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Delivery System Design in Topically Applied Formulations

Nisha Mary Joseph*, Senait Shimelis

School of Pharmacy, Addis Ababa University, Addis Ababa, Ethiopia

ABSTRACT

The skin provides a natural physical barrier against particle penetration. Delivery systems design can be used to overcome these barrier properties of the skin. One long-standing approach for improving topical drug delivery uses penetration enhancers which, penetrate into skin to reversibly decrease the barrier resistance. This review focuses on skin penetration pathways, different types of penetration enhancer and the technology for topical drug delivery as well as the probable mechanisms of action.

Keywords: Topical drug delivery, penetration enhancers

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***Address for Correspondence:**

Nisha Mary Joseph, Associate Professor, Department of Pharmaceutics & Social Pharmacy, Addis Ababa University, Addis Ababa, Ethiopia

INTRODUCTION

Topical drug delivery is the administration of a therapeutic agent through intact skin for local and systemic effect. Human Skin serves as one of the most easily accessible routes of drug administration. However, the presence of stratum corneum (SC) on the surface makes it selective towards applied drugs or delivery systems. Although, SC has been regarded as the major barrier to penetration of substances into and through the skin (Paramjit, et al., 2000). To move, molecules through the barrier drugs have to overcome a different resistance in each tissue. Transport across the skin membrane is obviously a complex phenomenon, challenging in analysis .To relate results on different penetrants, it is necessary to consider the transfer mechanism across skin. Therefore designing of topical formulation require specific delivery systems like vesicular systems, are the most controversial methods for transdermal delivery of active substances (Ijeoma, et.al., 1998). This review focuses some delivery systems, uses of the more widely investigated physical and chemical penetration enhancers with their possible mechanisms of action. This review also gives an overview of design of suitable delivery system for topical drug delivery.

PHYSIOLOGY AND ANATOMY OF THE SKIN

Skin consists of two main layers. The underlying dermis contains a variety of cell types, nerves, blood vessels and lymphatics embedded in a dense network of connective tissue. Above the dermis and separated from it by the basement membrane, the epidermis is composed mostly of layers of stratified keratinocytes, where the SC cells or corneocytes are bathed in a protein rich envelope with an outer lipid envelope, surrounded by an extracellular lipid matrix (Monteiro., 2010). The skin can also be considered to have four distinct layers of tissue. These are:

a. Non-viable epidermis (sc)

b Viable epidermis

c. Viable dermis

d. Subcutaneous connective tissue (hypodermis)

NON-VIABLE EPIDERMIS (SC)

Sc is the outer most layer of the skin, which is the actual physical barrier to most substance that comes in contact with the skin. It composed of dead keratin filled cells known as corneocytes with a matrix of intercellular lipids (5-15%), protein (75-85%) which is mainly keratin & water with 10 to 20 m flat cell layer thick over most of the body(Inayat and Mallikarjuna ,2009).

VIABLE EPIDERMIS

The structures of the cells in the viable epidermis are physico chemically similar to other living tissues. 90% of it is water which is resides between the sc and the dermis and has a thickness ranging from 50- 100 µm. The density of this region is not much different than water.

VIABLE DERMIS

Just beneath the viable epidermis is the dermis. The dermis layer is hydrophilic, loose connective tissue composed of fibrous protein embedded in an amphorphose ground substance. Dermis thickness ranges from 2000 to 3000μm.

SUBCUTANEOUS CONNECTIVE TISSUE

The subcutaneous tissue or hypodermis is not actually considered a true part of the structured connective tissue .It is white, fibrous connective tissue containing blood and lymph vessels, secretory pores of the sweat gland and cutaneous nerves (Inayat and Mallikarjuna, 2009)

THE PERMEATION BARRIER

Skin as a Barrier

One of the primary roles of the skin is to act as an effective and selective barrier to protect humans from chemical exposures (Scheuplein and Blank,1971), (Barr, 2007). In particular, the outermost layer of the epidermis, the sc, provides a formidable barrier to dermal absorption that determines the rate of dermal penetration. A number of other factors influence the permeation of chemicals through skin, including: lipophilicity, area of contact (site and size), duration of exposure, molecular weight, concentration, integrity of the sc layer, thickness of the epidermis and the mixture in which it is presented (Monte, 2007)

The Hydrophilic Properties of the Skin

Hydrophilicity of the skin increase as the depth increases from the surface, such that the viable epidermis represented by the stratum granulosum, the stratum spinosum and the stratum basale, respectively is significantly hydrophilic (Forster, et.al, 2009). The dermis layer is also hydrophilic, hence favoring the uptake of hydrophilic chemicals. Active transport and facilitated transport processes are absent from the sc. This is because the corneocytes are a nucleated and keratinized and cannot produce the specialized protein structures needed for active or facilitated transport. So, it is commonly assumed that the mechanism of transport through the sc is by diffusion (Scheuplein and Blank, 1971).

The Polarity of the Solute

It is also considered a major determinant of the partitioning pattern observed in the sc. If the solute is highly non-polar, the rate of partitioning between the sc and the viable skin can be a rate limiting factor due to the more polar nature of the deeper layers of the skin (Guy and Hadgraft, 1988). Although the sc lipid matrix is the most common route of dermal absorption for many chemicals, other routes such as hair follicles and sweat glands may also play a role but are considered to be negligible.

Potential Dermal Interaction Sites

The fate of chemicals exposed to the skin includes evaporation from the skin surface, partitioning into the sc followed by reversible or irreversible binding, penetration into the sc followed by metabolism or penetration to the dermis, and absorption into the systemic circulation or binding to tissues (Riviere, 2006).

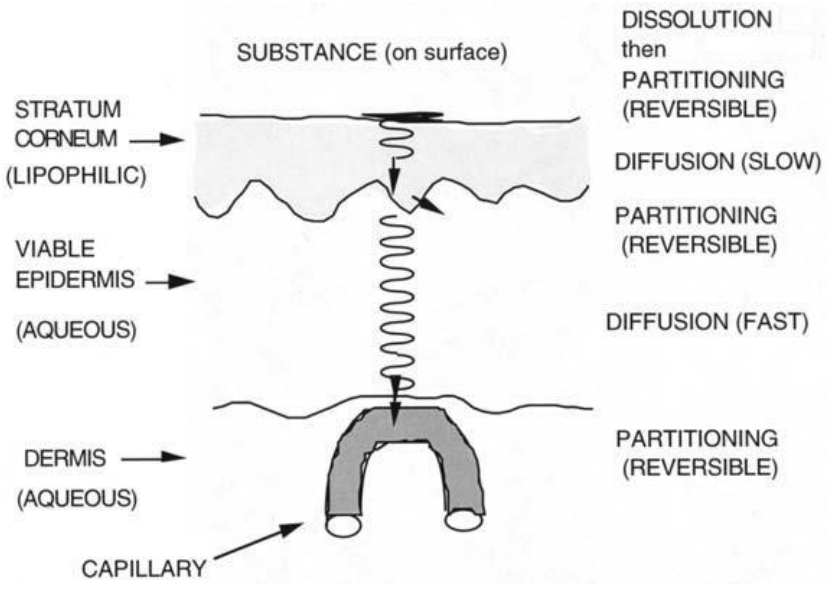


Figure.1 Different barriers for drug penetration

Fig.1 shows different barriers for drug penetration. During exposure there is a complex interaction between the drug and chemical, the vehicle and the skin, all which may affect the partitioning into and diffusion through the skin barrier. These interactions may occur simultaneously and may be classified according to the physical location of the occurrence surface of the skin, sc, epidermis and dermis (Katz, 1973).

Surface of the Skin

The most widely studied area of chemical–chemical interactions is on the surface of the skin. Factors such as altered solubility, precipitation, supersaturation, solvation, volatility and physicochemical effects such as altered surface tension from the presence of surfactants, changed solution viscosity and micelle formation, all contribute to increasing the potential of interaction (Barry, 2001).

Stratum Corneum (SC)

The SC represents the main physical barrier of the skin, so that for a substance permeating across the skin, diffusion through the SC is the rate limiting step. Conversely, the SC is also the main barrier for diffusion of water out of the skin. Interactions between the component like organic vehicles and chemicals and the constituents of the sc alter the

permeability of the chemical within the intercellular lipids of the sc (Rastogi and Singh, 2001).

