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Review Article

DERMATOLOGICAL PREPARATIONS, FORMULATION AND EVALUATION OF VARIOUS SEMI-SOLID DOSAGE FORM

Sharma Sanjeev*, S.P. Singh

Department Of Pharmaceutics, Kota College Of Pharmacy, Rajasthan.

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ABSTRACT:

There are many dosage forms in present era, which also include dermatological preparations or topical product which are applied over skin part for their desire action. Dermatological preparations are manufacture to local action on skin and by pass first pass metabolism. The purpose of this study is preparation, formulation and evaluation of various semi-solid dosage forms like ointment, creams, paste, gels.

Key Words: Dermatological Preparation, Evaluation, Skin, Stratum corneum, Semi-Solid Preparation, Ointment, Creams, Paste, Gels.

INTRODUCTION:

Dermatological preparations constitute a significant proportion of pharmaceutical dosage forms. They serve as carriers for drugs that are topically delivered by way of the skin, cornea, rectal tissue, nasal mucosa, vagina, buccal tissue, urethral membrane, and external ear lining. A wide range of raw materials is available for the preparation of a semisolid dosage form. Apart from the usual pharmaceutical ingredients such as preservatives, antioxidants, and solubilizers, the basic constituents of a Dermatological preparations are unique to its composition the choice of suitable raw materials for a formulation development is made on the basis of the drug delivery requirements and the particular need to impart sufficient emolliency or other medicinal qualities in the formulation. Because of their peculiar theological behavior, semisolids can adhere to the application surface for sufficiently long periods before they are washed off.

This property helps prolong drug delivery at the application site. A semisolid dosage form is advantageous in terms of its easy application, rapid formulation, and ability to topically deliver a wide variety of drug molecules. Semisolid dosage forms usually are intended for localized drug delivery. In the past few years, however, these forms also have been explored for the systemic delivery of various drugs [1].

ANATOMY AND PHYSIOLOGY OF THE SKIN:

- The human skin comprises two distinct but mutually dependent tissues, the stratified, avascular, cellular epidermis and an underlying dermis of connective tissue.
- At the bottom of the dermis lies the fatty, subcutaneous layer which is called hypodermis.
- The epidermis varies in thickness, about 0.8 mm on the palms and soles down to 0.06 mm on the eyelids.
- There are five typical layers (strata). Starting with the outermost layer, they comprise the stratum corneum, stratum lucidum, stratum granulosum, stratum germinativum.

*For Crosspondance:

Sanjeev Sharma

Kota College Of Pharmacy

SP-1, RIICO Industrial Area, Jhalawar Road, Ranpur,
kota, Rajasthan, India.

Mail id: pharmlife54@gmail.com

- In parts of the body other than the palms and soles, only the stratum corneum and stratum germinativum are regularly present.
- In the stratum germinativum, the basal layer is composed of basal cells, which are nucleated, columnar and about 6 μm .
- Mitoses of the basal cells constantly renew the epidermis and this proliferation in healthy skin balances the loss of dead horny cells from the skin surface, thus the thickness of the epidermis remains constant.
- The basal cell layer also includes melanocyte.
- Below the basal cell layer lies the complex dermoepidermal junction, which constitutes an anatomic function unit.
- The stratum lucidum appears only in the palms of the hands and soles of the feet, translucent layer acting as a protective shield against the ultraviolet (UV) rays of the sun and preventing sunburns
- The dermis, at 3 to 5 mm thick, is much wider than the overlying epidermis and it is considered the bulk of the skin, essentially of a matrix of connective tissue woven from fibrous proteins (approximated composition: collagen 75%, elastin 4% and reticulin 0.4%).
- The dermis needs a rich blood supply which regulates temperature and pressure delivers nutrients to the epidermis and removes waste products, mobilizes defense forces, and contributes to skin color.
- Branches from the artery network (the arterial plexus) convey blood to the hair follicles, the sweat glands, the subcutaneous fat, and the dermis itself.
- The blood supply reaches to within 0.2 mm of the skin surface.
- The hypodermis (subcutaneous fat) spreads all over the body as a fibro fatty layer with the exception of the eyelids and of the male genital region [2][3].

