emotional stimuli [28,29]. Dermis is made up of fibroblasts and creates a tough, supportive cell matrix for the skin. It is consisted of two layers; thin papillary layer attached to epidermis with thin loosely arranged of collagen fibers and a thick reticular layer containing bundles of collagen extends from the base of the papillary layer to the hypodermis [30]. The subcutaneous hypodermis layer is a specialized layer of connective tissue containing adipocytes. The depth of the subcutaneous fat layer varies between body

regions and is based on the age, sex, and nutritional status of the individual. Hypodermal adipose functions as insulation from extremes of hot and cold, as a cushion to trauma, and as a source of energy and hormone metabolism [31]. Menon K.G. et.al. discussed the effect of skin aging and measure the skin responses, parameters, and physiological functions. Rabe J.H. et.al. discussed photoaging its histopathologic and clinical alterations as well as the molecular and genetic changes. Rawlings A. et.al. perform in vitro experiments and concluded that glycerol improves the stratum corneum desquamatory enzyme activities and desquamation itself. Hence it is an enzymically mediated digestion of superficial desmosomes in subjects with skin xerosis thus improving the desquamatory process. Defensive functions of the skin are lies in either cellular or extracellular region. Elias P. M. discussed the individual protective functions of skin, they are linked biochemically or by common regulatory mechanisms. Factors affecting the protective function such as stress, pH and how one defensive function can alter the other functions of skin. Moskowitz D. G. et. al. discussed the impaired epidermal permeability barrier is present in many of the children with ichthyosis can result in ample chronic losses of water and calories to impair growth. Instead of being uniformly dispersed, the highly hydrophobic lipids in normal stratum corneum are sequestered within the extracellular spaces, where this lipid-enriched matrix is organized into lamellar membranes that surround the corneocytes. This provides the structural and biochemical basis for site-related variations in permeability [32]. Corneocytes are surrounded by a highly cross-linked, resilient sheath, the cornified envelope, while the cell interior is packed with keratin filaments embedded in a matrix composed mainly of filaggrin and its breakdown products also refers as “natural moisturizing factors” [33]. Ceramides account for approximately 50% of the total stratum corneum lipid mass, and are crucial for the lamellar organization of the stratum corneum barrier functioning. Cholesterol is the second most abundant lipid by weight in the stratum corneum, promotes the intermixing of different lipid species and regulates its phase behaviour. The stability of the stratum corneum lipid mixture may be enhanced by the presence of large quantities of cholesterol. Free fatty acids, which account for 10 – 15% of stratum. A decrease in the concentrations of any of these critical lipid species compromises barrier integrity [34, 35]. Norlen L. et.al. In vivo relate the relative composition of three lipids free fatty acids, cholesterol, ceramide to transepidermal water loss, stratum coneum electrical impedance and corneometer values. Substances are transported across the stratum corneum primarily by a passive diffusion process via transcellular and intercellular route. Transcellular pathway means transport of molecules across epithelial cellular membrane. These include passive transport of small molecules, active transport of ionic and polar compounds, and endocytosis and transcytosis of macromolecules. Intercellular pathway means transport of molecules around or between the cells. Tight junctions or similar situations exist between the cells. The principal pathway taken by a permeant is decided mainly by the partition coefficient (log k). Most permeants permeate the stratum corneum by both routes. However, the tortuous intercellular pathway is widely considered to provide the principal route and major barrier to the permeation of most drugs [36, 37]. Tortuous extracellular pathway, an alternative model is based upon the presence of lacunar domains embedded within the lipid bilayers. It is a pore pathway for the permeation of polar molecules [38]. The skin acts as both a physical-mechanical and immunological barrier, able to avoid microorganism invasion and trigger an immune response. This immune response is caused by the production of anti-microbial peptides, that destruct gram-positive and gram-negative bacteria, fungi and some virus. Langerhans cells, present in the viable epidermis, act as antigen-presenting cells. Furthermore, the dryness and barrier of the SC prevents growth of microorganisms on the skin. T-cells are transient in the epidermis and are typically found around post-capillary venules in the dermis and around the skin appendages [39]. Ultraviolet radiation is composed of electromagnetic energy. Radiation is responsible for actinic damage to the skin and can act as a co-carcinogen. The stratum corneum reflects radiation, so reducing the exposure dose. Sun exposure increases the activity of melanocytes, the number of melanosomes produced and the rate of transfer of melanin to the epidermal keratinocytes. This helps to decrease absorption of UV radiation by DNA and cellular constituents [40]. The pH of human skin is 5.4-5.9, which makes the skin an inhospitable environment for potential pathogens. Furthermore, the dramatic difference in pH levels between the skin and the blood (pH = 7.4) serves as a secondary defensive mechanism in the event that microbes breach the skin tissue and enter the circulation [41,42].