Epidermis

One obvious point of potential interaction in the epidermis is when a chemical undergoes biotransformation. Induction or inhibition of drug metabolizing enzymes or competitive or noncompetitive inhibition for occupancy at the enzyme's active site may occur with mixture components. Other structural and functional enzymes may be affected (e.g. lipid synthesis enzymes) which could modify the barrier function (Elias, and Feingold, 1992).

Dermis

The dermis is the next level for potential interaction. Here, a component chemical may directly or indirectly (e.g. via cytokine release in the epidermis and dermis) modulate vascular uptake of the penetrate (Williams and Riviere,1993) which could also affect the depth and extent of chemical penetration into underlying tissues.

Inter-Cellular Spacing

For most penetrates the intercellular route is favored. Small molecules are able to move freely within the intercellular spaces and diffusion rates are governed largely by their lipophilicity (Watson, et.al2007).

Tight Junctions

The existence of functional tight junctions has been demonstrated in mammalian stratum granulosum. Although many constituent tight junction proteins have been identified in other epithelial layers, as well as follicles (Brandner et al.,2003). Tight junctions are regarded as important elements of the epidermal barrier system and localization and expression of tight junction proteins have been shown to be altered in diseases characterized by a compromised skin barrier. (Kirschner, et.al, 2009).

ADVANTAGES OF TOPICAL DRUG DELIVERY

Topical drug delivery offers the following advantages over the oral route.

- Avoidance of hepatic first pass metabolism.
- Ability to discontinue administration by removal of the system.
- The ability to control drug delivery for a longer time than the usual gastrointestinal transit of oral dosage form.
- The ability to modify the properties of the biological barrier to absorption.

FACTORS THAT INFLUENCE THE PENETRATION OF THE SKIN

The factors that influence the penetration of the skin barrier can be divided into physiological and physicochemical variables. Additional variables are the condition of the skin, the skin age, the area of skin treated, the thickness of the skin barrier phase, the species variation, and the skin moisture content. Skin Condition-"Intactness" of the skin is one of the most important factors preventing penetration. Injurious agents such as mustard gas, acids, and alkalis injure barrier cells and increase permeability. When the sc is damaged, diffusive water loss is increased. Complete removal of the barrier by stripping enhances the absorption of almost any substance in contact with the skin surface. These physical and structural differences obviously affect the penetration pathways and the penetration resistance of skin (Marzulli, et.al.,1969).

ROUTES FOR SKIN PENETRATION

The potential interaction between the delivery system, the "formula," and the skin are all of major importance Potential routes for skin penetration and the active's fate upon application should all be taken into account throughout formulation development (Nava D.2005). The success of a dermatological drug to be used for systemic drug delivery depends on the ability of the drug to penetrate through skin in sufficient quantities to achieve the desired therapeutic effect. There are potentially three distinct routes of penetration through the sc, these are intra cellular path way, intra follicular pathway and polar path way (Malkinson and Rothman, 1961).

SKIN PENETRATION PATH WAYS

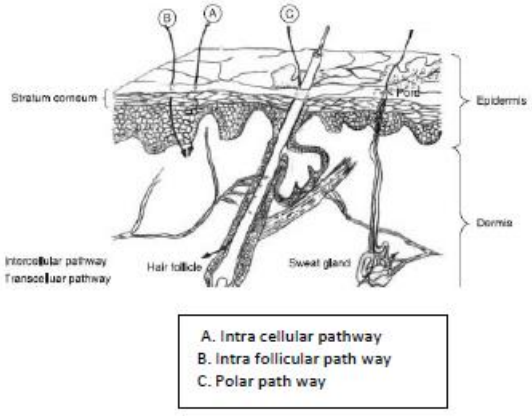


Figure 2.the three main skin penetration path ways

Intercellular Pathway

This pathway occurs between the corneocytes, and through the intercellular lipids. It covers 5%–30% of the total volume of the stratumcorneum and provides the permeability barrier for most molecules. Water has been found to penetrate the skin via the intercellular pathway (Nava, 2005).

The Intrafollicular Pathway

This pathway occurs via penetration through hair follicles. Although the available area for diffusion in this pathway is approximately 0.1% of the total skin area it is mainly a route for very lipophilic molecules and molecules used in combination with certain surfactants and glycols as penetration Enhancers.

The Polar Pathway

This route is believed to be hydrophilic in nature. It is composed of aqueous regions surrounded by polar lipids that create the walls of micro channels. It is known to have a high penetration resistance to lipophilic compounds but low resistance to hydrophilic compounds. It is also thought to be the route by which water evaporates through the skin (Daya, 2005).

SKIN PENETRATION ENHANCER

The goal of dermal penetration enhancement is for the accelerant to reversibly reduce the barrier resistance of the sc without damaging viable cells (Finnin and morgan, 1999).The method employed for modifying the barrier properties of the sc to enhance drug penetration and absorption through skin may be classified into four these are

chemical, physical, vesicular carrier and Enzymatic penetration enhancers. Here only the first three penetration enhancers are discussed.

Ideal characteristics of penetration enhancers

- They should be non toxic, non irritating and non allergenic.
- They would ideally work rapidly; the activity and duration of effect should be both predictable and reproducible.
- They should have no pharmacological activity within the body.
- The penetration enhancers should work unidirectionally, i.e., they should allow therapeutic agents into the body whilst preventing the loss of endogenous materials from the body.
- When removed from the skin, barrier properties should return both rapidly and fully to normal.
- They should be cosmetically acceptable with an appropriate skin feel **(**Pathan and Mallikarjuna, 2009).

CHEMICAL ENHANCER

Chemical substances temporarily diminishing the barrier of the skin and known as accelerants or sorption promoters can enhance drug flux. These include materials such as azone, urea, fatty acids, Dimethylsulphoxide, and Oxazolidinones.

Azone

The figure below shows structure of Azone (1-dodecylazacycloheptan-2-one or laurocapran) which is the first penetration enhancer. It was the first molecule specifically designed as a skin penetration enhancer.

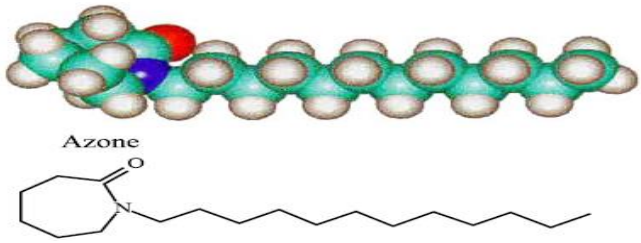


Figure 3.Azone, the first molecules synthesized to act as a skin penetration enhancer

Azone is a colourless, odourless liquid with a melting point of -7 ºC. Azone is a highly lipophilic material and it is soluble in and compatible with most organic solvents including alcohol and propylene glycol. Azone enhances the skin transport of a wide variety of drugs including steroids, antibiotics and antiviral agents. Azone is most effective at low concentrations, being employed typically between 0.1- 5% but more often between 1- 3% 13. Azone partitions into a bilayer lipid to disrupt their packing arrangement but integration into the lipid is unlikely to be homogeneous (Adrian, and Brian, 2004)

Urea

Urea promotes transdermal permeation by facilitating hydration of the sc and by the formation of hydrophilic diffusion channels within the barrier. Cyclic urea permeation enhancers are biodegradable and nontoxic molecules consisting of a polar parent moiety and a long chain alkyl ester group. As a result, enhancement mechanism may be a consequence of both hydrophilic activity and lipid disruption mechanism (Singh, and Choudhury, 2007).

Fatty Acids

Percutaneous drug absorption has been increased by a wide variety of long chain fatty acids, the most popular of which is oleic acid. Oleic acid greatly increased the flux of many drugs such as increasing the flux of salicylic acid 28 fold and 5-flurouracil flux 56 fold through human skin membrane. The enhancer interacts with and modifies the lipid domains of the SC as would be expected for a long chain fatty acid with cis configuration (William and Barry, 2004).

