World Journal of Clinical Pharmacology, Microbiology and Toxicology
World J. Clin. Pharmacol. Microbiol.Toxicol.
Vol. 1 [1] May 2015; 09-26

URL: http//wjcpmt.com

REVIEW ARTICLE

Formulation and Evaluation of Ointment and Cream with Their Mathematical Treatment of Absorption Through Skin: A Review

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INTRODUCTION

Ointments and creams are the semisolid dosage forms and intended for topical application to the skin, placed on the surface of eye, or used nasally, vaginally or rectally for therapeutic or protective action or cosmetic function. These preparations are used for the localized effects produced at the site of their application by drug penetration in to the underlying layer of skin or mucous membrane. These products are designed to deliver drug into the skin in treating dermal disorders, with the skin as the target organ. [Ansel, Howard C.,et al., (2000)]

Ideal Properties of Semisolid Dosage Form

1) Physical Properties:-
- a) Smooth texture
- b) Elegant in appearance
- c) Non dehydrating
- d) Non gritty
- e) Non greasy and non staining
- f) Non hygroscopic

2) Physiological Properties:-
- a) Non irritating
- b) Do not alter membrane/ skin functioning
- c) Miscible with skin secretion
- d) Have low sensitization effect

3) Application Properties:-
- a) Easily applicable with efficient drug release
- b) High aqueous wash ability

For the delivery of these semisolid preparations transdermal drug delivery system is designed.

OINTMENT

Ointments are soft, semisolid dermatological preparations intended for application to skin and mucous membrane for therapeutic or protective action. They may be applied to the skin placed on the surface of the eye, or used nasally, vaginally, or rectally with or without inunction. Ointments are designed to deliver drug into the skin in treating dermal disorders, with the skin as the target organ.

Ointments serve mainly three functions.

1) Lubricating-emollients
2) Treat skin disorder (Medicinal effect)
3) Protective coverings [Carter, S.J.,(2000)]

CLASSIFICATION OF OINTMENTS:-

i) According to their therapeutic properties based on penetration
ii) According to their therapeutic uses **[Mehta, R.M., (1997)]**

i) Ointments classified according to their therapeutic properties based on penetration

- **Epidermic ointment:-** These are act on epidermis and produce local effect. They are not absorbed. These ointments are used as protective, antiseptics, local anti-infective and parasiticides.

- **Endodermic ointment:-** These are act on deeper layer of cutaneous tissues. They are Partially absorbed and act as emollients, stimulants and local irritants.
- **Diadermic ointments**:- These ointments are used for deeper penetration and release the medicaments that pass through the skin and produce systemic effects. [Mithal, B.M.,(1980)]

ii) Ointments classified according to their therapeutic uses

- **Antibiotic ointment**:- These are used to kill micro-organisms. The antibiotics used are bacitracin, neomycin, etc.
- **Antifungal ointments**:- These are kill the fungi. The antifungal used are benzoic acid, salicylic acid, etc.
- **Anti- inflammatory ointments**:- These are used to relieve inflammation, allergy, pruritic condition of skin. Betamethasone valerate, hydrocortisone and its acetate are some anti- inflammatory agents.
- **Antipruritic ointment:-** These are used to relieve itching. The commonly used agents are benzocain, coal tar, etc.
- **Astringent ointment:-** These causes contraction of the skin and decrease discharges. The commonly used agent calamine, ZNO,tannic acid, etc
- **Antieczematous ointments**:- These are used to prevent oozing and excreation from vesicle on the skin. The drugs which are commonly used are hydrocortisone, coaltar, salicylic acid, etc.
- **Keratolytic ointments**:- These are used to remove or soften the horny layer of the skin. The drugs which are commonly used are salicylic acid, sulphur, etc.
- **Counter- irritant ointments:-** These are applied to irritate the skin, thus reduing other irritation or pain. The drugs which are commonly used are capsicum, methyl cellulose, etc.
- **Ointments used for dandruff treatment:-** These are used to relieve from dandruff. The drugs which are commonly used are cetrimide, etc.
- **Ointment for psoriasis treatment:-** Coal tar, corticosteroids are incorporated with a suitable ointment base for treatment of psoriasis.
- **Parasiticide ointment:-** These are destroy or inhibit living infestation, such as lice and ticks. The drugs commonly mixed with ointment bases are benzyl benzoate. Sulphur, etc.
- **Protectant ointment**:- These ointments protect the skin from moisture, air, sun rays or other substances such as soaps or chemicals. The drugs which are commonly used are calamine, silicones, etc. [Mehta, R.M.,(1997)]

Figure 1: Ointment
[http://www.google.co.in/imgres?imgurl=http://en.heilkraeuter.net/ointment/rescue-remedy-ointment-05.jpg&imgrefurl=http://en.heilkraeuter.net/ointment/rescue]

2.2) FORMULATION

The row materials generally used for manufacturing of ointments

a) Drug
b) Base
c) Preservative
d) Anti-oxidants
e) Chelating agents
f) Perfumes

a) Drug: - Drug is the active pharmaceutical ingredient which produced desired therapeutic action.

b) Ointment Bases

The ointment base is that substance or part of an ointment, which serves as carrier or vehicle for the medicament. The nature of a base also controls its performance. Hence the selection of base is very important. The selection of ointment base is depending upon the action desire nature of the medicament to be incorporated and the stability of an ointment is to be considered. **[Mehta, R.M.,(1997)]**

Ideal Properties of Ointments Bases

1) They should be non-irritating.
2) They should be non-dehydrating.
3) They should be non grease, non-staining.
4) They should be compatible with common medicaments.
5) They should be Stable.
6) They should be easily removable with water.
7) They are able to absorb water and/or other liquids.
8) They do not alter skin function.
9) They should be miscible with skin secretion.
10) Even phase distribution.
11) They should be non-gritty.
12) They should have good texture.
13) They should have no microbial contamination.
14) They should have Smoothing and elegant properties
15) Compatible with skin secretion.

Classification of Ointment Base

Ointment bases are classified by the USP into four general groups:

i) Oleaginous bases
ii) Absorption bases
iii) Water-removable bases
iv) Water-soluble bases [Mithal, B.M.,(1980)]

i) Oleaginous bases:

❖ They are also termed as *hydrocarbon bases*.
❖ They are not absorbed by the skin
  - Restricts loss of moisture and keeps the skin soft but water logging, with maceration of the skin, if application is prolonged.
  - Retains body heat, which may produce an uncomfortable feeling of warmth.

➢ They are immiscible with water
➢ They are sticky
➢ They are almost inert
➢ Water absorption is low
➢ Their constituents are readily available and cheap [Carter,S.J., (2000)]

Constituents of the hydrocarbon bases

➢ **Petrolatum** is a purified mixture of semisolid hydrocarbons obtained from petroleum. It is an unctuous mass, varying in color from yellowish to light amber. It melts at 38 to 60·C and may be used alone or in combination with other agents as an ointment base. Petrolatum is also known as yellow petrolatum and petroleum jelly. Commercial product is Vaseline. White soft paraffin is never used in the preparation of ophthalmic ointments because it may contain small traces of bleaching agents. It may cause irritation to the eye. [Mehta, R.M.,(1997)],
[Ansel,Howard C.,et al., (2000)]

➢ **Hard paraffin**:- It is purified mixture of solid hydrocarbons. It is used to harden or soften the ointment base.