3. Skin Diseases

Skin diseases are the most common problem worldwide. Most of the skin conditions are not life threatening but they have major impact on the life of patient. Lamberth study suggested 55% of the population have some skin diseases but only 22.5% actually had received medical attention [43]. Sanclemente G. et.al. conduct a study to evaluate the impact of skin diseases on quality of life. Occupations associated with an increased risk of skin diseases. Most risks are related to irritants and allergy-inducing materials present at the workplace. Sometimes water also work as an irritant for those working in wet conditions. Skin contact

with organic solvents always poses a risk to the skin. Contact dermatitis developed as a result of the combination of occupational exposure and individual predisposition to diseases [44]. Viral replication is slow and is closely dependent on the differentiation of the host cells. Viral DNA is present in the basal cells, but the viral antigens and the infecting virus are produced only when the cells start to become squamous and keratinized once they reach the surface [46]. Viral diseases are observed as viral infection on mouth, foot and, hand, scientifically known as Rubella or Human Papilloma virus. The types of HPV are associated with the particular consequences of infection. Infection is primarily of the squamous epithelium. These viruses are everywhere in nature and self-limiting [45]. As several as 75% of herpes simplex virus (HSV) are asymptomatic infection. HSV is divided into types 1 and 2 according to a number of features including DNA fragment size after endonuclease restriction analysis. Also likely is there being no direct mechanism for one infection influencing the other. HSV-2 is likely to have evolved so that it is not influenced by previous HSV-1 infection. Since the risk behaviours associated with HSV-1 infection occur at a younger age than those associated with HSV-2 infection [47]. The measles virus causes a common childhood disease with high fever and typical skin rash [48]. Bacterial skin flora in humans is composed of gram positive and gram negative bacilli. The Gram-positive bacilli are represented by four genera of coryneform bacteria: Brevibacterium, Corynebacterium, Dermabacter and Propionibacterium. Dermabacter spp. are not associated with skin infection, whereas Propionibacterium spp. are associated with skin infection and have an important role in acne [49]. The staphylococci collectively known as the 'coagulase-negative' staphylococci. Many species of staphylococci found in the skin, out of which S. epidermis, S. haemolyticus and S. hominis are the most abundant. They are rarely found in skin disease but have clinical importance [49]. Infectious diseases are necrotizing soft tissue infections (NSTIs), gangrene and methicillin-resistant Staphylococcus aureus (MRSA) [50]. Liu C. et.al. prepared an evidence-based guideline for the treatment of MRSA infection in adults and children. Cellulitis is a common infection of the skin and its underlying tissues. Staphylococcus aureus and group A streptococcus (GAS) are the most common causes of cellulitis. Given the rise of methicillin resistant S. aureus (MRSA) as the predominant cause of suppurative skin infections [51]. Impetigo is a superficial soft tissue skin infection involving the epidermis. Nonbullous and bullous impetigo constitute the different types of impetigo. The most common organisms isolated include group A hemolytic streptococci and Staphylococcus aureus. The nonbullous type impetigo associated with sore, cluster of erosions, or small vesicles or pustules that have an adherent or oozing honey-yellow crust. The bullous form of impetigo presents as a large thin-walled area containing serous yellow fluid [52, 53]. There are many skin fungal infections and superficial fungal infections were reported. Tinea capitis, a communicable fungal infection of the scalp and hair shaft. It is the most common fungal infection in children. Tinea corporis is a dermatophyte infection of the body, often referred to as ringworm. It can be caused by any dermatophyte that infects humans. It is most commonly caused by Trichophyton species, especially Epidermophyton, Microsporum, and Trichophyton [54]. Dermatophytes grow aerobically over a wide range of temperatures and pH. Dermatophytosis is an infection of skin hair and nail. Dermatophytes have been shown to have keratinolytic, general proteolytic and lipolytic activity. Serine proteinase which are involved in extracellular protein catabolism, have been found in dermatophytes which play a major role in the invasion of skin [55]. Tines pedis is the infection of feet associated with fissuring of toeweb. Tinea unguium, or onychomycosis, may be caused by a number of dermatophytes and other molds like Candida sp., T mentagrophytes and T rubrum, E floccosum, T tonsurans, and T verrucosum involved in infection of nails [56, 57]. Predominently these infections are caused by T rubrum. Biofilms have recently been recognized to play an important role in the pathogenesis of onychomycosis [57]. Onychomycosis clinically presents with nail discoloration, nail separation (onycholysis), brittleness, nail thickening, and subungual accumulation of scale. More severe cases may exhibit ridging and onychocryptosis (ingrown nail). Dermatophytomas are fungal abscesses that present as white and yellow, or orange and brown longitudinal streaks within the nail plate, Yeast infections present as yellow-white discoloration with inflammation and purulent discharge, and bacterial *Pseudomonas* infections of the nail appear green [57, 58]. Dandruff is a scalp disorder characterized by flaking of the scalp and hyperproliferation. Clavaud C. et. al. conducted a study and compared the dandruff versus nondandruff scalp and correlate disequilibrium between M. restricta and Staphylococcus epidermidis or Propionibacterium acnes. Malassezia spp. were found to be the most abundantly occurring fungi on both healthy and diseased skin with M. restricta, M. globosa, M. sympodialis, and M. furfur occurring on both and M. slooffiae only on nonlesional skin. M. restricta being more dominant at lesional skin and M. globosa on nonlesional skin [59]. Major events that cause the dandruff are colonization of Malassezia, sebum production and individual predisposition. They are interdependent and play major role in dandruff development. The sebaceous glands mature and produce greater amounts of sebum in both men and women at puberty. The Malassezia utilizes sebum lipids as a