Dimethylsulphoxide

Dimethylsulphoxide (DMSO) is colourless, odourless, hygroscopic penetration enhancers. It is a powerful aprotic solvent which hydrogen bonds with itself rather than with water; and is often used in many areas of pharmaceutical sciences as a "universal solvent". DMSO is used as a co-solvent in a vehicle for a commercial preparation. DMSO alone has also been applied topically to treat systemic inflammation. The penetration enhancing activities of DMSO is by promoting both hydrophilic and lipophilic permeants and is concentration dependent .generally co-solvents containing >60% DMSO are needed for optimum enhancement efficacy. However, at these relatively high concentrations DMSO can cause erythema and may cause some proteins denature. (Kligman, 1965).

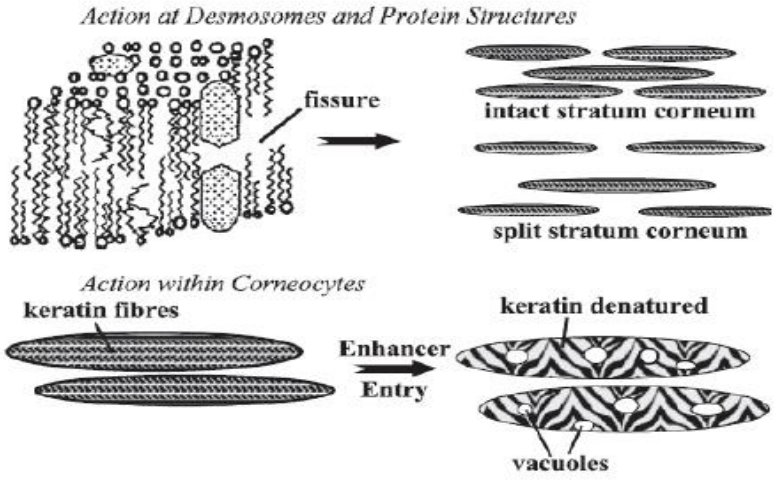


Figure 4.Dramatic action of enhancers on the integrity of SC. This Figure shows the action of enhancers and how it alters the sc integrity.

Oxazolidinones

Oxazolidinones are a new class of chemical agents which have the potential for use in many cosmetic and personal care product formulations. This is due to their ability to localize co administered drug in skin layers, resulting in low systemic permeation (Seth B.1999). Oxazolidinones such as 4-decyloxazolidin-2-one has been reported to localize the delivery of many active ingredients such as retinoic acid and diclofenac sodium in skin layers. This compound has a higher molecular weight and lipophilicity than other solvent type enhancers, physical characteristics that may be beneficial in terms of a reduction in local toxicity because of the lack of effective absorption of these enhancers into the lower skin layers where irritation is likely to be occurring. (Inayat and Mallikarjuna, 2009).

PHYSICAL ENHANCER

Although many different physical approaches to enhancing percutaneous absorption have been attempted, the most notable approaches are Microneedles, sonophoresis (ultrasound), Iontophoresis & Electroporation. None of these enhancement methods is passive in that they require the input of energy to achieve their effects. To date, these methods show most promise for TDD systems that incorporate a large drug reservoir on the surface of the skin (Guy,1996).

Microneedles

Standardized micro dimensional needles that are robust enough to create pores that reach throughout the entire depth of the Sc. Such pores have been observed to facilitate the rapid absorption of drugs including even those with large molecular weights.

First Generation Microneedles

First generation devices were from non-hollow Silicon. These micro needles are coated on the outside by the drug or active agent. Use of this technology has been shown to increase the permeation of calciene (623 Da) by 1,000-fold when the micro needles were left embedded in the skin for one second, 10,000-fold when removed from the skin after being embedded for ten seconds, and 25,000-fold when the micro needles were removed from the skin after one hour application. Application of these micro needles permitted an increase in the permeation of both insulin (5,800 Da) and bovine serum albumin (64,000 Da) by more than 10,000-fold above the sensitivity limit. (Mcallister, et.al., 1999)

Second Generation Microneedles

Second generation micro needles are constructed from hollow metal or silicon and are filled with drug solution. Use of this technology can raise the in vitro permeability of calciene, insulin, and bovine serum albumin through human skin by more than 100,000 fold above the sensitivity limit. Crucially, with this method, creating microscopic pores in the skin is not observed to produce any pain. (Michniak, 2005)

Sonophoresis

Sonophoresis is the use of ultrasound to enhance topical or TDD. The technique has been applied for over 40 years by physiotherapists in order to treat various arthritic and inflammatory conditions. Typically, ultrasound in the 0.5 to 3 MHz frequency range has been employed for this purpose. Very low frequency of ultrasound (i.e., in the 0.02 to 0.1 MHz range) can substantially, and reversibly, increase the permeability of the Sc. (Terahara, et al.,2002). This enhancement process is a result of the development of cavitations, which is the major mechanism of skin permeabilization. The cavitations phenomenon is inversely related to the frequency of the applied ultrasonic beam (Gaertner and Acoust, 1954). Cavitations is the ultrasonically induced formation of gaseous cavities. The volumetric oscillations and collapse of cavitations bubbles generate sufficient disorder in the lipid bilayers of the Sc to temporarily permeabilize the membrane. The host of parameters including the frequency, intensity, and time of application of the applied ultrasonic beam are determine the extent of cavitations produced (Gaertner and Acoust, 1954).Low frequency sonophoresis has been reported to facilitate the TDD of proteins like insulin, erythropoietin, and gamma interferon in vitro.(Mitragotri et al., 1995)Advantage of sonophoresis is that the skin barrier function is returned to normal levels only several hours after sonication is completed

Iontophoresis

This technique is based on the principle that application of electric current provides external energy to drug ions for passage across the skin, thereby increasing drug permeability through the membrane.10A typical iontophoretic drug delivery system consists of an anode, a cathode and two reservoirs, The movement of ions in Iontophoresis follows the basic rule of electricity, i.e. like charges repel each other (Priya B.et al 2007). Iontophoretic drug delivery occurs by a combination of concentration gradient and electrochemical potential gradient developed across the skin; increased skin permeability under applied electric current and a current induced water transport effect. There is an inverse relationship between the molecular weight of the permeating molecule and its iontophoretic flux. The delivery rate of a divalent cation was half that of the monovalent species. This is attributed to the stronger binding of the divalent ion with the fixed negative charges in the skin. (Del Terzo, et al.,1989). The Nernst-Planck flux, equation mathematically describes iontophoresis. The equation indicates that the flux of an ion across a membrane under the influence of an electric field is modulated by three components: a diffusive component, an iontophoretic component, and an electro-osmotic component. The equation is symbolically written as (Michniak, et.al., 2005)

$$J = Cu - D\left(\frac{dC}{dx}\right) + D\frac{zEFC}{kT} \qquad \text{Eq.1}$$

Where:

J = molar flux
C = molar concentration
u = convective water flow
D = diffusivity coefficient
dC/dx = molar concentration gradient in the direction of the low
z = ionic valence
E = electric field
F = Faraday's constant
k = Boltzmann constant
T = temperature (Kelvin)

According to eq.1, the efficiency of drug transport depends upon the polarity, valency, and mobility of the charged species, as well as upon the electrical duty cycle and formulation components selected (Michniak, et.al., 2005).

Electroporation

Electroporation is the process of applying electrical field to a living cell for only microsecond or millisecond, approximately 100–1000 V/cm. This electrical field causes a transient reversible breakdown of the cellular membrane. This results in the formation of pores which allow delivery of drug to the cell. Electroporation occurs when an applied external field exceeds the capacity of the cell membrane. It is proposed that water enters the cell membrane during the dielectric break down and that transient hydrophilic pores are formed. When such defects form, both low and high molecular weight compounds can be made to rapidly permeate through the skin. The formation of permeable areas happens in the frame in less than a second whereas resealing happens over minutes. The pores created by electroporation can also serve as additional transport pathways during Iontophoresis (William, et.al., 2004).

Anionic lipids have been shown to greatly enhance the permeation of both small and large molecules .Under electroporation conditions. This effect was both charge and size dependent. Transport enhancement for molecules smaller than 1,000 Da occurred irrespective of their net charge, while in the case of large molecules (4,000–10,000 Da) enhancement was observed only for negatively charged ions. (Bozena, 2005)

Effects of Skin Hydration

Hydration of the sc is among the most important factors in skin penetration, increasing the rate of passage of all substances that penetrate the skin. Hydration results from water diffusing from underlying epidermal layers or from perspiration accumulating after application of an occlusive vehicle or covering on the surface. Under occlusive conditions, the sc is changed from a tissue that normally contains very little water (5-15%) to one that may contain as much as 50% water. Permeability increases four to five fold. (Kligman, 2000).Hydration apparently "opens" the compact substance of the sc. (Krame and Wurster,1961) measured the rate of penetration of esters of salicylic acid through skin with dry and hydrated sc. When the tissue was hydrated, the rate of penetration of the most water soluble ester increased more than that of the other esters studied. Further evidence of the importance of hydration can be found in investigations employing occlusive plastic films in steroid therapy. Here the prevention of water loss from the sc and the subsequent increased water concentration in this skin layer apparently enhance the penetration of the steroid (Smith 1962).