Liquid paraffin:- It is purified mixture of solid hydrocarbons and obtained from petroleum by distillation. It is soluble in ether and chloroform but insoluble in water and alcohol. It is used along with hard paraffin and soft paraffin to get desired consistency of the ointment.

Limitations of Oleaginous bases:-

1) Very greasy
2) They are sticky and difficult to remove from skin
3) Retain body heat
4) Not help in absorption of medicament
5) Prevent drainage on oozing areas.

ii) ABSORPTION BASES: These bases are anhydrous substances which have the property of absorbing considerable quantity of water but still retaining their ointment like consistency.

They are mainly classified into two groups.

Non-emulsified Bases

Water in oil emulsion **[Mehta, R.M.,(1997)]**

Non-emulsified Bases: These absorb water and aqueous solutions producing W/O emulsions.

- Less occlusive but good emollients.
- They assist oil-soluble medicaments to penetrate the skin.
- They are easier to spread.

Constituents of non-emulsified bases:

- **Wool Fat** is used in which the proportion of aqueous or hydro-alcoholic liquid is too large for incorporation in a hydrocarbon base. It is too sticky for use alone but is an important constituent of almost half of the official ointments including simple ointment. It assists absorption of active ingredients.
- **Beeswax** which contains small amounts of cholesterol is an ingredient of paraffin ointment. It is used as a stiffening agent in pastes and ointments.
- **Wool alcohol** These are the emulsifying fraction of wool fat, is a constitute of wool alcohol ointment B.P., which contains wool alcohols and hard, liquid and white soft paraffin.
- **Cholesterol** hydrophilic petroleum U.S.P. is an absorption ointment base. It contains cholesterol (3%), stearyl alcohol (3%), white bees wax (8%), and white soft paraffin (86%).

Water in Oil Emulsions Bases: These are capable of absorbing more water.

Constituents of water in oil emulsion bases:

- **Hydrous wool fat (lanolin)** is prepared from wool fat and water. It is used alone as an emollient and is an ingredient of several ointment bases. **[**Carter,S.J., (2000)]

iii) Emulsion Bases (Water-Removable Bases):-

Both O/W and W/O type of emulsions have been used as bases. O/W emulsions are mainly used so these bases are known as Water removable bases. They have cream like consistency. Because the external phase of the emulsion is aqueous, they are easily washed from skin and often called as water-washable bases. They may be diluted with water or aqueous solutions. Examples are white soft paraffin and liquid paraffin.

Certain advantages are:

- Miscibility with exudates from lesions.
- Reduced interference with skin functions.
- Good contact with the skin.
- High cosmetic acceptability. [Ansel,et al., (2000); Mehta, R.M.,(1997)]

iv) WATER-SOLUBLE BASES:

Water-soluble bases do not contain oleaginous components. They developed from the macrogols (polyethylene glycols). The macrogols are mixtures of polycondensation products of ethylene oxide and water. Example of polyethylene glycol 400, 3350, Macrogols 200, 300, 400. They are completely water washable and referred as greaseless. They soften greatly with addition of water

Advantages

- Water solubility: Easily removed from skin.
- Good absorption by the skin: As water soluble easily penetrates through skin for the drugs which are poorly soluble.
- Good solvent properties.
- Freedom from greasiness.
- Compatible with many dermatological medicaments

Disadvantages

- Limited uptake of water
- Less bland than paraffin due to their hygroscopic nature
- Reduction in activity of certain anti bacterial agents.
- Solvent action on polythene and backelite, these plastics should not be used in containers or closures for Macrogols ointments.

Other ingredients of ointment bases are

1) Vegetable oils
2) Synthetic esters of fatty acids
3) Higher fatty alcohols
4) Polar organic solvents [Carter,S.J., (2000)]

- **SELECTION OF DERMATOLOGICAL VEHICLES:-**

There are large numbers of ointment bases which are available. There are various factors which govern the selection of an ideal base for ointments

i) Dermatological factor
ii) Pharmaceutical factor

i) Dermatological factor

- *Absorption and penetration*:-

Absorption means actual entry in to blood stream (systemic absorption). Penetration indicates passage through the skin (cutaneous absorption)

The skin has three main layers, the epidermis, dermis and hypodermis. The ointment base penetrates deep into tissues of the skin along with the medicament and which in turn allows the systemic absorption of the medicament in to blood stream.

The animal fats (lard and wool fats) and fixed oils penetrate more readily through the skin in comparison to mineral oils (paraffin).

- *Effect on skin function*:-

Greasy bases may interfere with the skin function like heat radiation and sweat excretion. Moreover, they are irritated to skin. The water soluble bases and O/W emulsion provides a cooling effects.

- *Miscibility with skin secretions and serum:-*

Skin secretions are more readily miscible with emulsion bases as compared to greasy bases. Hence drug is more rapidly released to the skin. Due to this reason lesser proportion of the medicament is needed. O/W emulsion bases being readily mixed with serum from broken skin are very useful for weeping eczema.

- *Compatibility with skin secretions:-*

Generally neutral ointment bases are preferable because they do not cause discomfort in use and are compatible with majority of medicaments. The ointment bases should have a ph about 5.5 which is the average ph of skin secretions.

- *Freedom from irritant effect:-*

The ointment bases should be non irritant. Greasy bases cause irritation and may cause oedema.

- *Emollient properties:-*

Dryness and brittleness of the skin cause discomfort to the skin. Therefore, the ointment bases should posses emollient properties that should be able to keep the skin moist. The glycerin and propylene glycol keep the skin moist and soft. Wool fat, lard and paraffin keep the skin soft by preventing rapid loss of moisture from the skin.

- *Ease of application and removal:-*

The ointment base should be easily applicable and at the same time they are easy to be removed from the skin. Stiff and sticky bases are not suitable because they may cause damage to the newly formed tissues of the skin.

ii) Pharmaceutical factors

Synthetic modification of the chemical structure of a drug may yield compounds with increased potency and prolonged action of the drug.

- *Stability:-*

The fats and oils obtained from animal and vegetable are liable to undergo oxidation. This can be prevented by incorporating a suitable antioxidant in desired concentration. O/W emulsion bases are liable to microbial growth and needs a proper preservative.

- *Solubility:-*

Most of the medicament insoluble in the ointment base. Hence, for the uniform distribution, it is necessary to mix finely powdered drug in the ointment base.

- *Emulsifying properties:-*

Hydrocarbon bases can absorb only a small amount of water in comparison to animal fats which can absorb large quantities of water. Example, wool fat can absorb about 50% of water, and mixed with other fats can take up several times its own weight of water or hydro- alcoholic liquids. Hence, wool fat is included for the preparation of base meant for eye ointments.

- *Consistency:-*

The ointment should be of suitable consistency. It should neither be too hard nor too soft. The consistency of a base should be that it withstands wide variation in temperature condition.