nutrient source, required to support growth of Malassezia. Increase in sebum production and Malassezia proliferation triggers the development of dandruff [60]. Pityriasis versicolor is a superficial skin infection of M. globosa. Development of filaments and stratum corneum damage through tissue invasion, dyspigmentation and minor inflammation associated with Pityriasis versicolor. This infection may occur in healthy individuals and in immunocompromised patients [61]. Pityriasis versicolor present with a rash consisting of well demarcated, scaling, thin plaques. A concerning feature of the disease is that hyperpigmentation or hypopigmentation associated with the rash often persists for months after the fungal infection is appropriately treated [62]. Atopic dermatitis is a very common inflammatory skin disorder. It is associated with an increased risk of developing allergy (food allergy, asthma and allergic rhinitis). The term 'atopic march' is often used to describe this progression from atopic dermatitis to other allergic diseases [63]. A genetic defect in the filaggrin protein is thought to cause atopic dermatitis by disrupting the epidermis. Results in contact between immune cells in the dermis and antigens from the external environment, which leads to intense itching, scratching, and inflammation [64]. Deckers I. A. G. at. al. investigated the review of epidemiological studies on atopic eczema. Flohr C. et. al. Evaluate the evidence for measurement of IgE antibodies in diagnoses of atopic dermatitis. Parasitic skin infections are restricted to the stratum corneum, the upper layer of the epidermis, which is where the ectoparasites complete their life-cycles, in part or entirely. In other parasitic skin diseases, such as leishmaniasis, loiasis or onchocerciasis, other layers of the dermis are also affected [65]. Parasitic infections of the skin and subcutaneous tissues are caused by a variety of parasites ranging from single-celled protozoa to complex multicellular worms and arthropods [66]. The human itch mite, Sarcoptes scabiei is an obligate human parasite that involves in skin infection. Scabies mites are confined to the stratum corneum they cause primary damage to the skin in cases of classical scabies. Development of erythematous papules, vesicles and scaly plaques were observed in crusted scabies [66, 67]. Demodicidosis caused by Demodex folliculorum and Demodex brevis, they are ubiquitous mites found on the skin of most adults worldwide [68]. Tungiasis caused by the penetration of the female sand flea, Tunga penetrans, into the Skin [69]. Louis S. J. et. al. examined and interviewed tungiasis patients to determine disease related behavior, prevalence, demographics and clinical presentation. Myiasis refers to the infestation of tissue by the larvae of flies. Myiasis causing flies belong to the order Diptera. Any site with exposure to the environment (i.e, cutaneous, oral, ophthalmic, nasopharyngeal, urogenital, anal, and wounds) can be vulnerable. Cutaneous myiasis is the most common form of the disease [70]. A part from these infections leishmaniasis and amebae Infections are protozoal infections of skin. Onchocerciasis and loiasis are the some of the infections spreaded by helminthies [66]. Psoriasis is an immune-mediated disease with genetic predisposition, but no distinct immunogen has been identified [71]. It is a chronic, genetically influenced, remitting and relapsing scaly and inflammatory skin disorder [72]. Gudjonsson J. E. et. al. reviewed the epidemiology of psoriasis and suggests that contribution of multiple genes in the development of psoriasis occurs. Hence several different genetic combinations may precipitate the psoriatic phenotype. If this is the case, it is probable that different genetic subgroups of psoriasis exist and will be triggered by different environmental factors. Topical drug delivery are recommended first-line treatment for mild-to-moderate psoriasis. Svendsen M. T., et. al. demonstrated the patient perspectives on treatment preferences of psoriasis. Treatment may be affected by factors such as gender, age, ethnicity, and type, extent, and severity of psoriasis as well as tolerability, efficacy and price of the drugs. Skin cancers are most common malignancy of humans. Skin cancers are named according to the cell from which they arise and the clinical behaviour. The three commonest types are basal cell carcinomas, squamous cell carcinomas, and cutaneous malignant melanoma [73]. Melanomas are the most aggressive type of skin cancers. One of the greatest risk factors for the development of skin cancer is ultraviolet radiation from sun exposure [74]. Norval M. el. al., discussed the effect of UVR exposure to the development of skin cancer. UVR produces DNA damage, gene mutations, immunosuppression, oxidative stress, and inflammatory responses, cause photoaging of the skin and skin cancer. UVR induced cyclobutane pyrimidine dimer formation that leads to immune suppression. UVR induced free radical damage [75]. Genetic factors and organ transplantation are the risk factors for skin cancer.

4. Conventional approaches of topical drug delivery

Drug delivery systems ensure the delivery of drugs into the body where they are needed. This is directly concerned with the site of action and the desired effect of the preparation. Generally, topical preparations meant for systemic or local effects. Semi-solid formulations are more promising over solid and liquids considering its property to cling to surface of application for reasonable duration before they worn off [76]. Physicochemical properties, formulation composition and rheological properties provide a more scientific

basis for the classification and distinction of topical dosage forms [77]. The vehicle plays a key role in the appearance, feel, and successful application of a topical drug. Therefore, the composition of a topical drug vehicle should be considered. Composition alone cannot be used to define a dosage form since one ingredient can have multiple functions (e.g. poloxamer functions as a suspending agent, gelling agent, thickening agent, emulsifier and/or wetting agent), and the manufacturing process can change product properties. Ointment are a semisolid preparation intended for external application to the skin or mucous membranes. Creams are semisolid dosage form containing one or more drug substances dissolved or dispersed in a suitable base. Lotions are topical suspensions, solutions and emulsions intended for application to the skin [78].