Super Saturation of Drug

Drug delivery can be optimized by using saturated solutions or suspensions of drugs. Supersaturated systems have been prepared by three techniques heating and cooling, use of cosolvent mixtures in which the drug has a very low solubility in one component. (William, et.al., 2004). and solvent evaporation methods employing a range of volatile and nonvolatile solvent mixtures. Unfortunately, supersaturated formulations commonly exhibit instability and both drugs and salts may precipitate out during manufacturing, storage or application. Stability of such supersaturated systems can be promoted by incorporating polymers that act as antinucleant crystal growth inhibitors such as hydroxpropyl methylcellulose (HPMC) and methyl-cellulose (MC).By adjusting concentrations of the antinucleant crystal growth inhibitors and supersaturation levels, can modulate the crystallization process and enhance topical delivery (Raghavan, et al., 2000).

Improvement of Therapeutic Index

The therapeutic index is a parameter that indicates the relative efficacy of a compound to its relative toxicity at various concentrations. It is calculated by dividing the toxic dose by the therapeutic dose .This parameter is an important measure of the relative safety of an active being used for a particular treatment. The use of the Therapeutic Index is well known in pharmaceutical practice and is growing for the evaluation of active compounds used in cosmetics. (i.e."Cosmeceuticals"). Examples of such compounds include: alpha hydroxy acids, ceramides, and hyaluronic acid. (Fesq, et al., 2003). The release rate of an active compound from a delivery system can affect the skin's reaction to the compound. It can be generally stated that sustained release is recommended for actives that tend to irritate the skin, are applied at significantly high doses, or demonstrate rapid skin penetration. By extending the exposure time and reducing the amount released per unit of time, not only is effectiveness increased, but the reduced release rate allows the skin periods that enable it to adjust and, there by improve its ability to tolerate the new conditions**.** **(**Nguyen, 2003).

DESIGN OF DELIVERY SYSTEM

DELIVERY SYSTEM

A delivery system is simply a way of holding, carrying, and transporting an active to a substrate. A delivery system can control the rate of release from a formulation as well as the rate of active absorption. It can minimize the concentration of active in the epidermis and dermis and there by minimize the potential for irritation. It can also maximize the concentration of active in a part of the substrate a concept known as the "Reservoir" effect delivery system is any type of vehicle that makes an "active" available to a target site. An effective delivery system is one that reaches the target and creates a high concentration reservoir for the active. Delivery systems may provide sustained release, controlled release, or release, without release into the substrate (Kasting, et.al.1987)

They concentrate the payload. The bulk concentration is low but the concentrated material is delivered to the intended site. Delivery systems can be liquid/liquid systems such as oil-in-water or water-in-oil emulsions, micro emulsions, or multiple emulsions. Some delivery systems allow the incorporation of oil soluble actives in water based formulations while others enable the incorporation of water soluble actives in oil-based systems .Other forms of delivery systems include liquid/solid systems such as dispersions of inorganic materials like zinc oxide and titanium dioxide for sun screens. They can also be solid/solid systems such as freeze-dried Liposomes, or be actives encapsulated in molecular or macromolecular matrices to provide a dry powder form **(**Nguyen, 2003).

IDEAL CHARACTERISTICS OF DELIVERY SYSTEM

The ideal delivery system would be non toxic to skin or hair, It would carry the actives into the substrate, provide controlled release (if desired), penetrate deeply or superficially (as needed), should be small enough to penetrate and be similar in polarity to target permeation paths of the skin (Meye, 2005).

DELIVERY SYSTEM FACTORS

Delivery System Factors clearly, transdermal absorption of actives into the sc is a complex process and the design of transdermal formulations remains highly challenging. Such systems must not only maintain the stability of the active drug, but also insure that it will be released at a sufficient quantity and rate into the target tissue. Therapeutic moieties have to travel through the barriers and deliver into the systemic (Chapman, et al.,2002). Not all drugs are suitable for topical delivery. The low permeability of the skin limits the choice of candidates to those of high potency (usually <10 mg/day) and low molecular weight. Other considerations such as skin metabolism and the involvement of the immune system further limit the available drug choices.

The permeability of a drug through the skin depends not only on the properties of the therapeutic moiety itself but upon various formulation factors. Examples of these include compatibility and irritancy or factors related to skin metabolism as well as inter-site, or inter-subject variability in skin permeability. The penetration of the active agent also depends upon the type of delivery system (Schmidt, 1989).

Molecular Weight of the Drug Molecule

Due to the presence of rigid corneocytes and intercellular lipids in the sc, the diffusion process is complicated. Molecular permeation through this structure can be described by the free volume theory where diffusion occurs by the dynamic exchange of molecules within free volume regions contained within the membrane (Lieb and Stein, 1986) The equation describing this behavior can be expressed as the following eq.

$$\text{Eq.2. } D = D0 \exp(-\beta MV)$$

Where, β is a constant and D0 is the diffusivity of a hypothetical molecule exhibiting zero molecular volume. This exponential dependence of solute diffusivity on molecular volume has a great impact in terms of the predictability of mathematical models in describing skin permeation (Kasting, et.al.,1987).As a rule of thumb, the maximum cutaneous flux of a permeant decreases by a factor of five for every 100 Da increase in molecular weight. Furthermore, it has been observed that molecules exhibiting a molecular weight greater than 500 Da will generally not absorb through the skin. However, novel approaches to transdermal drug delivery such as the electrically assisted technologies have upwardly shifted the 500 Da limit towards a cut off in the 5,000 to 10,000 Da range (Berner and Cooper, 1987).

Lipophilicity of the Active Molecule

The Lipophilic nature of the sc and the aqueous nature of the underlying tissue indicate that the diffusant has to possess an optimal balance between lipophilic and hydrophilic properties. Generally, the skin is most permeable to moderately lipophilic compounds. Molecules that are more lipophilic will tend to become entrapped within the sc and not partition into the viable epidermis. Hence, quantitative structure permeability equations used to describe passive diffusion controlled penetration incorporate molecular weight (or molecular volume) and lipophilicity as the main determinants of transdermal absorption (Moser K, 2001).

Effect of the Delivery System on Permeation

The delivery system contains not only the active drug but also contains other formulation components such as penetration enhancers, stabilizers, and preservatives. All of these functional molecules are necessary for achieving successful drug or active delivery. The physical form of the delivery system/carrier/vehicle is crucial to the absorption process. These systems range from very small nano size particles or dispersions to emulsions of both the o/w type and w/o type, as well as lipid lamellar gels and the many other variations. The first step in transdermal absorption is the release and partitioning of the active agent from the delivery system into the sc. (Michniak, et.al.,2005).

A process governed by the drug or active's partition coefficient. A vehicle should be carefully selected so that it has a high active-holding capacity but, at the same time; it does not suppress transport from the vehicle into the sc. The thermodynamic activities of the active molecule will continuously change in a volatile vehicle that undergoes evaporation. Moreover, the vehicle may itself absorb into the skin, and there can be variations in the degree of absorption depending upon which part of the body is involved. If the drug or active has a high affinity for the vehicle, it will be carried along as the solvent in the vehicle permeates into the tissue (Moser K, 2001). An absorbed vehicle may also change the partitioning of the drug or active from the formulation into the skin. Additionally, occlusive vehicles can hydrate the skin thus enhancing its permeability to a hydrophilic drug or active. Many studies have documented a synergistic effect exerted by some vehicles on the activity of penetration enhancers. Examples of this type of interaction include Azone-propylene glycol and fatty acids-propylene glycol (Venkatesan, et al 2009).