- *Dissociation constant:-*

Passage of drug (ions) is blocked by electrostatic interactions deep penetration of an ionic medicament is influenced by its dissociation constant and ph of the surroundings.

- *Particle size:-*
  Reducing the particle size of poorly soluble drugs improves the therapeutic activity by increasing the dissolution rate. [Mehta, R.M., (1997)], [Carter,S.J., (2000)]

c) PRESERVATIVES:-

The antimicrobial compounds are added to prevent contamination, deterioration or spoilage of ointment base by microbes. The first consideration in selection is the irritancy or toxicity of the compound to the tissue to which the ointment is to be applied. Sometimes preservatives get complexed by other ingredients and are not available in sufficient concentration. In the presence of tween 80, methyl paraben, benzalconium chloride, benzoic acid, etc get inactivated. The bactericidal activity also depends upon partition coefficient of the antimicrobial compound between aqueous and oily phase.

d) ANTIOXIDANT:-

These should be incorporated when there is a possibility of oxidative degradation of the base. The concentration of antioxidant depends upon their partition coefficients between aqueous and oily phase. Generally compounds like butylated hydroxyl anisole, propyl gallate, nor- dihydroguaiaretic acid etc. are used.

a) CHELATING AGENTS:- When traces of metallic ions are likely to catalyse oxidative degradation small amounts of substances of such as citric acid, maleic acid, phosphoric acid may be added to chelate the metallic ions. [Mehta, R.M.,(1997)], [Mithal, B.M.,(1980)]

b) PERFUMES:-

Most ointments have a pleasant smell imparted by incorporation of selected perfumes.

2.3) PREPARATIONS OF OINTMENT BASES:

There are mainly four methods:

- By triturating
- By fusion
- By chemical reaction
- By emulsification
- By ointment mills

➢ **By Triturating:-** This method is used when soft fats and oil part of the base and medicament is solid and insoluble or liquid in small amount.

- Powder the solid medicament
- Triturating (levigating) the ingredients in a mortar until smooth ointment is obtained.
- Mortars to be preferred when much liquid is to be incorporated. [Mehta, R.M.,(1997)]

➢ **By Fusion:-** when ointment base contains a number of solid ingredient of different melting point, such as white bees wax, stearic acid, hard paraffin, it is necessary to melt them in decreasing order to their melting point. This will avoid the overheating of the substances having low melting points. The medicament incorporated to the melting mass with stirring. In case any aqueous substances are incorporated, that should be heated to same temperature as base. After mixing the two portions the stirring should be done to make a homogenous mass.

Precautions:-

1) Vigorous stirring should be avoided to prevent air entrapment in the ointment.
2) Rapid cooling should be avoided to prevent separation of waxy solid from ointment [Mehta, R.M.,(1997)]

➢ **By Chemical Reaction:**

- It involves both fusion and mechanical mixing.
- Here new product is formed by chemical reaction
- Certain hydrophilic base which involves the formation of soaps may be said to be made by chemical reaction
- E.g. Ointment containing free iodine, Ointment containing combined iodine,

➢ **By Emulsification Method:-**

In this, the fat, oil, and waxes are melted together on a water bath at a temperature of 70^0C. The aqueous solutions of all of the heat stable water soluble components are also heated almost at the same temperature as that of melted bases. The solution is added to the melted mass with continuous stirring until the product cools and ointment prepared. [Mehta, R.M.,(1997)]

➢ **By Ointment Mills**

- In this method, ointment is prepared by using the specific type of mill that is “Triple roller mill”

PRESERVATION:

- Ointment contain fat and water so easily oxidisable, so add proper anti-oxidants
- They are contaminated by micro organism and get spoiled. It can be prevented by antimicrobial agent.
- They must not react with material of container.

PACKAGING

Container:

- Ointments are usually dispensed in either ointment jars or tubes
- Tin and aluminum tubes are also used

Now plastic tubes are available. [Mehta, R.M., (1997)]

2.4) EVALUTION OF BASES:-

There are two methods for evaluation of ointment base

i) Physical Methods

ii) Microbiological methods

i) Physical Methods

a) Test for Rate of Absorption: **-** Diadermic ointments are those from which the drug moves into deeper skin tissues and finally into the systemic circulation. Such ointments should be evaluated for the rate of absorption of drugs. The ointment should be applied over a definite area of the skin by rubbing. At regular intervals of time, serum and urine samples should be analyzed for the quantity of drug absorbed. The rate of absorption i.e., the amount of drug absorbed per unit time should be more.

b) Test for Rate of Penetration

The rate of penetration of a semisolid dosage form is crucial in the onset and duration of action of the drug. Weighed quantity of the preparation should be applied over selected area of the skin for a definite period of time. Then the preparation left over is collected and weighed. The difference between the initial and the final weights of the preparation gives the amount of preparation penetrated through the skin and this when divided by the area and time period of application gives the rate of penetration of the preparation. The test should be repeated twice or thrice. This procedure is tedious and not followed anymore.

Using flow-through diffusion cell or microdialysis method, the rate of penetration of the preparation can be estimated. Animal or human skin of definite area should be collected and tied to the holder present in a diffusion cell. The diffusion cell is placed in a fluid bath. Measured quantity of the preparation is applied over the skin and the amount of drug passed into the fluid is measured at regular intervals by analyzing the aliquots of fluid using a spectrophotometer.

c) Test For Rate Release Of Drugs

A clean test tube is taken and the internal surface is coated with the preparation as a thin layer. Saline or serum is poured into the test tube. After a certain period of time, the saline is analyzed for the quantity of the drug. The amount of drug when divided by the time period gives the rate of drug release.

d) Test for Rheological Properties

The viscosity of the preparation should be such that the product can be easily removed from the container and easily applied to the skin. Using cone and plate viscometer the viscosity of the preparation is determined.

e) Test for Content Uniformity

The net weight of contents of ten filled ointment containers is determined. The results should match each other and with the labeled quantity. This test is also called minimum fill test.

[http://www.pharmainfo.net/evaluation-ointments]

f) Uniformity of weight

Ten tubes were filled randomly and weighed. Ointment was removed from each tube and each empty tube was washed with methanol. The empty tubes were dried and their weight was taken. The difference between two weights was calculated as net weight of the ointment of tube. The average of net weight of ointment of ten tubes was noted.

g) pH: The pH **of** ointment solution was measured with the help pH meter.

h) Hardness of Ointment: It was measured by Penetrometer. Three containers were filled carefully and completely, without forming air bubbles and stored at 25+ 0.5^{0}C for 24 hrs. Three samples were stored at 25± 0.5^{0}C and with shear for 5min. Three samples were melted and carefully and completely filled three containers, without forming air bubbles stored at 25 ± 0.5 ^{0}C for 24 hrs. Test samples were placed on Penetrometer. Temperature of penetrating object was adjusted at 25±0.5^{0}C and position was also adjusted such that its tip just touches the surface of sample. Penetrating object was released for 5sec. Depth of penetration was measured. Same was repeated with remaining containers10.