A gel is a semisolid dosage form contains a gelling agent to form solution and colloidal dispersion. Gels are classified on the basis of colloidal system (Inorganic gels and organic gels), based on the nature of solvent (hydrogels, organic gel and xerogel), based on rheological properties (plastic, pseudoplastic and thixotropic gel), based on physical nature (elastic and rigid gel) [79]. Gels that consist of an aqueous dispersion medium that is gelled with a suitable hydrophilic gelling agent are known as hydrogels. Gels containing oil or non-polar liquids as a dispersion medium are known as organogels. Bigels are topical formulations that are obtained by combining an aqueous (hydrogels) and lipophilic (organogels) system [80]. Silica xerogels evaluated as drug delivery implants and as a drug delivery device. Xerogels are expensive and associated with biodegradation of pure silica [81]. When gels and emulsions are used in combined form the dosage forms referred as emulgel. Major objective of this formulation is delivery of hydrophobic drugs [82]. Mekkawy A. et. al. prepared and evaluate fluconazole topical gel. Bachhav Y. G. et. al. performed in vitro and in vivo evaluation of meloxicam topical gel. Singh M. P. et. al. prepared the topical gel with different gelling agent and compare it with marketed formulation.

Ointments are greasy semisolid preparation of dissolved or dispersed drug. Ointment bases influence topical drug bioavailability due to their occlusive properties of the stratum corneum. An ideal ointment base should be pharmaceutically well designed. They are absorption bases, oleaginous bases, emulsion bases, water soluble bases [83]. Noda Y. el. al. prepared blended ointments having water absorption capacity which can be modified depending on the state of the wounds. They are helpful in treatment strategies of pressure ulcers. Ahuja et. al. demonstrate the NSAID efficacy enhancement in eye preparation.

Paste are semisolid or stiff preparations containing high proportion of finely powdered solid such as starch, zinc oxide, calcium carbonate, kaolin and talc. Classification of pastes include two phase pastes they are consisting of two immiscible components in which dispersed phase is suspended in a continuous phase. Three phase pastes consist of a two phase emulsion with concentration of incorporated powder [84]. Abid W. K. et. al. published the efficacy of paste formulation for traumatic ulcers. Flagothier C. et.al. discussed the strategy of miconazole paste which is differs from conventional topical treatments because it is intended to decrease the visibility of acne papules, particularly erythema, in a short period of time.

Creams are viscous liquid or semi-solid emulsions, they are oil-in-water or water-in-oil type dosage forms. In comparison to ointments, creams are significantly less greasy, less viscous, and more spreadable. Creams contains >20% water and volatiles and/or <50% of hydrocarbons, waxes, or polyethylene glycols as the vehicle for external application to the skin [86]. According to function creams are classified as cleansing, foundation, massage creams. According to characteristics properties they are cold creams, vanishing creams. According to the use case they are all-purpose cream and general creams, Night creams, skin protective creams and hand creams [85]. Simoes A. et. al. give the insite into the design and development of topical creams by quality by design approach. Gisby J. et al. Developed a mupirocin cream formulation for skin infection and compared it with oral agents. Naeimifar A. et. al. develop an antiwrinkle cream formulation having saffron extract and avocado oil.

Solutions are composed of two or more solutes dissolved to clarity. They can be aqueous, nonaqueous, or hydroalcoholic. The advantage is they are very simple to produce and easily spreadable to hair-bearing and nonhair-bearing areas [87, 88]. Loftsson T. et. al., studied the effect of cyclodextrin solution on topical drug delivery to the eye. Miro N. et. al. conducted clinical trial to understand the efficacy and safety of preservative-free formula of ciprofloxacin solution in otitis media.

Suspension is a liquid dosage form. It is two-phase system consisting of a O-20% concentration of a finely divided, insoluble solid drug, dispersed in a liquid [78]. The main problem is precipitation of the active drug which lead to nonuniform dosing and instabilities. The concentration of the drug is also critical to dispersion. Less than 2% of the drug will freely settle to the bottom of the suspension, while concentrations of 5-100% encounter more hindrance and remain suspended [89]. Bunge A. L. discussed the release rate of topical formulations containing drug in suspension. Lansdown A. B. G. evaluate the dermal irritancy of six zinc compounds in animal models.

Lotions are liquid suspension or medicated dispersions meant for external use. It is applied on the skin without friction. After application it dries forming a thin film of medicament over the affected area. It should be shaken vigorously before each application to have homogeneity and container must bear a label. “For external use only” [90, 91]. The lotions are clear solution containing 25-50% alcohol [76]. Liniments are usually alcoholic and oily liquid preparation or emulsion, intended for external use with friction. They are applied on the skin with rubbing and should never be applied on the broken parts of the skin [91]. Rigat M. et. al. conducted an ethnobotanical survey on the amount and reliability of plant traditional uses. They use arnica montana lotion, betula pendula lotion, hypericum perforatum lotion, petroselinum crispum liniment and ramonda myconi liniment. Anning S.T. discussed the role of calamine lotion, zinc oxide lotion and steroid lotion in treatment of eczema. An oily lotion or liniment is used for less acute eczema. Rahmen I. R. A. prepared anise and thyme lotion for topical use. Topical lotions are used to treat mild to moderate acne, pilot study was preformed on the subject [92].