RATIONALE REQUIRED FOR THE DEVELOPMENT OF A DELIVERY SYSTEM

The fundamental reasons for the development of a delivery system are to improve penetration of actives and increase its stability. Table 1 shows the rationale involved in the development of a delivery system and based upon this there are some examples of delivery system designed for topical delivery of drugs.

Rationale for Delivery System	Example
Improve stability	Protection from light/air, prolongation of shelf life, sensitivity to elevated temperature
Modulation of skin penetration properties	Controlled, sustained, or delayed release of active
Protection from component interactions	Prevent contact of incompatible ingredients in the formulation
Change of form	To resolve solubility/incorporation/application limitations. For example, incorporation of oil into a powder to allow the creation of powdered formulation.
Improve skin tolerance	To expand therapeutic index, improve efficacy, and improve safety
Improved esthetics	Consumer appeal
Mask undesirable properties	Change color or eliminate undesired odor

Table1. Rationale Required for the Development of a Delivery System

EXAMPLES OF DELIVERY SYSTEMS

MICROENCAPSULE

Microcapsules are produced by microencapsulation technique. Microencapsulation is the coating of small solid particles, liquid droplets or gas bubbles with a thin film of coating or shell material **(** John and Sons 2005) with the purpose to enable controlled release of the encapsulated material.In microcapsule applications where mechanical rupture is the controlled release mechanism .Topical preparation are encapsulated to reduce volatility and sustained release. There are three possible capsules structures Parameters used to characterize microcapsules include particle size, size distribution, geometry, actives content, storage stability, and core material release rate(John W. 2005). Figure 5 shows the different possible capsules based upon the core and coating material employed

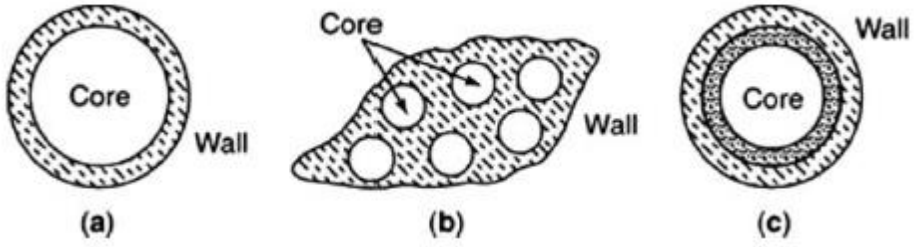


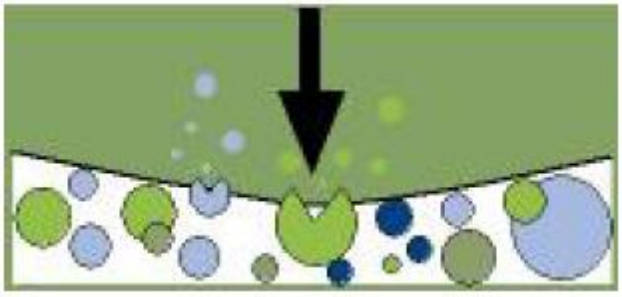
Figure5. Schematic diagrams of several possible capsules (a)continuous core/shell microcapsule(b)multi nuclear microcapsules(C) continuous core capsule with two different shells

Microcapsule Release Mechanisms

A variety of release mechanisms have been proposed for microcapsules. The structure and components of the capsule wall determine the release mechanism of the encapsulated active compound. There are four typical mechanisms by which the core material is released from a microcapsule these are mechanical rupture of the wall, melting of the wall, dissolution of the wall and diffusion through the wall (Venkatesan P.et.al.2009)

Mechanical Rupture

In microcapsule applications, mechanical rupture is the controlled release mechanism. Release of the core material is either by applying direct pressure or abrasion during the application of the formulation to the skin. Rupture strength is inversely proportional to the size of the capsule. Figure 6.shows that a compressive force breaks open the capsule by mechanical means.



The wall is dissolved away from around the core such as when a liquid flavoring oil is used in a dry powdered beverage mix. The wall melts away from the core releasing the core in an environment such as that occurring during baking.The core diffuses through the wall at a slow rate due to the influence of an exterior fluid such as water or by an elevated temperature (Schugens, 1994)

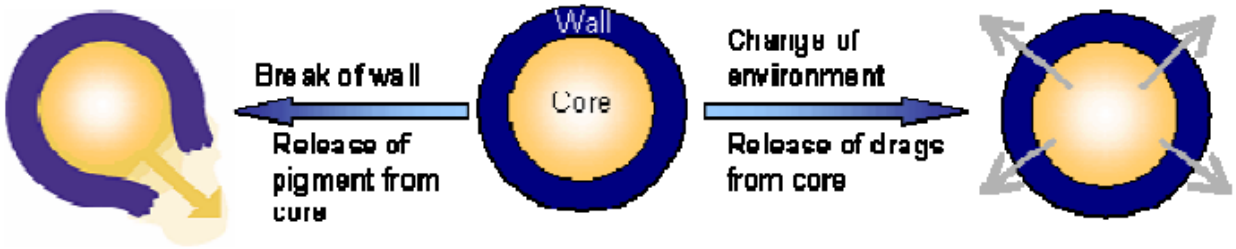


Figure 7.Release mechanism

Controlled Release

The controlled release of material from capsules is deliver the drug in controlled manner .The capsules serve as vehicles to deliver beneficial agents . In the controlled release system, biodegradable microcapsules are one of the most useful devices to deliver materials in an effective, prolonged and safe manner (Fassihit, et.al., 2004).Drugs which formulated in controlled release dosage forms in polymeric devices are released either by diffusion through the polymer barrier, or by erosion of the polymer material, or by a combination of both diffusion and erosion mechanisms (William, et.al.2006).

Encapsulation by In Situ Polymerization

Different microencapsulation techniques have been used to control drug release form topical delivery systems (Rasool, et.al., 2003). In situ polymerization is one type of encapsulation techniques, it is a chemical formulation by supplying monomer from either inside or outside of the core material and polymerizing it on the surface of the core material (Schugens, 1994). This process is ideal for protecting hydrophobic materials and involves the deposition of a polymeric material at the solid/liquid interface. In situ polymerization is a process in which the capsule shell is formed by the polymerization of monomers added to the encapsulation reactor .In this process, polymerization occurs exclusively in the continuous phase and at the interface formed by the dispersed core material and the continuous phase. Polymerization of reactants located in the continuous phase produce a low molecular weight pre polymer. As this pre polymer grows in size, it deposits onto the surface of the dispersed core material. Continued polymerization, with cross-linking, continues to generate a solid capsule shell (Matsen, et.al.,1970).

VESICULAR

Vesicular systems are one of the most controversial methods for transdermal delivery of active substances.(Gupta, et.al., 2012) Depending upon their composition and physical properties, vesicles can either serve as a compound's carriers, skin permeation enhancers, or as a vehicle base which provides a reservoir. Such a reservoir can be created in the sc, epidermis, or even in the hair follicles and sebaceousglands (Verma, et.al. 2003)

LIPOSOME

Liposomes are microscopic vesicles composed of one or more lipid bilayers (Egbaria and Weiner, 1990).Which are used as carriers for drugs and delivers actives through the skin. Liposomes can direct a drug to a certain target. It can also prolong the duration of drug exposure, acting as a slow release reservoir Liposomes can protect a drug against degradation (for example metabolic degradation). Liposomes might be useful for increased local activity while diminishing the Percutaneous absorption of the drug. The mechanism by which liposomal vesicles deliver actives is not fully understood. It is believed that variations in vesicle properties can influence rate and degree of penetration and thereby produce a range of delivery profiles. (Kadir, et.al.,1999).

The applicability of liposomal hydrocortisone as a selective drug delivery system for cutaneous administration of glucocorticoids has been studied by Wohlrab and Lasch (Wohlrab, and Lasch, 1987). Topical application of a liposomal preparation of hydrocortisone resulted in higher concentrations of drug in the individual layers of human skin as compared to a similar application of hydrocortisone formulated as an ointment. (Liposomes can be loaded with different hydrophilic, lipophilic, or amphiphilic actives including vitamins (Egbaria and Weiner, 1990).