[http://www.ijpbs.net/issue-4/Ph-2.pdf]

ii) Microbiological Methods

a) Test of microbial content

Micro-organisms like pseudomonas aeruginosa and staphylococcus aureus may contaminate the preparation and finally infect the skin. So ointments should be tested for the absence of

Such micro-organisms. Solutions of different samples of the preparation are made. Each sample is inoculated into separate volumes of 0.5 ml of rabbit's plasma under aseptic conditions and incubated at 37 degrees C for 1-4 hours. No formation of the clot in the incubated mass indicates the absence of the micro-organisms.

b) Test of Preservative Efficacy

Using pour plate technique the numbers of micro-organisms initially present in the preparation are determined. Solutions of different samples of the preparation are made and mixed with Tryptone Azolectin (TAT) broth separately. All cultures of the micro-organisms are added into each mixture, under aseptic conditions. All mixtures are incubated. The number of micro-organisms in each sample is counted on 7th, 14th, 21st and 28th days of inoculation.[http://www.pharmainfo.net/evaluation-ointments]

3) CREAMS

Creams are semisolid emulsion system with opaque appearance as contrasted with translucent ointments and contain one or more medicinal agents dissolved or dispersed in either O/W and W/O emulsion or in other type of water washable base. Creams are intended for application to the skin and mucous membrane. Their consistence depends on whether the (1) emulsion is water in oil or oil in water and on the (2) nature of solids in internal phase.

1) Their affectivity should be high.
2) They should give rapid onset of action
3) They should be biocompatible and bio-miscible
4) Free from grittiness.
5) They should be smooth
6) They should be readily washable
7) They should be non-irritant
8) They should be non-allergic
9) They should be non-toxic
10) They should be physically and chemically stable

[http://semisolidpreparationcream.blogspot.in/2011/07/semisolid-preparation-cream.html]

Figure 2: Creams
[http://www.google.co.in/imgres?imgurl=http://botox.co/wp-content/uploads/2011/02/skin-creams.jpg&imgrefurl=http://www.botox.co/botox-creams-do-they-]

3.1) CLASSIFICATION OF CREAMS:

All the skin creams are classified on different bases-

1) According to function e.g. cleansing, foundation, massage cream, etc.
2) According to characteristic properties e.g. cold creams, vanishing creams
3) According to the nature and type of emulsion

The most widely accepted classification is based on function. According to functions the creams can be classified as follows-

1) Cleansing and cold cream
2) Foundation and vanishing creams
3) Night and massage creams
4) Hand and body creams
5) All purpose and general creams [Mithal, B.M. (2000)]

3.1.1) CLEANSING AND COLD CREAMS

Cleansing cream or lotion is required for removal of facial make up, surface grime, oil, and water and oil soluble soil efficiently, mainly from the face and throat. It also removes applied cosmetics such as face powder, rouge, foundation bases, cake makeup and lipstick.

Ease of application is an important feature of the cleansing cream and so most of the creams are liquids so that excess creams and soil are then easily removal with tissue. The resultant layer left on the skin must not be occlusive but should be sufficient emollient to prevent drying.

A good cleansing cream should have the following characteristics:

- It should effectively be able to remove oil soluble and water-soluble soil and surface oil from the skin, specifically face and throat.
- As a cosmetic it should be stable and have a good appearance.
- It should melt or soften on application to the skin
- It should spread easily without too much drag. During application, it should not feel greasy or oily.
- After evaporation of any water, the cream should not become viscous.
- A light emollient film should remain on the skin after use of the cream.

Types of cleansing creams

i) Beeswax – borax type

ii) Liquefying Cleansing creams

i) Beeswax – borax type:- They liquefy on application to the skin and spread with ease. They are O/W type of emulsion. After the creams are rubbed on the skin, a sufficient quantity of water evaporates to impart a phase inversion to the W/O type. The solvent action of the oil, as external phase, imparts the cleansing properly.

Formula of beeswax borax cream

Mineral oil	28.0 gm
Isopropyl myristate	14.0 gm
Acetoglyceride	2.5 gm
Petroleum jelly	7.5 gm
Beeswax	15.0 gm
Borax	1.0 gm
Water	32.0 gm
Preservative	q.s.
Perfume	q.s

ii) Liquefying Cleansing cream: - They are translucent liquefying anhydrous cream of thixotropic character.

Formula of Liquefying Cleansing creams:

Mineral oil	80.0 gm
Petroleum jelly	15.0 gm
Ozokerite wax	5.0 gm
Preservative	q.s.
Perfume	q.s.

3.1.2) VANISHING CREAMS

They are called vanishing creams because they seem to disappear when rubbed into the skin. These are stearic acid based and part of stearic acid saponified with the alkali and rest of the stearic acid is emulsified with the soap in a large quantity of water.

Formula of Vanishing cream

Stearic acid	20.0 gm
Cetyl alcohol	0.50 gm
Triethanolamine	1.20 gm
Sodium hydroxide	0.36 gm
Glycerin	8.00 gm
Water	69.94 gm
Perfume	q.s.
Preservative	q.s

3.1.3) FOUNDATION CREAMS

Foundation creams are applied to provide a smooth emollient base or foundation before the application of the power and other make up preparations. They help the powder to adhere to the skin due to possession of good holding power.

Foundation creams are of two types

Pigmented creams

Unpigmented creams

Formula of foundation creams

1.	Lanolin	2.00 gm
	Cetyl alcohol	0.50 gm
	Stearic acid	10.00 gm
	Potassium hydroxide	0.40 gm
2.	Propylene glycol	8.00 gm
	Water	79.10 gm

Perfume	q.s.
Preservative	q.s

3.1.4) *NIGHT AND MASSAGE CREAMS:*

Skin nourishment is important and required to provide the normal characters of the skin or as a treatment for dry skin. To supplement foods for the skin and to treat the dry skin various creams containing different ingredients are used. Common features are that they are generally applied on the skin and left for several hours, say overnight. They are easy to apply but not easy to rub in because of presence of oil/wax it is sticky and greasy.

As normally these creams are applied at night time, the time normally assigned to skin preservation and feeding, they are called night creams. These preparations are used to supplement hormones or vitamins to the skin and they may be termed as hormone creams or vitamin creams respectively.

Formula of night and massage creams

Mineral oil	38.0 gm
Petroleum Jelly	8.0 gm
White beeswax	15.0 gm
Paraffin wax	1.0 gm
Lanolin	2.0 gm
Borax	1.0 gm
Water	35.0 gm
Perfume	q.s.
Preservative	q.s.
Antioxidant	q.s.

Formula of Vitamin Cream:

1.	Mineral Oil	40.0 gm
	Beeswax yellow	15.0 gm
	Lanolin	0.5 gm
	Isopropyl myristate	5.0 gm
	Acetylated lanolin	0.5 gm
	Concentrated solution of Vitamin A & D	1.0 gm
2.	Borax	1.0 gm
	Water	37.0 gm
	Perfume	q.s.
	Preservative	q.s.
	Antioxidant	q.s.