Emulsions are heterogeneous systems composed by two immiscible liquids in which one is uniformly dispersed as fine droplets throughout the other [93]. Emulsions can be classified into two groups: simple emulsions and multiple emulsions. Simple emulsions are oil-in-water (O/W), and water-in-oil(W/O). Multiple emulsions are oil-in-water-in-oil (O/W/O) or water-in-oil-in-water (W/O/W) double emulsions [94]. Emulsions are most commonly stabilized by synthetic surfactants, which must be added at a minimal concentration as they can disrupt the skin barrier function, and consequently, cause skin irritation. Some surfactants can be intrinsically toxic or may alter the pharmacokinetics of co-administered drugs. Emulsions facilitate drug permeation into and through the skin by their occlusive effects and by the incorporation of penetration-enhancing molecules [93]. Pickering emulsions are emulsions stabilized by solid particles instead of classic emulsifiers. The stabilization of emulsion droplets by solid particles is due to particle dual wettability. Wettability allows the spontaneous accumulation of particles at the oil-water interface, which is stabilized against coalescence by volume exclusion and steric hindrance [95, 96]. Otto A. et. al. describes the formulation perspective of emulsions. They discussed the vehicle properties, thermodynamic activity, supersaturation, effect of penetration modifiers, surfactants, droplet size as well as the fate of emulsion. Marku D. et. al. characterise the starch based Pickering emulsions to evaluate their possible use as vehicles for topical drug delivery. Dry emulsions are powdery, lipid-based formulations from which an O/W emulsion can easily be reconstituted when exposed to an aqueous solution. From a pharmaceutical point of view, dry emulsions are attractive because they are physically and microbiologically stable solid formulations [97]. Gallarate M. et. al. prepared Vitis vinifera dry emulsion for topical application. Laugel C. et al. prepared and evaluated the multiple emulsion oil–water–oil system it can be utilized as a potential prolonged release dosage form of hydrocortisone.

Foams are triphasic topical delivery system. They consist of 3 phases—oil, water, and organic solvent. More specifically, the foam’s constituents include ethanol, purified water, cetyl and stearyl alcohol, polysorbates, citric acid, and potassium citrate, or formaldehyde or nonformaldehyde preservatives. The foam exists as a liquid pressurized in an aluminum can with a hydrocarbon propellant which upon valve actuation forms a foam lattice. This matrix is thermolabile although stable at room temperature [98]. Stein L. examines the clinical studies on efficacy and safety of betamethasone valerate and clobetasol propionate. They have become available in a novel, thermolabile, low-residue foam vehicle for topical application. Classes of foam formulation are aqueous foam, ointment foam, hydroalcoholic foam, potent solvent foam, saccharide foam, suspension foam, oil foam and emulsion foam. They are classified on the basis of their primary component of formulation [99]. Kanti V. et. al. evaluated the effect of minoxidil foam formulation. It was found to be effective in stabilizing hair density, hair width and scalp coverage in both frontotemporal and vertex regions.

A shampoo may be described as a cosmetic preparation meant for the washing of hair and scalp, packed in a form convenient for use. Its primary function is of cleansing the hair of accumulated sebum and scalp debris

[100]. Shampoos also contain conditioning agents, antibacterial agents, natural essential oils or extracts for treating dandruff, dermatitis and other hair diseases. A shampoo normally consists of 10 to 30 ingredients in the formulation. Shampoo usually contains a mix of primary and secondary surfactants for cleaning, viscosity builders, solvents, conditioning agents, preservatives, pH adjusters and other components such as fragrance and colour [101]. Surfactants form the 'heart' of most shampoo formulations. Key benefits associated with shampoo surfactants are cleaning, foaming, rheology control, skin mildness and polymer deposition [102]. Kumar Ashok et. al. prepared a herbal shampoo and compare this with marketed shampoos. They observe the aesthetic attributes, such as lather and clarity, of the laboratory shampoo are not comparable with the marketed shampoos. The foam volume was on a par. Although the retail products were not fare so well in the tests conducted by us, they enjoy market popularity, especially if they foam well. This is mainly due to the false notion among consumers that 'a shampoo that foams well, works well'. Dias M. F. R. G. et. al., discussed the effect of pH of shampoo on the hairs. Mainkar A. R. et. al. discussed the evaluation of herbal shampoos.

5. Noval approaches of topical drug delivery

In search of safe and effective therapy, the development of new drugs has been the common practice historically. However, it involved numerous time, efforts, and huge cost. Alternate approach of drug delivery involved, carrier systems were used to deliver the molecules to specific receptor sites without afflicting the normal tissues and organs of the body [103]. The novel carriers have been exploited through almost all the routes of administration. In contrast to the conventional formulations, these novel dermatological systems are different in their composition and constructs including their exterior and interior design [103,104].