LIPOSOME GEL

Liposome gel are formed in the presence of intelligent polymers. It was expected that the stabilization approach of a single vesicle illustrated in (Fig. 8) could be modified into a polymer-mediated stabilization process in the presence hydrophobically modified water soluble polymers .In this case, where the length of the water-soluble part of the polymer (PEG as an example) exceeds the average distance between two vesicles (in a vesicle dispersion), a bridge is easily formed. The hydrophobic ends of the polymer (for example, stearic acid or cholesterol) have a strong tendency to insert into the bilayer membrane of the liposomes by a self organization process (Fig. 9).

In a way, the polymers are expected to behave intelligently because they build up a more complex nanoscale structure without the assistance of the formulator. This network is transient because the polymer end groups are able to leave the bilayer membrane. However, this is an unlikely process, because the hydrophobic end groups of the polymer tend to minimize their contact with water. Further, addition of such polymer molecules leads to a three-dimensional network of connected liposomes (Wolfgang and Jörg, 2005).

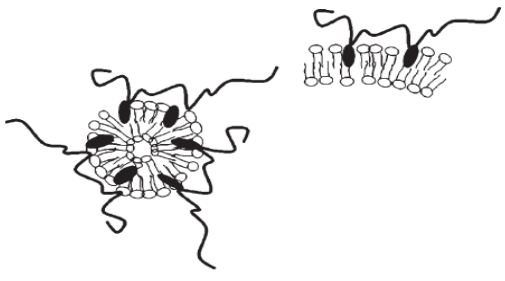


Figure 8. Stabilization of a single vesicle by a hydrophobically modified water soluble polymer.

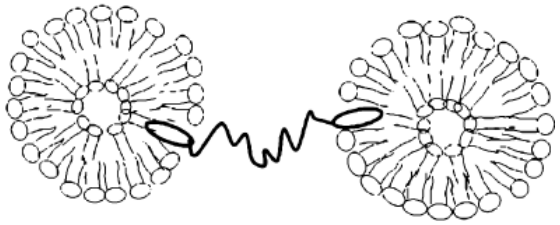


Figure 9.Crosslinkingof two liposomes by

A hydrophobically modified water soluble polymer

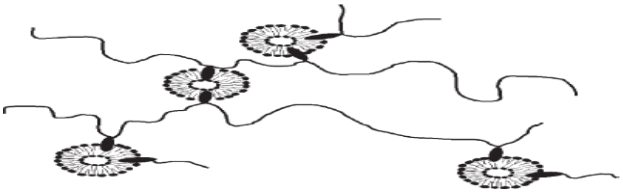


Figure 10.Gel formation by crosslinking of several liposomes with ahydrophobically modified water soluble polymer

Mezei et al. (Mezei, and Gulasekharam, 1982b) compared the deposition of topically applied gels of free and liposomally entrapped triamcinolone in rabbit skin. They found that application of the liposomal gel resulted in a concentration of triamcinolone acetonide approximately five times higher in the epidermis and three times higher in the dermis, than application of the free drug gel. The results of this study (Mezei, and Gulasekharam, 1980a) suggested to them the inherent potential of liposomes as a selective drug delivery system for cutaneous application.

ELASTIC VESICLES

Elastic vesicles have been designed to facilitate the delivery of active compounds to and through the skin. It enhances skin permeation by deformable "fluid" nature of the vesicles and it carries the active in to deeper layers of the skin. By this means, the lag time for penetration and the amount of active compound that penetrates is significantly decreased and increase respectively (Trotta, et.al.,2004).

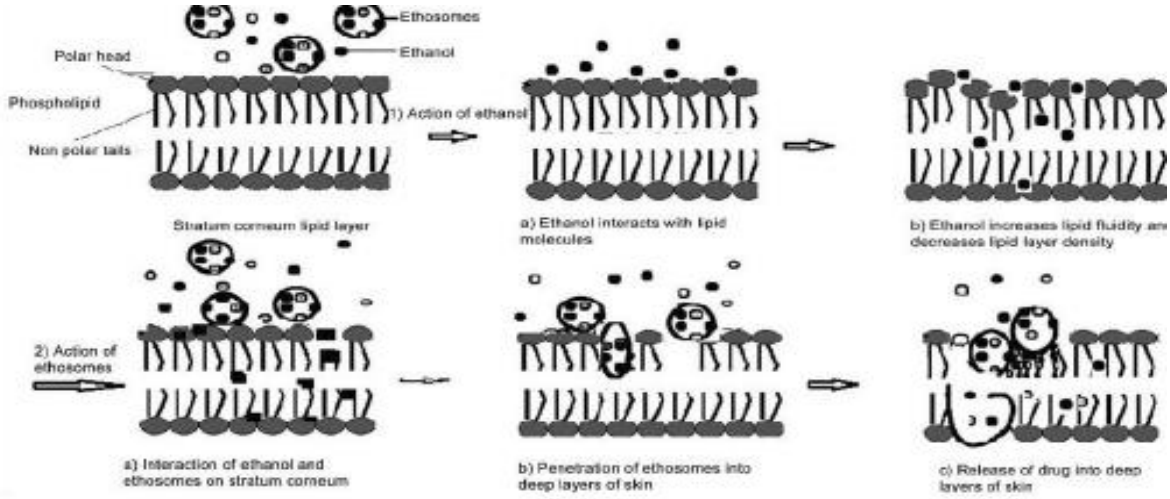
Examples of Elastic Vesicle

Ethosomes

Ethosomes are soft, lipid vesicles containing phospholipids, alcohol and water. It is novel carrier system used for delivery of drugs having low penetration through the biological membrane mainly skin. Ethosomes permeate through the skin layers more rapidly than liposome.

The mechanism of Ethosomes for better permeation is still not clear. But the synergistic effects of combination of phospholipids and ethanol in vesicular formulations have been suggested to be responsible for deeper distribution and penetration in the skin lipid bi-layers.

Ethanol acts as a penetration enhancer by increasing the fluidity of cell membrane lipids and decrease the density of lipid bilayer of cell membrane so the Ethosomes can permeate easily inside the deep skin layers and releases the drugs into deep layer of skin (Gupta, et. al.2012).



Firure11.Diagrammatical representation of mechanism of action of ethosomes.

PARTICULATE SYSTEMS

Particulate systems can be designed to specifically target follicular structures based on particle diameter and vehicle composition. The particulate delivery systems used in topical formulations include: Porous polymeric systems, Microparticulates, Nanoparticulates

Porous Polymeric Systems

Porous polymeric particles with high internal surface area like cellulose are used to entrap active compounds and serve as delivery systems. The active compound is released from the particle by means of simple diffusion (Lieb, 1992).The spheres can be programmed to release the entrapped active ingredient to the skin in a controlled time release pattern or a pre-programmed manner through the use of several different triggers such as rubbing or pressing the system after it has been applied to the skin, elevating the skin surface temperature, introducing solvents such as water, alcohol, perspiration for the entrapped material. Entrapment systems can control the release of actives onto the epidermis with assurance that the actives remain primarily localized and do not enter the systemic circulation in significant amounts, thus reducing toxicity while maintaining efficacy (Patravale and Mandawgade, 2008).`

Microparticulates

Micro particles are solid polymeric particles falling in the range of 0.1–1000 µm and include microcapsules and microspheres. Micro particles are used in cosmetics to avoid incompatibility of substance, reduce odour of actives and for protection of substances prone to oxidation or action by atmospheric moisture.

Porous Microparticles

Porous polymeric particles with high internal surface area are used to entrap active compounds and serve as delivery systems. These materials can be incorporated into gels, creams, liquids, or powders. They can be synthetic in origin, such as polyacrylates, polymethacrylates and polyamides. Since these porous particulates are "open" systems,the entrapped active compound is released from the particle by means of simple diffusion.Key physical properties of these particles include *(Schott,2000).*

- Particle density (g/cm3), mass per volume
- Total specific surface area of pores (m2/g)
- Average pore diameter (µm)
- Oil absorption capacity (ml/100g)
- Particle average size (nm or µm) and size distribution
- Zeta potential (mV)

Zeta potential can be a significant and useful tool for predicting and controlling the stability of colloidal suspensions or emulsions. When the absolute value of the zeta potential is above 50 mV, the dispersion has better likelihood of being stable due to mutual electrostatic repulsion of the particles.