DRUG ABSORPTION:

Semisolid dosage forms for dermatological drug therapy are intended to produce desired therapeutic action at specific sites in the epidermal tissue. A drug's ability to penetrate the skin's epidermis, dermis, and subcutaneous fat layers depends on the properties of the drug and the carrier base. Although some drugs are meant primarily for surface action on the skin, the target area for most dermatological disorders lies in the viable epidermis or upper dermis. Hence, a drug's diffusive penetration of the skin, percutaneous absorption is an

important aspect of drug therapy. The main portals of drug entry into the skin are the follicular region, the sweat ducts, or the unbroken stratum corneum between these appendages. A substance's particular route mainly depends on the physicochemical properties of the drug and the condition of the skin [4].

Mechanism of Absorption through Skin Including Mathematical Treatment:

Skin penetration is of great importance, clinically, occupationally as well as environmentally. Chemicals penetrate the stratum corneum by passive diffusion where active transport plays an important role. Chemicals pass the upper skin structures into the viable epidermis and then continue passing through dermis then reaches to dermal-epidermal junction where the blood vessel will transport it to the systemic circulation. A pharmacokinetic model has been made to describe the absorption through the skin. The model is linear & describes the percutaneous absorption using three first order rate constants.



Where,

K_1 – Describes diffusion across the stratum corneum.

K_2 – The transport to the viable epidermis.

K_3 – Reflects the affinity of penetration for stratum corneum vs. viable epidermis.

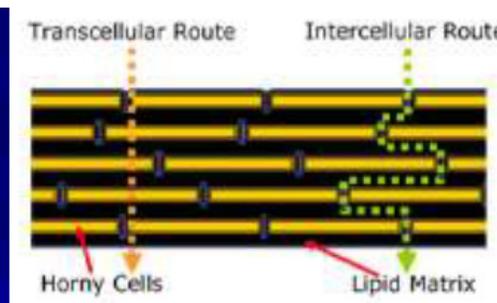
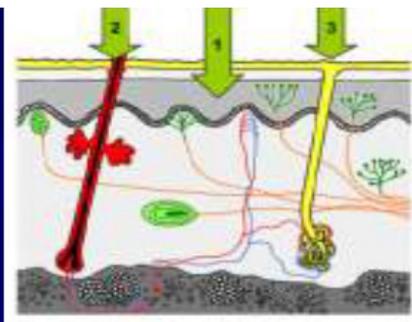
The figure also illustrates the potential for an accumulation of the penetrant in the stratum corneum. The K_3/K_2 ratio provides the effective partition coefficient of the penetrant between the two layers. The permeability coefficient depends on the solute size, lipophilicity & diffusion path length through Fick's law describes the thickness of skin having an influence on penetration indicates that the skin thickness as being the controlling factor in skin penetration. There were indications that the intracellular lipids were important factors in the regulation of epidermis permeability. Later works show that penetration depends more on lipid composition than skin thickness. Even though different sites have the same thickness or lipid content does not mean that they have same penetration rate. For a substance to be transdermally absorbed some key events must take place:

- The substance interacts with the stratum corneum.

- Diffusion of the substance through stratum corneum.
- Crossing from lipophilic stratum corneum to the more aqueous viable epidermis.
- Continuing from the avascular epidermis to the highly perfused dermal tissue.
- Uptake through the microcirculation to the systemic circulation.

Where A Substance Has To Pass Stratum Corneum, It Generally Has Three Pathways:

- **Intercellular**
- **Intracellular**
- **Transappendageal**



-Simplified diagrams showing routes of drug penetration.

(a) Macroroutes of drug penetration (1) across the continuous stratum corneum; (2) through the hair follicles with their associated sebaceous glands or (3) via the sweat duct.

(b) Representation of the stratum corneum membrane, illustrating two possible microroutes for permeation. (1) Intercellular (2) transcellular

The major route being the intercellular pathway implying that stratum corneum lipids play an important barrier function. However for very lipophilic & large molecule the appendages & other diffusion shunts may also play an important role.

$$J = K_p \cdot C_{app}$$

Where,

K_p – Permeability co-efficient = KD/H .

C_{app} – similar to ΔC [5][6].