Hormone Cream:

1.	Acetylated lanolin	15.0 gm
	Isopropyl myristate	3.0 gm
	Mineral oil (heavy)	4.0 gm
	Hormone (in vehicle)	1.0 gm
	Beeswax	7.0 gm
	Cetyl alcohol	3.0 gm
	Stearyl alcohol	3.0 gm
	Emulsifying agent (o/w type)	15.0 gm
2.	Water	49.0 gm
	Perfume	q.s.
	Preservative	q.s.
	Antioxidant	q.s.

3.1.5) HAND AND BODY CREAMS:

Softness of the skin is very important and also wanted. Sebum, a substance which is secreted from the skin, acts as a natural lubricant and keeps the skin soft and conditioned. The film produced by secreted sebum also helps to keep the skin wet by preventing the evaporation of moisture. The repeated or constant contact with soap and detergent does the damage or causes removal of the film sebum.

Frequent removal of this sebum makes the skin dry, scaly and less protective against infection and lead to dermatitis. A protection required to maintain the skin in normal condition. So, hand and body creams are used. These preparations can be liquid creams, solid creams, lotions, jellies or non aqueous types.

The main function of hand and body creams are expected to be

- Replace water loss or reduce the water loss from the surface of the skin.
- Provide an oily film to protect the skin
- Keep the skin soft, smooth but not greasy
- Easy to apply

Formula of hand and body creams

1.	Stearic acid	15.0gm
	Isopropyl myristate	2.0gm
	KOH	1.0gm
2.	Sorbitol solution	18.3gm
	Water	63.7gm
	Perfume	q.s.
	Preservative	q.s.

3.1.6) ALL PURPOSE CREAMS:-

They are also known as sports creams as they were used by sport men. They are oily and non greasy type and can easily spread on the skin to give protective film. They are nourishing cream, or protective cream for prevention or alleviation of sunburn, for the treatment of roughened skin areas.

Manufacturing of creams:-

- The total ingredients can be classified in to oil phase and aqueous phase.
- Ingredients of oil phase should be mixed gradually in increasing melting order, starting with lowest melting point substances.
- Components of aqueous phase should be mixed together and warmed to about same temperature of oil phase and mix with oil phase with continuous stirring until a smooth cream is formed.
- Add perfume after cooling and mill further through roller mill

Formula of all purpose creams

Wool alcohol	2.5 gm
Microcrystalline wax	6.0 gm
Mineral oil	21.0 gm
Petroleum jelly	5.0 gm
Glycerin	5.0 gm
Magnesium sulphate	0.7 gm
Water	59.8 gm
Perfume	q.s.
Methyl parahydroxybenzoate	q.s.
Propyl parahydroxybenzoate	q.s. [Mithal, B.M. (2000)]

3.2) FORMULATION OF CREAMS:

Solvents: - various fat solvents are used in preparation of cream such as acetone, chloroform, glycerol, kerosene, white gasoline, dioxane, 95% ethanol.

Humectants: Humectants are agents which control the moisture exchange between the product and air, both in the jar and on the skin.

Glycerol, polyhydric alcohol, like ethylene glycol, propylene glucol solution of sodium lactate, glucose, fructose. Various synthetic humectants are furyl glycerine, allantoin, fruit and vegetable extract etc

Spreading agents: fatty acid esters, acetylated glycerides

Emollient agents: Emollients are the most important ingredients of skin softening. Agent which are used as emollient are lanoline, cetyl alcohol, spermaceti and cocoa butter

Opacifyin agents (2%):-zinc oxide, titanium di oxide. Magnesium stearete, zinc stearate, hydrous lanoline

Thixotropic agents: wax (paraffin)

Wax and oils:- vegetable oils, fatty acid esters, mineral oil, petrolatum. The proportion of mineral oil and wax is very important to avoid separation, sweating, and granular appearance.

Neutralizing agents:- These agents mainly neutralize free fatty acid by the use of alkali. Example: potassium hydroxide, tryethanolamine.

Pearlescent agents: They provide conditioning to the skin like liquid paraffin, spermaceti, cocoa butter, starch, almond oil.

Hydrating agents:- vegetable and fruit extract bamboo extract

Nourishing agent:- vitamins , vitamin A, D ,E, F are used and various hormones are also used. Examples are estrogen, progestin, pregnenolone and androgen. They show limited restorative effects on aged skin. The hormones may be absorbed and produce side effects. To prevent this, the concentration of hormones used should be very less and a suitable vehicle is required to dissolve hormone.

Gelling agents (Thickening agents):- These are hydrophilic substances used to increase the viscisity. Examples are tragacanth, starch, pectin, gelatin, etc

Emulsifiers:- They reduce the surface tension for proper emulsification and prevent coalescence. They are effective at low concentration. Eg. Cetyl pyridinium chloride, Alkyl dimethyl benzyl ammonium chloride.

Film formers:- These prevent the evaporation of water from the surface of skin. Examples are carboxy cellulose poly vinyl alcohol.

Healing agents:- The inclusion of healing agents in creams is justified because of the severe chapping accompanied by cracking of the epidermis. These cracks are often painful. Agents that act as skin healers urea, uric acid.

Antioxidents:- They prevent oxidation are butylated hydroxyl arisol

Preservatives:- They protect the cream from microbial contamination. Examples are methyl parahydroxy benzoate, propyl parahydroxy benzoate.

Perfumes:- All creams have a pleasant smell imparted by incorporation of selected perfumes like geranium, bois the rose, ylang yalng, lavendrol oils, linalool.

Coloring agents:- These are added ao impert a colour effect according to the need.

Red (Pink) : FD&C Red No. 1, D&C Red No. 19, D&C Red No. 33. Blue : FD&C Blue No. 1, D&C Blue No. 4. Yellow: FD&C Yellow No. 5, D&C Yellow No. 6. Green : D&C Green No. 5. . [Mithal, B.M. (2000)]

3.3) EVALUATION OF CREAMS

Generally tests like quantitative and qualitative determination of ingredients. Some others tests are important.

Methods of Evaluation:-

a) Rheology test
b) Determination of pH
c) Sensitivity test (Patch Test)
d) Photo Patch test.
e) Peroxide Stability test
f) Test for thermal stability
g) Irritancy test
h) Drug Content Uniformity

a) Rheology Test :-

Rhealogy is very2 important as these creams are marketed in tube or containers. The rheology or viscosity should remain constant. As these products are normally non-Newtonian in nature, the viscosity can be measured using viscometers used for such liquids.

Procedure:- The formulated cream was found to be non - Newtonian. Take a fixed quantity 10gms of cream in a 10ml beaker. Keep it impact for 1 hr. The beaker was inclined to one side see whether the cream is liquefied or not. beaker is shaken to and fro for continuous 5mins and checked whether consistency has changed or not. The beaker was again tilted and checked for pourability of the cream. The formulation showed no thixotropic (shear thinning) characteristics. [http://www.ijppsjournal.com/Vol3Suppl2/396.pdf]

b) Determination Of pH

Weigh accurately 5± 0.01gm of the cream in 100ml beaker. Add 45 ml of water and disperse the cream in it. Determine the pH of suspension at 27^0C using the pH meter.