When the zeta potential is close to zero, interparticle coagulation, the formation of large particle assemblies, can be rapid and cause sedimentation or creaming depending on the relative density of the particles and the external phase. Different external phase conditions can also affect the zeta potential. These include salt concentration, pH, and surfactant concentration (Lieb, 1992*).*

NANOPARTICULATE SYSTEMS

Nanoparticles for Topical Delivery Of Drugs

Nanoparticle defined as single particles with a diameter under 100 nm. Due to their small size, it can pass through biological barriers easily and serve as delivery systems for topical formulations. With potential nanoparticle distribution sites that include the surface of the skin and hair follicles *(*Prow, et.al.,1998). Nanoparticle also used as carriers for sun screens to prolong residence time in the sc, and to target vitamin A to the upper layers of skin. The particle size and composition of nanoparticle are influence the interactions between particle and skin and the rate and extent with which it releases an incorporated 'active' ingredient into the sc (Landfeste, et.al.,2010).

Poly (lactide-co-glycolide) has been used as a polymer for creation of matrix-type nanoparticles used to entrap the antiviral drugs cidofovir, and acyclovir. When applied to the skin and compared to polyvinyl alcohol solution, the particles significantly increased drug retention in the epidermis and decreased permeation through the skin (Blanco, 2002).

Figure 12, describes different Sites in skin for nanoparticle delivery. Topical nanoparticle drug delivery takes place in three major sites, these are sc, dermal-epidermal junction and blood vessels.

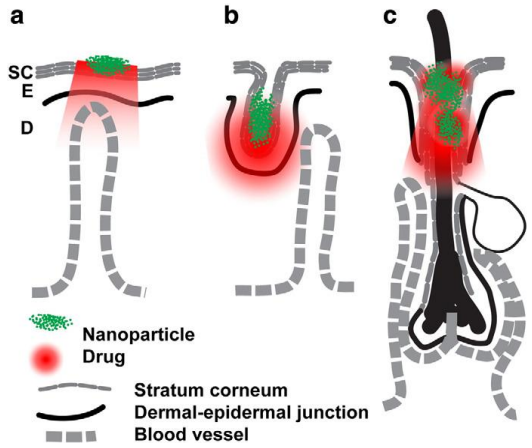


Fig.12.Stratum corneum (SC) surface (panel a), furrows (dermatoglyphs) (panel b), and openings of hair follicles (infundibulum) (c). The nanoparticles are shown in green and the drug in red. Other sites for delivery are the viable epidermis (E) and dermis (D).

SOLID LIPID NANOPARTICLES AND NANO-STRUCTURED LIPID CARRIERS

Solid lipid nanoparticles and nanostructured lipid carriers are novel drug delivery complexes with many cosmetic and dermatological applications.Their attributes include, increased absorption, enhanced penetration and control release properties. The sc of the skin prevents the penetration of hydrophilic compounds more efficiently than of lipophilic ones, thus lipid based carriers may be used to transport hydrophilic drugs (Moser, 2001).

A multitude of cosmetic ingredients have been incorporated into various lipid particles, SLNs have shown efficacy when utilized to treat eczema and acne, as UV absorbers in sun blocks, and as carriers of moisturizers. (Hoffman, 1998)

A NOVEL APPROACH FOR TRANSDERMAL DRUG DELIVERY

TRANSFEROSOMES

Transferosomes are self aggregates, with an ultra flexible membrane which delivers the drug reproducibly into or through the skin. Transferosomes, when applied under suitable condition, can transfer 0.1 mg of lipid per hour and square centimeter area across the intact skin. This value is substantially higher than that typically driven by the transdermal concentration gradients. The reason for this high flux rate is naturally occurring "transdermal osmotic gradients.Transferosomes overcome the skin penetration difficulty by squeezing themselves along the intracellular sealing lipids of the sc. (Jain, 2003). These vesicles have been seen to improve the therapeutic index of topically applied glucocorticosteroids. Elastic vesicles have also been found to perform better than rigid vesicles or traditional micelles in promoting the transdermal delivery of the receptor agonist rotigotine that is being used to treat parkinson's disease.

Studies on the elastic vesicles were shown to act as the molecule's carrier and not solely act in the role of penetration enhancers. Flexible vesicles have been found to interact differently with the skin when compared to rigid vesicles. While no ultrastructural changes were observed in rigid vesicle (Honeywell, 2003).

MOLECULAR SYSTEM –DENDRIMERS

Dendrimers are three dimensional, large manmade macromolecules with a branched structure. They can act as a "molecular micelle" to entrap other molecules (Mandawgade and Patravale, 2008). Dendrimers typically consist of a core that is usually composed of an amine, or of sugar molecules, and consist of alternating layers of two monomers. Different types of Dendrimers have been shown to enhance the transdermal delivery of indomethacin, an anti-inflammatory drug. Dendrimers have been used as delivery systems for topical application of NSAIDs, and chemotherapeutics or antineoplastics.(Wang, et.al.,2003)

ECHODERM BASED TOPICAL FORMULATIONS

(Anuska's, 2005) new products use Advanced Delivery System,the next generation of potent penetration after the liposome. (Echoderm™) expedites the process of Cellulite reduction by activating the natural skin structure in a body. This allows for optimized penetration and anchors the active ingredients between the layers of the skin allowing for prolonged release. Echoderm helps in two ways it reduce the growth of agents that are responsible for creating excess fat and stimulates anti-cellulite enzymes in the body

MICRO SPONGE

Microsponges are polymeric microspheres, with a very porous surface and are used mostly for topical administration. Microsponges are efficacious APIs delivery systems using a minimum dose and stability enhancers, it modify drug release and reduce side effects. Microsponge delivery systems (MDSs) consist of macroporous beads, with diameter size ranging between10 and 25 microns. The MDS are loaded with active agents which are released. The rate of active ingredients release of is depends on the partition coefficient of the active ingredient between the polymer and the vehicle or the skin, and also on some of the parameters that characterize the beads as surface area and mean pore diameter. Release can also be controlled through diffusion or other triggers such as moisture, pH, friction, or temperature (Sharon.et.al.,2012).

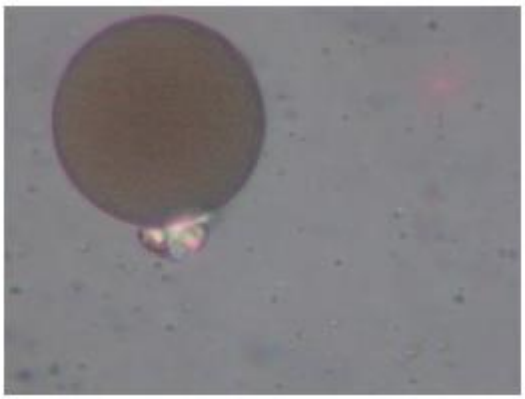


Figure 13.Shows that incorporation of actives into microsponge

CUBOSOMES

Cubosomes are submicron, nanostructured particles of bicontinuous cubic liquid crystalline phase. Cubosomes possess the same microstructure as the parent cubic phase but have much larger specific surface area with much lower viscosity than the bulk cubic phase. The relative insolubility of cubic phase-forming lipid in water allows cubosomes to exist at almost any dilution level, as opposed to most liquid crystalline systems that transform into micelles at higher levels of dilution. As a result, cubosomes can be easily incorporated into product formulations and serve as vehicles for drug delivery .

Cubosomes are typically produced by high-energy dispersion of bulk cubic phase followed by colloidal stabilization using polymeric surfactants (Landh, 1994). After formation of the cubosomes, the dispersion is formulated into a product and then applied to a substrate of interest, usually bodily tissue. Thereafter materials are either absorbed or released via diffusion.