5.1.Liposomes

Drug delivery research took a great leap with the discovery of liposomes. Liposomes can be regarded as the first generation of novel drug delivery systems and have been extensively investigated. They are microscopic vesicles consisting of one or more concentric spheres of lipid bilayers separated by aqueous or buffer compartments [105]. A class of phospholipids commonly used to construct liposomes for drug delivery is phosphatidylcholine. The ability of phospholipids to form a bi-layer structure is because of their amphipathic character resulting from the presence of a polar or hydrophilic (water-attracting) head-group region and a non-polar, lipophilic (water-repellent) tail. The hydrophilic head groups orientate toward the aqueous phase and the lipophilic tails orientate to each other in the presence of water. Therefore, liposomes contain a lipophilic compartment within the bi-layer membranes and hydrophilic compartments between the membranes. Under the right conditions, water-soluble substances can be stored into the water phase and lipophilic substances into the lipid phase [106]. Three mechanisms of the penetration of liposomes into the skin have been described. First is lateral diffusion of liposomes in the stratum corneum. The molecular structure of liposomes is similar to that of endogenous skin lipids. Lipid exchange between human membranes is a common physiological phenomenon. The exchange occurs via molecular diffusion from one membrane to the other. Second is *trans* -epidermal osmotic gradient and hydration force through which liposomes are sucked into the epidermis. Third is through the pilosebaceous units [107, 108, 109]. The rationale of using liposomes in topical drug delivery is as follows. 1. Due to their biphasic character, liposomes can act as carriers for hydrophobic as well as lipophilic therapeutic agents. 2. Liposomes may help in improving solid-state stability of the drug by encapsulating it. 3. They may serve as local depot for the sustained release of dermally active compounds thus offering reduction in the frequency of administration. 3. By virtue of penetration of individual phospholipid molecule into the lipid layers of stratum corneum and epidermis, they may serve as penetration enhancer and facilitate the dermal delivery leading to higher drug localization in the skin with concomitant reduction in the systemic absorption. 4. Liposomes will help in reducing the problem of skin irritation associated with various topical agents by containment in either lipid bilayer or aqueous core. 5. Liposomes have shown the potential to target pilosebaceous structures and hence they can be employed for efficient treatment of hair follicle-associated disorders [105, 110, 111]. Liposomes are classified on the basis of size and number of lipid layers. They are unilamellar vesicles, oligolamellar vesicles (0.1-1.0 μm), multilamellar vesicles (More than 0.5 μm) and multivesicular vesicles (More than 1.0 μm). Based on method of preparation they are lamellar vesicle of a single or oligo formed by reverse phase evaporation, stable pluri lamellar vesicle, frozen and thawed multi lamellar vesicle, vesicle prepared by extrusion technique, dehydration-Rehydration method. Composition of liposomes may vary depending upon the application. They are classified as conventional liposomes, fusogenic liposomes, pH sensitive liposomes, cationic liposomes and immune liposomes [112, 113].

Liposomes are frequently used as vehicles in pharmaceuticals and cosmetics for a controlled and optimized delivery to particular skin layers. Studies performed some years ago indicated that tetracaine and lidocaine encapsulated in liposomes provide better local anesthesia than a conventional anesthetic cream [114]. Wasankar S. R. et. al. developed dexibuprofen liposomal hydrogels for topical delivery. Agarwal R. at. al. discussed the recent developments related to liposomes in topical ophthalmic drug delivery. Jain S., et. al., report that benzoyl peroxide and adapalene liposomes embedded in gel, were evaluated for acne treatment and showed higher dermal bioavailability and lower skin irritation, compared to the free drug and a marketed acne treatment product. Chin J., et. al., studied the effect of topical liposomal gel containing a combination of zedoary turmeric oil and tretinoin for psoriasis activity. Liang X. et. al., report the in vitro and in vivo topical administration of sponge Haliclona sp. Spicules (SHS) combined with cationic flexible liposomes to increase the delivery of small interfering RNA (siRNA) into viable skin cells. Lajunen T. at. al., developed methods of liposome preparation utilizing a microfluidizer to achieve adjustable nanoparticle size and high loading capacity of plasmid DNA. Transferrin was used as a targeting ligand directed to retinal pigment epithelium. Size dependent distribution of liposomes to different posterior segment tissues was seen. Liposomes with the diameter less than 80 nm permeated to the retinal pigment epithelium whereas liposomes with the diameter of 100 nm or more were distributed to the choroidal endothelium. Active targeting was shown to be necessary for liposome retention to the target tissue. Microfluidizer produced small liposomes in eye drops are an attractive option for drug delivery to the posterior segment tissues of the eye. Margalit R. et. al., focuses on bioadhesive liposomes for topical drug delivery systems.

5.2.Niosomes

Niosomes are spherical and consist of microscopic lamellar (unilamellar or multilamellar) structures. The bilayer is formed by nonionic surfactants, with or without cholesterol and a charge inducer. Different types of surfactants at variable combinations and molar ratios are used to form niosomes. Niosomes can be categorized into 3 groups based on their vesicle size, namely, small unilamellar vesicles (0.025–0.05 mm), multilamellar vesicles (>0.05 mm), and large unilamellar vesicles (>0.10 mm) [115]. The assembly into closed bilayers is rarely spontaneous and usually involves some input of energy such as physical agitation or heat. The result is an assembly in which the hydrophobic parts of the molecule are shielded from the aqueous solvent and the hydrophilic head groups enjoy maximum contact [118]. Niosomes possess a bilayer structure, which is similar to liposomes. The concentration of cholesterol is higher in liposomes than in niosomes. As a result, the drug entrapment efficiency of liposomes is less than that of niosomes. Niosomes are cost-effective for industrial manufacture and do not require special storage conditions, which are essential while manufacturing liposomes. The cost of liposome preparation is high because of the unstable chemical ingredients (phospholipids), which undergo oxidative degradation. Liposomes therefore require special handling methods. The materials used to prepare niosomes confer better stability on them [116, 117]. Bartelds R. et. al. compared the niosomes and liposomes features and concluded that niosomes can be used as an alternative for liposomal delivery. Drugs with low therapeutic index and low water solubility could be maintained in the circulation via niosomal encapsulation, through niosomes sustained release action can be obtained [119]. Paolino D, et. al., prepared bola-surfactant niosomes for treatment of skin cancer. Shah P., et. al., Evaluate the impact of niosomes for topical drug delivery by using quality by design elements. Desoximetasone-loaded niosomes with desired particle size ranges and entrapment efficiencies for topical administration routes may be obtained by carefully selecting the correct combination of components. Goyal G. et. al., prepared the benzoyl peroxide loaded niosomes. Niosome gel is advantageous because it enhances the transdermal permeation of the drug, control the release of the drug and prevent the degradation of benzoyl peroxide. Skin irritation side effects of the drug were also reduced.