[**www.ijbs.net/issue-3/86.pdf]**

c) Sensitivity Test (Patch Test) :-

As various types of ingredients are used with occasional use of Antiseptic hormones etc. there is a possibility of sensitization or photosensitization of the skin.

Sensitivity testing of cosmetics may perform as diagnostic patch test. It is intended to discover. Whether the cosmetic used has caused dermatitis.

Procedure of Patch Test:-

Place about 0.1 – 0.3 g of cosmetic to be tested on a piece of cotton fabric or flannel (2-3 Sq. cm. in size) and apply this to the Skin of arms, thighs or back. This patch is covered with a patch of cellophane (about 5 sq. cm) and sealed with adhesive plaster (about 40 Sq. cm). Apply more then one patches at a time control patches should also applied which is of similar cream of other brand available in market and known not to cause any harm to the Skin. These patches are allowed to remain on the Skin for 24-72 hours. If there are no reaction.

The Same patch may be reapplied fill –

(a) Either a reaction is produced.
(b) On the investigator is confirmed that no reaction will occur.

i) Photopatch test:-

Some substances are not harmful by themselves but they become harmful when exposed to sunlight so photo patch test is necessary. For this test two patches of testing cream are prepared as in patch test and one is exposed to sunlight for 30 minutes. This sits acts as control after further 24 hours the patch are removed and examined. It the patch not expose to light and the Skin are exposed to light does not show reaction nut the patch site. This has been exposed to light shows reaction. The Substance may be taken as nonphototoxic.

j) Peroxide Stability Test:-

The test for peroxide stability can be carried out by placing about 1 gram cream in a test tube and heating it in a constant temperature bath. Upper surface of the cream should be in level with the fluid of the bath. The tube is kept in the constant temperature bath for 24 hours at 95°C. The contents of tube are transferred to a 250 ml flask and peroxide contents determined.

Stability of peroxide in cream can be found out be initial concentration of hydrogen peroxide in cream can be found out by initial concentration of hydrogen peroxide in cream and by final concentration of hydrogen peroxide in cream after above

Mentioned treatment from the following formula.

$$\% \text{ Stability} = \frac{\text{Final } H_2 O_2 \text{ Concentration}}{\text{Initial } H_2 O_2 \text{ Concentration}} \text{ X } 100$$

Stability of peroxide cream should be better than 95 %

Procedure of Peroxide Stability Test:-

Place about 1 gm accurately weighed sample in a 250 ml flask and add 10 ml. Chloroform to dissolve fats. Add 50 ml of water, 15 ml dilute hydrochloride acid and about 1 gram of potassium iodide. Add three drops of ammonia molybate solution. The Solution will turn dark due to liberation of iodine. Titrate with 0.1 sodium thiosulphate using starch as indicator. (End Point: Blue to colourless solution)

k) Test For Thermal Stability :-

Apparatus:

1) A humidity chamber/incubator controlled at 60 to 70 percent relative humidity and41°C
1) Clear glass bottles of around 30 ml capacities with plug and screw on cap for proper closure.

Procedure:-

- The help of spatula insert the cream into bottle and tap it to settle to the bottom.
- Fill up to two third capacity of bottle and insert plug and tighten the cap
- Keep the filled bottle erect in side the incubator at 45 + 1°C for 48 hr.
- The sample shall be taken to have passed the test, If an removal from the incubator shows no oil separation or any other phase separation.

l) Irritancy Test

Mark an area (1sq.cm) on the left hand dorsal surface. The cream was applied to the specified area and time was noted. Irritancy, erythma, edema, was checked if any for regular intervals up to 24 hrs and reported. [http://www.ijppsjournal.com/Vol3Suppl2/396.pdf]

m) Drug Content Uniformity

The formulation equivalent to 50 mg of drug was taken and dissolved in small quantity of methanol. Then the formulation is warmed on the water bath so that the drug present in the formulation was completely dissolved. Then the solution is filtered through Whattman filter paper in to 50ml vol. flask. The volume is made up to the mark which gives concentration of 1000mcg/ml. From this different concentration of solution was taken in 10ml volumetric flask and volume was made up to 10ml with methanol and Absorbance was measured by UV spectrophotometer at 231.6nm against blank. [www.ijbs.net/issue-3/86.pdf]

4) MATHEMATICAL TREATMENT OF ABSORPTION OF OINTMENT AND CREAM THROUGH SKIN

The extent and rate of drug absorption is influenced by various factors including skin physiology, physicochemical properties of drugs and excipients, as well as fabrication and design of the delivery systems.

Both topical and transdermal drug products are intended for external use. However, topical dermatologic products are intended for localized action on one or more layers of the skin.[http://inetce.com/articles/pdf/221-146-04-054-H01.pdf]

Skin structure: - The skin can be considered to have four distinct layers of tissue.

i) Non-viable epidermis (stratum corneum)
ii) Viable epidermis
iii) dermis
iv) Subcutaneous connective tissue (hypodermis)

i) Non-viable epidermis (stratum corneum)

The stratum corneum is the outermost desquamating 'horny' layer of skin, comprising about 10-20 cells of flat, partially desiccated, dead, keratinized epidermal cells. Depending upon the region of the body, the thickness of this layer ranges from 10-20 µm, with the thickest layer on the palms of the hands and soles of the feet. Of the various skin layers, it is the stratum corneum that is the rate-limiting barrier to percutaneous drug transport. In fact, the stratum corneum is a remarkably more formidable barrier to drug transport than the epithelial barriers of gastrointestinal, nasal, buccal, vaginal, or rectal delivery routes.

ii) Viable epidermis

This layer of the skin resides between the stratum corneum and the dermis and has a thickness ranging from 50- 100 µm. The structure of the cells in the viable epidermis is physiochemically similar to other living tissues. Cells are held together by tonofibrils.The density of this region is not much different than water. The water content is about 90%.

iii) Dermis

Just beneath the viable epidermis is the dermis. It is a structural fibrin and very few cells are like it can be found histologically in normal tissue. Dermis thickness range from 2000 to 3000 µm and consists of a matrix of loose connective tissue composed of fibrous protein embedded in an amorphous ground substance.

iv) Subcutaneous connective tissue

The subcutaneous tissue or hypodermis is not actually considered a true part of the structured connective tissue is composed of loose textured, white, fibrous connective tissue containing blood and lymph vessels, secretory pores of the sweat gland and cutaneous nerves. Most investigators consider drug permeating through the skin enter the circulatory system before reaching the hypodermis, although the fatty tissue could serve as a depot of the drug (Shembale, 2010).