The Physical Chemistry of Percutaneous Absorption:

There has been little evidence that there are many active processes involved in skin permeation therefore transport process is controlled by simple passive diffusion. Fick's law of diffusion can be used to analyses permeation data & can be simplified to:

$$J = DK \Delta C/H$$

Where

J – Flux per unit area.

D – Diffusion co-efficient in the skin.

K – Skin vehicle partition co-efficient.

C – Concentration difference across the skin.

H – Diffusional path length.

Under normal circumstances the applied concentration is very much larger than the concentration under the skin and equation is simplified to:

FORMULATION AND EVALUATION OF VARIOUS SEMI-SOLID PREPARATION:

OINTMENTS:

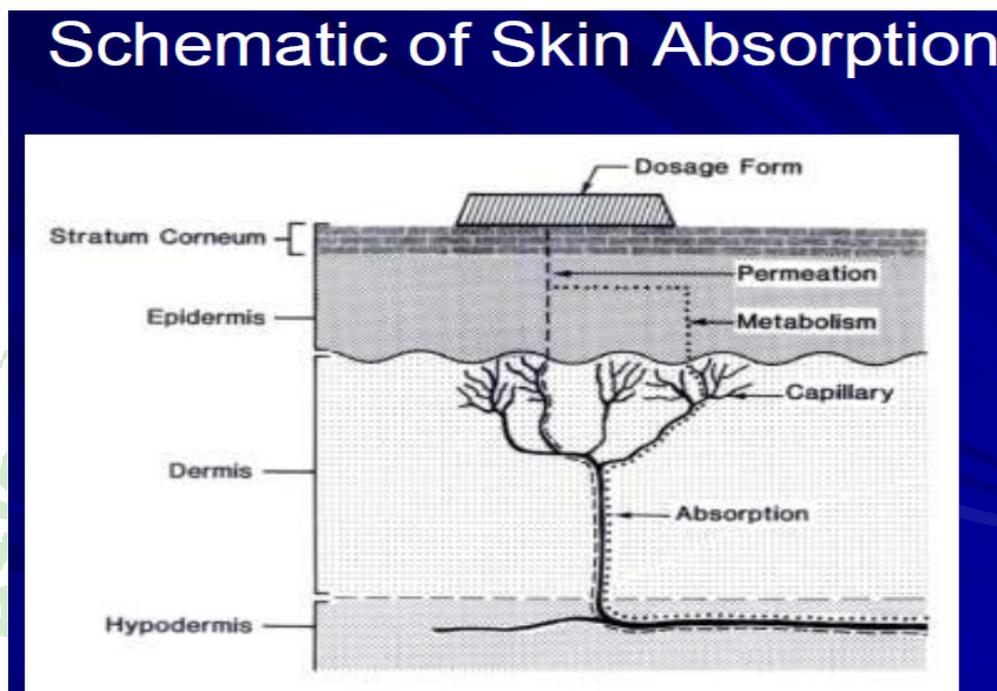
Ointments are semisolid preparation meant for external application to the skin mucus membrane. They usually contain a medicament or medicaments dissolved or suspended or emulsifying in an ointment base. They may contain suitable anti microbial agent, preservatives. The ointments are mainly used as protective or emollient for skin [5].

Mechanism of Drug Penetration/Absorption:

The absorption takes place by percutaneous absorption. Percutaneous absorption of drug generally results from direct penetration of drug through the Stratum corneum, 10-15 μm thick layer of flat, partially desiccated non-living tissue. Stratum corneum is composed of approx. 40 % protein mainly keratin, 40 %

water, with the balance be lipid, principally as tri glycerides, free fatty acid, cholesterol & lipids. Because drugs major route of penetration is through the intercellular channel, the lipid compound is considered an important determinant in 1st step of absorption. Hence through the Stratum corneum drug molecules pass through deeper epidermal tissue & into the dermis. When the drug reaches the vascularised dermal layer, it

becomes available for absorption into general circulation. The Stratum corneum behaves as semi-permeable membrane. The rate of drug movement across the layers depends on the concentration in vehicle, aqueous solubility & partition coefficient between Stratum corneum & vehicle. Substances with good aqueous & lipid solubility are good candidate for diffusion through the Stratum corneum, epidermis and dermis.