5.3.Transferosomes

Transfersomes are ultradeformable vesicles, elastic in nature, which can squeeze itself through a pore which is many times smaller than its size owing to its elasticity. They possess an aqueous core surrounded by the complex lipid bilayer. It also possesses some specially tailored properties due to the incorporation of "edge activators" into the vesicular strructure. Span 80, tween 80, sodium cholate, sodium deoxycholate, are some surfactants that have been used as an edge activators [120]. The nature and ratio of different edge activators affect the physicochemical properties of vesicles including their size, entrapment efficiency and zeta potential. They are more stable, high penetration due to high deformability, biocompatible & biodegradable,

suitable for both low and high molecular weight and also for lipophilic as well as hydrophilic drugs and reach upto deeper skin layers. They can be used for both systemic as well as topical delivery of drug [121]. Cevc G., et. al., demonstrates the topical corticosteroid delivery with very deformable vesicles. Paul A., et. al., concluded that transfersomes provide a key to the worlds of topically administered antigen solutions and carrier-associated antibodies. The ultradeformable carriers not only transport the antigens across the intact skin spontaneously, they also deliver their payload largely into the lymphatics where they accumulate, and are phagocytosed, in the proximal lymph nodes. In order to achieve an effective immune response, five factors play a role: (1) antigen type, (2) antigen dose, (3) route presentation of co-stimulatory antigen administration, (4) antigen and (5) the presence of appropriate factors. Therefore, for each antigenic drug applied on the skin with transfersomes, independent studies will have to be performed to check its immunogenicity. Transdermal immunization of transcutaneous hepatitis-B vaccines have given good result. A 12 times higher AUC was obtained for zidovudine as compared to nornal control administration. And NSAIDS are associated with number of GI side effects. These can be overcome by transdermal delivery using ultradeformable vesicles [122].

5.4.Ethosomes

Ethosomal system is a lipid vesicular nanocarrier that holds a high concentration of alcohols. Ethosomal systems could be classified into three distinct types according to the components incorporated into their formula namely, classic or traditional ethosomes, binary ethosomes, and transethosomes. Traditional or classical ethosomes are the initially developed ethosomal system that modified the liposomal composition via the incorporation of a relatively high amount of ethanol, up to 45%, along with phospholipids and water components. Traditional ethosomes showed a high potential for transdermal drug delivery when compared with traditional liposomes mainly due to their greater entrapment efficiency, smaller size, and negative surface charge [123]. Modification of the traditional ethosomes via the addition of different kinds of alcohol. The binary ethosomes have been studied in different research that widely used propylene glycol/ethanol mixture or isopropanol /ethanol mixture. Avasarala H., et. al., develop ethosomal gel for the topical delivery of the antipsychotic drug Ziprasidone Hydrochloride. Oral delivery of antipsychotic drugs like Ziprasidone HCl has a disadvantage of gastric disturbance. Ziprasidone HCl loaded ethosomal gel was formulated to avoid the disadvantages of oral delivery. The ethosomes were prepared using Lipoid S 75 with Isopropyl alcohol and Propylene glycol as the solvents. Transethosomal system is the latest generation of ethosomes they have same components as traditional ethosomes, but with the inclusion of an edge activator or penetration enhancer into the vesicular structure [124]. Ethosomal system have their limitations such as majority of the time, ethosomal drug delivery systems are designed for gradual, continuous release rather than fast injection. They have low yield [125]. Marto J., et. al., prepared griseofulvin loaded ethosomes for topical delivery. Rattanapak T., et. al., conducted a comparative study of liposomes, transferosomes, ethosomes and cubosomes. They observed from the in-vitro studies that cubosomes and ethosomes are promising lipid carriers for transcutaneous immunisation. Yu Z., et. al., develop ethosomes loaded formulation for the treatment of acne.