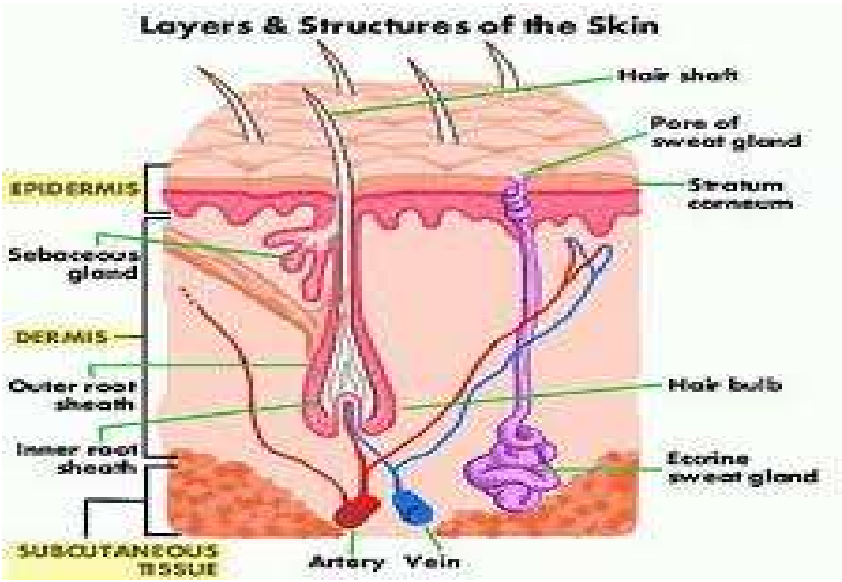

Figure 3:- Structure of human skin [http://www.wikimedia.org/wikipedia/commons/3/34/skin.jpg, (February2011)]

4.1) ABSORPTION OF DRUG:-

Dermal (percutaneous, skin) absorption is describes that the transport of chemicals from the outer surface of the skin to the systemic circulation. This is often divided into:

- **Penetration,** which is the entry of a substance into a particular layer or structure, such as the entrance of a compound into the stratum corneum;
- **Permeation,** which is the penetration through one layer into a second layer that is both functionally and structurally different from the first layer; and
- **Resorption**, which is the uptake of a substance into the skin lymph and local vascular system and in most cases will lead to entry into the systemic circulation (systemic absorption).

Transport of hydrophilic or charged molecules is especially difficult attributable to the lipid-rich nature of the stratum corneum and its low water content; this layer is composed of about 40% lipids, 40% protein, and only 20% water. Transport of lipophilic drug molecules is facilitated by their dissolution into intercellular lipids around the cells of the stratum corneum.. [http://inetce.com/articles/pdf/221-146-04-054-H01.pdf]

Factors influencing Absorption of Drugs

1. Drug release from dosage form
2. Drug concentration in the formulation
3. Drug oil/water partition coefficient
4. Drug affinity to the skin tissue
5. Surface area
6. Site of application
7. Hydration of the skin
8. Nature of the vehicle used
9. Rubbing or inuction
10. Contact period
11. Other factors [Venktasewarlu, (2000)]

Absorption can occur by diffusion via:

i) Transepidermal absorption
   - Transdermal absortion, through the stratum corneum.

ii) Transfollicular absoption (shunt pathway), via the hair follicle, sebaceous and sweat glands.

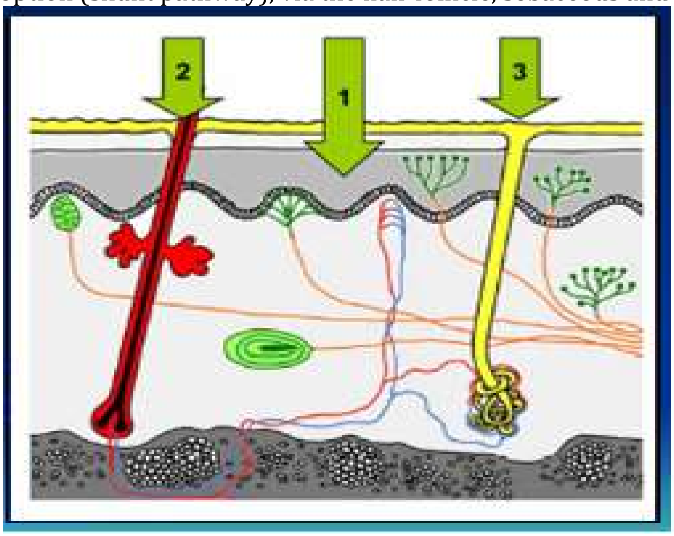

Figure 4:- Pathways of Transdermal Permeation (Stratum corneum, Transfollicular, Sweat gland) [Singh V. July(2009)]

i) Transepidermal absorption:

It is now generally believed the Transepidermal pathway is principally responsible for diffusion across the skin. The main resistance encountered along this pathway in the stratum corneum. Permeation by the Transepidermal route first involves the partitioning into the stratum corneum. Diffusion then takes place across this tissue. The current popular belief is that most substances diffuse across the stratum corneum via the intercellular lipoidal route. In the other extreme of polarity, lipophilic molecules concentrate in and diffuse with relative ease through the horny layer's intercellular region. When a permeating drug exits at the stratum corneum, it enters the wet cell mass of the epidermis and since the epidermis has no direct blood supply, the drug is forced to diffuse across it to reach the vasculature immediately beneath. (Jain, 1997).

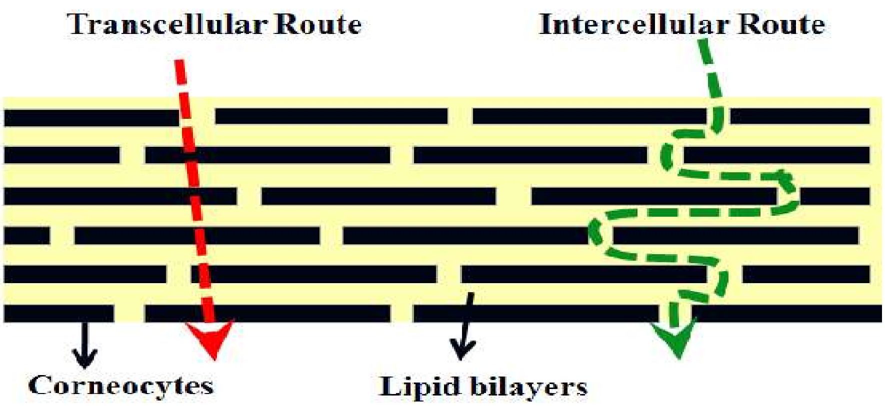

Figure 5:- Routes of Penetration **[Edith, (1999)]**

ii) Transfolicular (shunt pathway) absorption:

The skin's appendages offer only secondary revenues for permeation. Sebaceous and eccrine glands are the only appendages which are seriously considered as shunts bypassing the stratum corneum since these are distributed over the entire body. Drug molecules in contact with the skin surface can penetrate by three potential pathways: through the sweat ducts, via the hair follicles and sebaceous glands (collectively called the shunt or appendageal route) or directly across the stratum corneum. It is proposed that a follicular shunt route was responsible for the presteady state permeation of polar molecules and flux of large polar molecules or ions that have difficulty diffusing across the intact stratum corneum. However it is generally accepted that as the appendages comprise a fractional area for permeation of approximately 0.1% their contribution to steady state flux of most drugs is minimal. This assumption has resulted in the majority of skin penetration enhancement techniques being focused on increasing transport across the stratum corneum rather than via the appendages. **[**Jain,N.K. (1997)]

Methods of Evaluation:-

i) Rheology test
j) Determination of pH
k) Sensitivity test (Patch Test)
l) Photo Patch test.
m) Peroxide Stability test
n) Test for thermal stability
o) Irritancy test
p) Drug Content Uniformity

4.2) MATHMETICAL TREATMENT OF ABSORPTION

The rate of drug transport across the stratum corneum follows Fick's Law of Diffusion. In other words, the rate of drug absorption depends not only on its aqueous solubility, but is also directly proportional to its oil/water partition coefficient, its concentration in the formulation vehicle, and the surface area of the skin to which it is exposed; it is inversely proportional to the thickness of the stratum corneum.