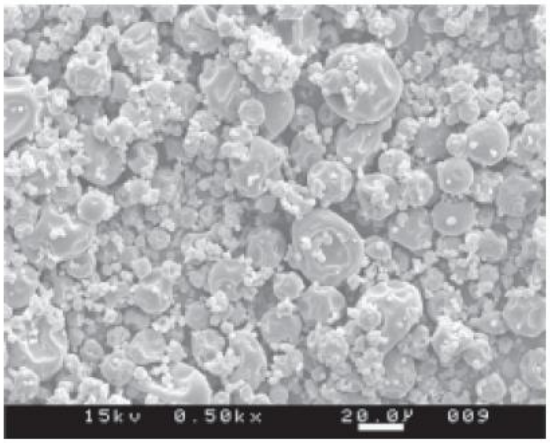


Figure 14. Photographs of spray-dried powder precursors of cubosomes

CHRONOSPHERES

Chronospheres were developed in the pharmaceutical and medical device industry. Originally, Chronosphere-type products had their origins as flexible sheets called Chrono Flex was derived from the reaction of a polyether with a difunctional isocyanate to form a polyurethane prepolymer. The polyurethane prepolymer was then reacted with a poly alcohol to form the flexible polyurethane sheet. The flexible polyurethanes, often referred to as polyurethane elastomers, have found unique medical applications in transdermal drug delivery and medical foams. Patents for the use of polyurethane foams as topical antifungal delivery devices were issued to Hydromer in 1988, PolyMedica introduced a pulverized powdered version of the ChronoFlex technology that they called Chronospheres. Polymedica had to modify the normal polyurethane elastomer technology so that more brittle polyurethanes could be made and they could be pulverized into powders. Chronospheres are unique, biocompatible, temperature-stable polymeric matrices into which useful active ingredients can be added. Inside the polymeric matrix, the actives are essentially protected from external threats such as oxygen and moisture (James, et.al.,2005).

OTHER FACTORS DETERMINING THE EFFICIENCY OF TOPICAL DRUG DELIVERY

Determination of Site of Action

Delivery systems for skin applications are designed to target the active compound into different sites of the tissue. These systems can be employed to retain the active on the surface of the skin, allow different partitioning patterns in the epidermis and dermis, and enhance the permeation of the active through the skin in order to provide transdermal delivery into the circulation. Determining the site of action and understanding the limitations of each of the approaches

described are critical to successful product development of a selected active. In today's demanding environment, just targeting the sub tissue for delivery may be insufficient for achieving all of formulations desired goals. If, for example, the target for the active is an intracellular enzyme, the cell membrane barrier should also be taken into consideration since the active has to cross the barrier (Nava, 2005).

Intracellular Delivery

Several in vitro experiments demonstrate inter-cellular penetration and effects on organelles and molecules that are located within the cell. While these results may be impressive, it is almost impossible to find a correlation between in vitro and in vivo activities. A few possible reasons for this include metabolism of the active component, its instability, penetration limitations, and differences in concentration. Further, when a "foreign" compound is applied to the skin and penetrates the sc, it may be identified as a "non self." As a result, the "foreign" compound is most likely to generate an immune system response. This response may alter the skin condition (i.e., create skin inflammation), change the penetration profile, and thereby affect the therapeutic index. In this system, the physical proper-ties of the delivery system were of high importance. Since cell membranes are negatively charged, cat-ionic lipid vesicles enhanced intracellular penetration in comparison to uncharged vesicles (Dayan, and Touitou, 2000).

Metabolism in Epidermis

The outer layer of the skin considered to be almost inert. As the skin is the outer most layer of the body, is highly sensitive to interaction with outside stimuli. Examples of such stimuli include physical pressure, contact with chemicals, and temperature change. Environmental, as well as intrinsic factors (such as aging or a disease), may alter sc function and structure, thereby affecting the skin's reaction. When developing a delivery system for skin, the metabolic changes of both the active as well as the delivery system components should be conceder. The epidermis is not simply a passive membrane that either blocks or permits entry of a drug. The skin, rich in enzymes, is the largest drug metabolizing tissue in the body. If the active is in a form of a "proactive", metabolic changes are important to convert in to its active form (Nava, 2005).There are multifaceted relationships between epidermal cell production and development, differentiation of keratinocytes to corneocytes, corneocytes maturation, and desquamation. The natural path of living keratinocytes is losing their nucleus, dying, and being filled with keratin during migration from the stratum granulosum to sc on their way to becoming corneocytes. This process is a dynamic cascade that is controlled by enzymatic reactions acting in different time frames and affected by environmental factors. It is this process that will eventually determine the barrier properties of the skin (Bielinska, et.al.,2000).

EXAMPLES OF TOPICAL APPLICATIONS

Reduction of Melanin Synthesis by Tyrosinase Enzyme

Melanin is the coloring agent of the skin. It synthesized in the melanocytes, the process of melanin generation is catalyzed by the enzyme tyrosinase one of the common approach to reducing skin pigmentation is limit melanin production by inhibiting activity of the enzyme tyrosinase. Melanosomes are specialized spherical shaped organelles that are the site of melanin synthesis and storage. In order to inhibit the tyrosinase enzyme, anti tyrosinase compounds have to penetrate the SC, reach the living epidermis, and permeate through the outer cell membranes of both the melanocytes and the melanosomes. The active compound or its delivery system must, therefore, possess cell membrane-permeating properties. (Nordlund , and Boissy, 2000). Ferulic acid is one of tyrosinase enzyme inhibitor. It is also anti-oxidant and photo protective, topical formulation of vitamin C and vitamin E with ferulic acid is more effective and it reduces irritation and increase stability (Nava 2005).

Improvements of Skin Condition and Intrafollicular Delivery

There are three basic ways to remove dead skin cells so, they don't clog pores and kill the bacteria that cause inflammation. The pilosebaceous pathway is primary target of action to improve skin condition. A few specific delivery systems, including liposomes and synthetic microspheres, have been found to localize in follicular and sebaceous areas. This localization serves to provide a reservoir for active compounds. Liposomes have been shown to enhance follicular delivery of both small polar molecules as well as macromolecules. Androgen hormone penetrated the sebaceous glands more effectively from Liposomes than from an alcoholic solution (Bernard, et.al., 1997). Salicylic acid is an active compound used in topically applied formulations. It acts as a keratolytic agent as well as having bactericidal and fungicidal properties. This organic acid has some drawbacks that limit its use. One of these limitations is its relative ease of absorption into the skin. This may lead, in some cases, to systemic toxicity, and, at the same time, result in reduced activity within its target of action i.e., the sebaceous gland within the living epidermis (Parfitt, 1999). A delivery system developed using polymeric, porous nylon particles containing an anhydrous solution of salicylic acid has been shown to create a reservoir of salicylic acid within the epidermis. This reservoir significantly reduces percutaneous absorption. Figure15 describes the flux of salicylic acid through the skin upon Application of two different formulations containing the same percentage of Salicylic acid

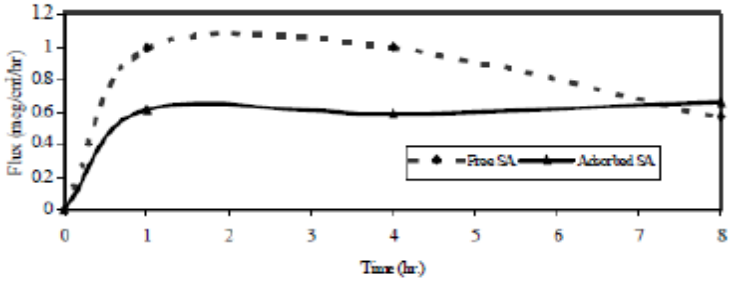


Figure 15.Flux through the skin of free salicylic acid (SA) vs SA adsorbed in porous nylon paricles

During the first eight hours of the experiment, the free salicylic acid flux through the skin was significantly higher than the flux obtained with the delivery system containing adsorbed salicylic acid. Extraction of the skin at the end of the experiment showed a higher reservoir of salicylic acid in the epidermis occurred when using the adsorbed salicylic acid (Nava 2005).,

Improving Superficial Delivery

Some important ingredients used in topically applied formulations are intended to protect the skin or alter its appearance by only affecting its optical properties. Such compounds need to be formulated and incorporated into delivery systems so their penetration into the skin will be minimal. Examples of such products include sunscreens and optically activated compounds. Here as well, the design of the formulation and the delivery system plays a major role in the prevention of penetration and reduction of irritation as measured by changes in the therapeutic index. The presence or absence of appropriate protective ingredients in the formulation may prevent irritation. An example of a delivery system developed to protect the active component and prevent its inter-action with the skin is a novel technology that combines fluorescence and light scattering. The product, called LipoLight™, exhibits an approach for the creation of a synergistic effect that results in a reduction of the perception of skin imperfections. This system is composed of a fluorescent molecule fixed to porous nylon particles and encapsulated in a translucent shell of cross-linked polyvinyl alcohol. When formulated properly into creams, lotions, or gels, these particles allow for a dramatic reduction in the appearance of skin imperfections (Sojka,2003).

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