5.5.Nanoemulsions

Nanoemulsions are emulsions with droplet size on the order of 50–200 nm. A typical nanoemulsion contains oil, water and an emulsifier. The addition of an emulsifier is critical for the creation of small sized droplets as it decreases the interfacial tension i.e., the surface energy per unit area, between the oil and water phases of the emulsion. The emulsifier also plays a role in stabilizing nanoemulsions through repulsive electrostatic interactions and steric hindrance. The emulsifier used is generally a surfactant, but proteins and lipids have also been effective in the preparation of nanoemulsions. Nanoemulsions are typically prepared in a two-step process where a macroemulsion is first prepared, and is then converted to a nanoemulsion in a second step [126]. Three methods may be applied for the preparation of nanoemulsions use of high pressure homogenisers use of low energy emulsification method at constant temperature or application of the phase inversion temperature, microfludization [127, 128]. Campani V., Et. al., developed a nanoemulsion for topical delivery of vitamin K1. Shaikh N. M. et. al., design and develop nanoemulsion of Econazole nitrate as treatment for tinea versicolor fungal disease. Due to econazole nitrate poor solubility, it is incompletely absorbed after oral dosing and bioavailability varies among individuals. The drug efficacy of topical formulation can be limited by instability due to its poor solubility in the vehicle and low permeability. Therefore, to overcome these problems nanoemulsions have been designed. Salim N., et. al., develop nanoemulsion of antipsoriatic drug for topical drug delivery.

5.6.Solid lipid nanoparticles

Solid lipid nanocarriers are colloidal carrier system composed of a high melting point lipid as a solid core coated by aqueous surfactant. In SLNs as compared to other colloidal carriers liquid lipid is replaced by solid lipid. The use of solid lipid as a matrix material for drug delivery is well known. The use of solid lipid instead of liquid lipid is beneficial as it has been shown to increase control over the release kinetics of encapsulated compounds and to improve the stability of incorporated chemically-sensitive lipophilic ingredients. The general excipients used in any SLN formulation are solid lipids, emulsifiers, co-emulsifiers and water. The term lipid is used here in a broader sense and includes triglycerides, partial glycerides, fatty acids, cholesterol and waxes. All classes of emulsifiers have been used to stabilize the lipid dispersion. It has been found that the combination of emulsifiers might prevent particle agglomeration more efficiently [129]. SLNs combine the advantages and avoid the drawbacks of several colloidal carriers. Potential disadvantages such as poor drug loading capacity, drug expulsion after polymeric transition during storage have been observed. The drug loading capacity of conventional SLN is limited by the solubility of drug in the lipid melt, the structure of the lipid matrix and the polymeric state of the lipid matrix [131]. An extremely fascinating application is pulmonary administration of SLN. SLN powders can't be regulated to the lungs because partical size is too little and they will be breathed out. An exceptionally straightforward approach is the aerosolization of fluid SLN scatterings [130]. Almeida A. J. et. al., focuses on solid lipid nanoparticle for drug delivery of proteins and peptides. Hou D., et. al., prepared and characterized mifepristone loaded solid lipid nanoparticles by high shear homogenizer and ultrasound technique. Sylvia A., et. al., focussed on cosmetic applications of solid lipid nanoparticles. Jain S. et. al., design and development of solid lipid nanoparticles of miconazole nitrate for topical application.

5.7.Nanostructured lipid carriers

Nanostructured lipid carrier (NLC) is second generation smarter drug carrier system having solid matrix at room temperature. This carrier system is made up of physiological, biodegradable and biocompatible lipid materials and surfactants. NLC exhibit superior advantages over other colloidal carriers viz., nanoemulsions, polymeric nanoparticles, liposomes, SLN etc. The whole set of unique advantages such as enhanced drug loading capacity, prevention of drug expulsion, leads to more flexibility for modulation of drug release and makes NLC versatile delivery system for various routes of administration [132]. NLC's are made up of a binary mixture of solid-lipid and a liquid lipid (oil) as a hybrid carrier having an average size of 10-500 nm. The mixture NLC's is consist of long chain of liquid and lipid (oil) of ratio 99.9: 0.1 and having a short chain of solid and lipid having a ratio of 70:30. NLCs have three very specific features. These properties are based up on the location the drug is going to be integrated three different methods were adopted for a development and formulation of nanostructure NLCs [133]. NLC type I also called as imperfect crystal. NLC type I also called imperfect crystal types have a badly structured solid matrix. The different fatty acids such as glycerides can be used to improve and modify the structure. The drug molecules lodges extra disorderly crystal as molecular form and amorphous clusters. To avoid this adding to a minor quantity of liquid lipid additional leans to increases the drug-loading [134]. Type II NLC`s are oil-in-lipid-in-water type they also called as multiple type. In type II NLC's, the solubility of oil is greater as compare to solubility of solid lipids. In type II NLC's high amount of oil are mixed with solid lipids. This kind of formulation permit controlled drug release and leakage of drug from lipid matrix [133, 135]. The III type of NLS's also called as amorphous type. In this technique of prepration of NLC's, the lipids are mixed in such a way that crystallizing can be prevented through mixing procedure. In type III lipid is in an amorphous state. The technique and method of crystallization often leads to drug expulsion [133, 136]. Pathak A. A. et. al., prepared nanostructured lipid carrier by using aceclofenac by modified hot sonication method. Gratieri T., et. al., explored the potential of treating oncomycosis by using voriconazole loaded nanostructured lipid carriers. Cirri M., et. al., explored a new delivery system based on drug cyclodextrin complexation and loading into nanostructured lipid carriers has been developed to improve ketoprofen therapeutic efficacy. The proposed strategy exploits both the solubilizing and stabilizing properties of cyclodextrins and the prolonged release, high tolerability and percutaneous absorption enhancer properties of NLC.

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