CLASSIFICATION OF OINTMENTS:

Ointment Classified According To Properties Based On Penetration:

- *Epidermic Ointments*
- *Endodermic Ointments*
- *Diadermic Ointments*

Ointment Classified According To Therapeutic Uses:

- **Antibiotic ointments**
- **Antifungal ointments**
- **Anti inflammatory ointments**
- **Antipruritic ointments**
- **Astringent ointments**
- **Antieczematous ointments**
- **Kertolytic ointments**
- **Counter-irritant ointments**
- **Ointment used for dandruff treatment**
- **Ointment for psoriasis treatment**
- **Parasiticide ointment**
- **Protectant ointments**

FACTORS AFFECTING PERCUTANEOUS ABSORPTION:

Among the factors playing part in percutaneous absorption are the physical & chemical properties of drug including its most solubility, partition coefficient & dissociation constant .the nature of the carrier vehicle & the skin.

Factor Associated With Skin:

- **Hydration Of The Horny Layer:** The penetration rate of the drug is marked improved if the hydration of the cells is raised by covering the area with the moisture proof plastic filter to prevent perspiration.
- **Thickness Of Horny Layer:** The horny layer is thickest at palms & thinnest on the face; therefore penetration rate varies accordingly. The larger the area of application, more drugs is absorbed. Percutaneous absorption appears to be greater, where the medicament is applied to a site where horny layer is thin and thick.

• **Skin Condition:** The permeability of skin is affected by age, diseases & injury e.g. Absorption occurs rapidly if the dermis is exposed by a wound or burn.

Factors Associated With The Medicament:

Synthetic modifications of the chemical structure of the drug may yield compound with increase potency & or more prolonged or rapid action with fewer or reduced side effects.

- **Solubility:** Both lipid & water solubility is thought to be essential for effective percutaneous absorption. But the aqueous solubility of drug determines the concentration presented to the absorption & partition coefficient influences the rate of transport across the absorption site. Drug generally penetrates the skin in their unionized form. The longer the medicated application is permeated to remain in contact with skin, the greater is the drug absorption.
- **Dissociation Constant:** Since, beyond the barrier layer passage of ions is blocked by electrostatic interactions, deep penetration of the ionic medicament is influenced by its dissociation constant & pH of its surrounding.
- **Particle Size:** Reducing the particle size of the poorly soluble drug in suspension improves the therapeutic activity by increasing dissolution rate & the release from the vehicle. Drug with most between 100-800 adequate aq. & lipid solubility can penetrate the skin.
- **Crystal Structure:** Formulation of a polymorphic drug should prevent changes into forms with physical properties which change into their solubility that is unfavorable for penetration.

Factor Associated With The Vehicle, Vehicle May Enhance The Penetration Of Drug By Following Ways:

- By ensuring good contact with body surface.
- By increasing the degree of hydration of stratum corneum.
- By penetrating the epidermis. Bases miscible with sebum penetrate into region of skin in with sebum is found.
- Alteration of skin permeability (dissolving the medicaments in ethyl or polyethylene glycol alters skin permeability).

PURPOSE OF OINTMENTS:

They act as vehicles for medicinal agent for topical application. They may protect or act emollient to the skin. A few are counterirritants ointments are limited only by number of medicinal that can be incorporated into them.

DESIRABLE QUALITIES IN OINTMENTS:

- Ointments, creams, and pastes must be smooth and never gritty.
- More trituration is necessary in preparing powders put into ointment than powder used in tablets or capsules.
- Ointments, creams and pastes are often applied to broken skin and may be absorbed into the body.
- Spatulas, ointment slabs and all the equipment used to make ointments must immaculate.
- The base in no way adversely affects a wound to which it is applied.
- It is pharmaceutically elegant.
- It does not cause sensitization or irritation, either to unabraded or traumatized skin.
- It is prepared with relatively little difficulty.
- It is neutral (neither acidic nor basic).
- It does not dehydrate the area to which it is applied.
- It is non greasy and non staining.
- It has permanency, good keeping qualities and neither becoming rancid for supporting microbial growth and.
- It is compatible with a wide range of medicinal substances and with other bases with which it is likely to be mixed.
- It releases the incorporated medication effectively to the site of application and if so intended passes through the skin.
- It is washable. Unfortunately, not all ointments, cream, and pastes meet the requirement.