[http://inetce.com/articles/pdf/221-146-04054H01.pdf]

Fick's first law:

$$J = -D\frac{\partial C}{\partial x}$$

J Which states that the flux (rate of transfer per unit area) of a compound (*J*, mass/cm^2 per second) at a given time and position is proportional to the differential concentration change *C* over a differential distance ∂x (i.e. the concentration gradient $\partial C/\partial x$).

The negative sign indicates that the net flux is in the direction of decreasing thermodynamic activity, which can often be represented by the concentration. Fick's second law describing concentration Within a membrane

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2}$$

is derived by combining a differential mass balance in a membrane with Fick's first law and, when considering the skin, assuming that the compound does not bind, the compound is not metabolized, and its diffusion coefficient does not vary with position or composition.

Fick's first law can be applied to describe the diffusion processes in the individual layers of the skin, which are treated as pseudo-homogeneous membranes.

For a membrane of thickness *h*, the flux at steady state (*J*ss) is given by:

$$J_{ss} = D\,(C_1 - C_2)\,/\,h \qquad \text{[Equation 1]}$$

Where C_1 and C_2 are the concentrations of the chemical in the membrane at the two faces (i.e.at x = 0 and x = h). When used to describe heterogeneous membranes like the stratum corneum, D is an effective diffusion coefficient.

Commonly, the stratum corneum controls dermal absorption, h is the thickness of the stratum corneum, and the concentration at $x = h$ is zero or very small (i.e. $C2 = 0$, which is sometimes called sink conditions). Also, the concentration of chemical at $x = 0$ is in local equilibrium with the vehicle (i.e. $C1 = K_m \cdot C_v$, in which K_m is the pseudo-homogeneous partition, or distribution, coefficient between the stratum corneum and the vehicle and C_v is the vehicle concentration).

Under these conditions, Equation 1 becomes:

$$J_{ss} = D \cdot K_m \cdot C_v\,/\,h \qquad \text{[Equation 2]}$$

The steady-state flux across the skin is sometimes written in terms of the permeability coefficient (*K*p) as follows:

$$J_{ss} = K_p \cdot C_v \qquad \text{[Equation 3]}$$

Comparing Equations 2 and 3,

$$K_p = K_m \cdot D / h \qquad \text{[Equation 4]}$$

Note that, although the partition coefficient *K*m is unitless, to be consistent with its use in Fick's law, it is the ratio of concentrations in the stratum corneum and vehicle in units of mass/volume.

Typically, the steady-state flux *J*ss and the permeability coefficient *K*p are assessed from an in vitro experiment in which the donor concentration of the penetrant is maintained (more or less) constant (i.e. infinite dose conditions), while the receiver phase provides "sink" conditions. Over time, the flux approaches a steady-state value (*J*ss), and the cumulative amount penetrating the skin increases linearly in time.

The slope of the linear portion of the graph of the cumulative amount penetrated as a function of time represents the steady-state flux *J*ss. As indicated by Equation 3, *K*p is the ratio of *J*ss and the vehicle concentration *Cv*. The lag time (t_{lag}) is the time intercept of the linear portion of the graph. The time required for the permeation rate across a membrane to reach 95% of the steady-state value is approximately 2.3 times the lag time (96% - 2.4, 97% -2.5, 98%- 2.8, 99% - 3.2)

Thus, estimates of steady-state flux and permeability coefficients should include data only from times greater than the time to reach steady state. Including data for times before the steady state is established will lead to a false estimate, usually underestimate, of the permeability

Coefficient and lag time. In reality, depletion of the donor phase, the use of non-sink receptor conditions, and a deterioration of the skin over time can occur and result in inaccuracies in steady-state flux and lag time estimations.

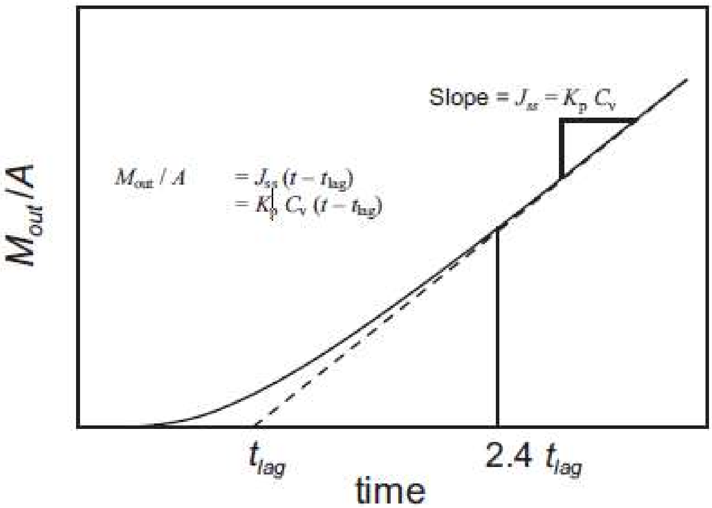

Figure 6:- Illustration of the relationship between the cumulative mass penetrating a membrane area (*M*out/*A*) and the steady-state flux, permeability coefficient, and lag time (*t*lag).

The maximum flux (*J*max,ss) of a solute through a membrane occurs for a pure solid or a saturated solution of a chemical in a vehicle when *C*2 = 0. At equilibrium, a saturated solution of chemical in a vehicle will be in equilibrium with the saturated concentration of solute in the stratum corneum (*S*sc). The maximum flux *J*max,ss is therefore given by Equation 5, which is derived from Equation 1. It is to be noted that *J*max,ss is also related to the permeability coefficient of a solute in a given vehicle *K*p,v and the solubility of the solute in that vehicle *S*v.

$$J_{max,ss} = S_{sc} \cdot D / h = K_{p,v} \cdot S_v \qquad \text{[Equation 5]}$$

In principle, higher than maximum fluxes can be observed in intrinsically unstable systems, such as supersaturated solutions.

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CONFLICT OF INTEREST : Nil
Received : 02.04.2015
Accepted : 30.04.2015

CITATION OF THIS ARTICLE

Sunil Y, Paras P, Sanjay B, Mohit S .Formulation and Evaluation of Ointment and Cream with Their Mathematical Treatment of Absorption Through Skin: A Review. World J. Clin. Pharmacol. Microbiol.Toxicol. Vol 1 [1] 2015. 09-26