CLASSIFICATION OF OINTMENT BASES:

Ointment bases can be classified according to composition and general characteristics. The ointment base or vehicle may or may not be therapeutically active. It may be used without active ingredients if only protection or emollient properties are desired. Ointment bases fall into one of these classes: oleaginous, absorption, emulsion, or water soluble.

	Oleaginous bases	Absorption bases	Emulsion bases		Water soluble bases
			W/O	O/W	
Solubility in water	Insoluble in water	Insoluble in water	Insoluble in water	Insoluble in water	Soluble in water
washability	Not water washable	Not water washable	Not water washable	Water washable	Water washable
Absorption of water	Not absorb water	Absorb water	May absorb water	Absorb water	Absorb water(to the point of solubility)
Examples	Hard paraffin, Soft paraffin (vasline)	Wool fat Wool alcohol Lanolin Bees wax	Cold creams Emollint Creams	Vanishing Creams, Shaving Creams, Cleansing Creams, Hydrophilic Ointments.	Macrogoals, liquid PEG 200, waxy solid PEG 4000.

OLEAGINOUS OINTMENT BASES:

Oleaginous ointment bases include not only vegetable oil and animal fats but also hydrocarbons derived from petroleum. Because of their nature, oils and fats become rancid and foul smelling on exposure to the atmosphere and to light. Preservatives and anti-oxidants are necessary ingredients in their bases.

Summary of Oleaginous Bases:

Properties:

Not good water absorbers, insoluble in water, not washable, not greasy.

Examples:

Fats and fixed oils such as lard olive oil, cottonseed oil, petrolatum, white ointment.

Petrolatum (Vaseline):

- Petrolatum is tasteless, odorless, yellowish, greasy solid with a melting point between 38°C and 60°C. White petrolatum is decolorized petrolatum.
- It is used more frequently than yellow petrolatum.
- Petrolatum is very stable, very compatible with most substances, and emollient to the skin.
- The consistency can easily be varied by the incorporation of mineral oil or white wax.
- Petrolatum-type ointment bases are more stable than vegetable- or animal-type bases.
- The degree to which they release the incorporated medication is questionable.
- They are absorbing only very small amounts of water, unless treated with cholesterol.

Advantages:

Highly compatible; all but the fats and oils are stable good emollients.

Disadvantages:

Difficult to remove from skin and clothing uncertain as to yield of medicament.

ABSORPTION BASES:

An absorption base absorbs water or aqueous solutions of medicinal. These bases are generally anhydrous (waterless), hydrophilic (water loving) bases.

Constituents:

The most common absorption bases are composed petrolatum mixed with animal sterols such as cholesterol. Aquaphor is a widely used and excellent example of an absorption base.

Summary of Absorption Bases:

We can sum up the absorption bases as follows:

Properties:

Anhydrous; will absorb water; most are not washable.

Example:

Hydrophobic Petrolatum, USP; aquaphor; Anhydrous lanolin, USP.

Jelene (Plastibase):

Jelene, a mixture of hydrocarbons in the liquid and wax ranges has a gel like consistency. It is better than petrolatum in many respects. It maintains its consistency over a wide range of temperature without additives. It releases medication more reliably and provides a better appearing ointment.

Advantages:

Highly compatible; relatively stable to heat, can use in anhydrous form or water can be added emolliency is desired.

Disadvantage: Greasy.**EMULSION BASES:**

Emulsion ointment bases of aqueous phase, oleaginous phase and a emulsifying agent. Emulsion bases may be either oil in water or water in oil usually depending upon the phase in which the emulsifier is more soluble. The phase varies from 10-80% of the completed ointment base.

Preparation:

Emulsion bases are made by melting the greasy and oily materials together in one container and heating the water and water-soluble materials in another container. At the temperature of 75°C, they are mixed together until smooth cream results. While the mixture is still warm and thin. It may be passed through a Homogenizer to improve the appearance and quality of the base. The mixture is then stirred until it congeals.

Summary Of Emulsion Bases:**Properties:**

The w/o emulsion bases are insoluble in water. The o/w emulsion bases are washable and non greasy.

Example:

Lanolin, USP (w/o); Hydrophilic Ointment, USP (o/w); vanishing creams (o/w).

Advantages:

Washable and non greasy if oil-in-water (o/w).

Disadvantages:

Subject to water loss if o/w, greasy, unwashable if (w/o), unless, a preservative is added, the emulsion bases are subject to mold growth.

WATER-SOLUBLE BASES:

The polyethylene glycol polymers or carbowaxes are of great importance in ointments. The names of the carbowaxes include numbersheet roughly indicate their average molecular weight. Carbowaxes with a molecular weight in area 1000 are soft, ointment like substances. As the molecular weight increases, they become harder and they finally become waxes. They are water soluble,

non-volatile and do not deteriorate or support mold growth.

PREPARATION OF OINTMENTS:

Ointments are prepared in the pharmacy by either incorporating the active ingredients into the chosen base or by melting the base and active ingredient (s) together.

The two methods are presented below:

Incorporation Method:**Equipment:**

Most ointments made in the pharmacy are prepared simple incorporation in a mortar either with a pestle or an ointment with a spatula. An ointment slab is a heavy piece of glass with a rough surface on one side to help reduce the size of the solid particles.

Procedure:

Triturate solid ingredients in a mortar until they are very fine. Then, in a mortar or on an ointment slab, make a paste of the powder with an equal amount of base. This is called levigation. Thoroughly mix the paste with another, volume of the base equal to that of the paste. Then continue this routine of mixing equal amounts of the paste and base until the entire base has been added and we have uniform preparation with a very small particle size. A mortar and pestle should be use for incorporating liquids into a base or for preparing larger quantities of an ointment.

Fusion Method:

The fusion method is particularly useful when solid waxes are included in the ointment to add viscosity. In this method first melt the substance with the highest point by using a water bath, but use as little heat as necessary. Then add the other ingredients on the basis of their decreasing melting points. When the entire mixture is liquefied remove it from the water bath. Then stir the mixture until it congeals, to prevent possible separation and crystallization.

DISPENCING OINTMENTS:

Ointments are packed in jars and collapsible tubes. The jars are made of glass that is either green or opaque white. Ordinary tin tubes are convenient to the patient because they are easier to carry and do not break when they dropped. They are especially valuable for

ointments that lose moisture or decompose on exposure to the atmosphere.

Filling Ointment Jars:

Ointment jars, available in many sizes ranging from ¼ ounce to a pound and larger may be filled by packing the ointment into them with a small spatula. In packing the sides and bottom all the way around should be covered first, adding the final portions to the center and the top in order to minimize air pockets. Melted ointment containing no material likely to settle out may be poured into containers while still warm and fluid. In either case, the ointment should be smoothed off at the top before the lid is closed.

Filling Ointment Tubes:

Ointment tubes can be filled by first rolling the ointment into a glassine powder paper to make a cylinder just smaller than the base of the tube. Remove the cap of the tube so that air will not be trapped when the ointment is inserted. Insert the roll, ointment and paper combined, as far into the tube as the roll will go and close it by carefully flattening the end of the tube. Hold the end of the tube closed with firm pressure from the side of a spatula pull the glassine paper out of the tube. The ointment is left in the tube. Fold the end of the tube over twice, crease it tightly, and score it several times with the spatula edge to prevent it from opening during use.

LABELING:

Select a label corresponding in size of the jar being used. Metal ointment tubes should be moistened with tincture of benzoin before the label is applied to help the label adhere. When the label has been put into the place, it should be covered with a strip of cellophane tube. The auxiliary label "For External Use Only" is required on all ointment, paste, and creams [4][6].

THE DIFFERENT METHODS OF EVALUATION OF OINTMENTS ARE:

PHYSICAL METHODS:

- *Test of Rate of Absorption*
- *Test of Non-Irritancy*
- *Test of Rate of Penetration*
- *Test of Rate of Drug Release*

- *Test of Rheological Properties*
- *Test of Content Uniformity*

MICROBIOLOGICAL METHODS:

- *Test of Microbial Content*
- *Test of Preservative Efficacy*

PHYSICAL METHODS:

Test of 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.

Test of Non-Irritancy:

The bases used in the formulation of ointments may cause irritation or allergic reactions. Non-irritancy of the preparation is evaluated by patch test. In this test 24 human volunteers are selected. Definite quantity of ointment is applied under occlusion daily on the back or volar forearm for 21 days. Daily the type of pharmacological action observed is noted. No visible reaction or erythema or intense erythema with edema and vesicular erosion should occur. A good ointment base shows no visible reaction.

Test of 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.

Test of Rate of Drug Release:

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.

Test of 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.

Test of 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.

MICROBIOLOGICAL METHODS:

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.

Test of Preservative Efficacy:

Using pour plate technique the number 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 are counted on 7th, 14th, 21st and 28th days of inoculation. On 14th day, the number of vegetative cells should not be more than 0.1% of initial concentration. On 28th day, the number of organisms should be below or equal to initial concentration [7][8][9][10].

CREAMS

INTRODUCTION:

Creams consist of medicaments dissolved or suspended in water removable or emollient bases. Creams are classified as water-in-oil or oil-in-water therefore, combining immiscible compounds is possible by mechanical agitation or heat. The wet gum, dry gum, bottle, ad beaker methods are employed. More recently, the term has been restricted to products consisting oil-in-water emulsions or aqueous microcrystalline dispersions of long chain fatty acids or alcohols that are water washable and more cosmetically and aesthetically acceptable.

Types:

Most commonly available creams classified on the basis of their function.

- ***Cleansing & Cold Cream Or Lotion***
- ***Vanishing & Foundation Cream***
- ***Night & Massage Cream***
- ***Hand & Body Cream***
- ***All Purpose Cream***

- **Moisturizing Cream**

REASON FOR THE SELECTION OF THE CREAM DOSAGE FORM:

In the treatment of acne, the vehicle may be as important as the active agent. Creams are appropriate for patients with sensitive or dry skin who require a nonirritating, nondrying formulation. Patient with dry skin may complain of a “dry” feel with gels. So the people are performing deal with cream. Patients who have dry skin may be more comfortable with creams, which have a Oily effect. Topical application of the cream at the affected site offer potential advantage of delivery of drug directly to the site of the action. Cream work best in patients with dry skin. Diacerein is used to treat psoriasis. It is used for psoriasis that did not get better after treatment with other medicines.

MATERIALS AND METHOD:

List of Instruments:

- Mettler wt. balance API / Excipients Weighing
- Electronic wt. balance API / Excipients Weighing
- Stirrer For uniform mixing/ dissolution/ dispersion of drug.
- Homogenizer For uniform mixing / dispersion
- pH meter Adjustment of pH
- Brookfield Viscometer To determine consistency of the cream
- Remi centrifuge To centrifuge the formulation
- Sonicator To increase the solubility of drug
- UV spectroscopy Absorbents concentration and standard curve
- HPLC For proper identification of Active ingredients.

List of Materials Used In Preparation of Formulation of Diacerein Cream :

- Diacerein
- Liquid Paraffin
- Cetostrearyl Alcohol
- Methyl Paraben
- Propylparaben
- Glycerin
- Propylene Glycol
- White Bees Wax
- Sodium Meta Bi Sulphate
- Benzyl Alcohol Loba
- Lavendar Oil Loba

FORMULATION DEVELOPMENT OF DIACEREIN CREAM:

Procedure for Preparation of Diacerein:

Melt the white bees wax in a china dish and add liquid paraffin to heat it to a temperature of 70°C. Dissolve the methyl paraben in water and increases the temperature of aqueous solution to 70°C. Formerly we prepare oily part with propylene glycol and glycerol. Propylene glycol used as solvent for dissolving drug (diacerein). Add aqueous part in the oily part and stir it continuously when a creamy emulsion is formed cool it and slowly add perfume at room temperature. Sodium Meta bi sulphate used for pH adjustment to the cream [11].

EVALUATION OF CREAMS:

Due to the use of number of additives, it is necessary to evaluate the effectiveness of skin products. Evaluation is carried out by two methods. They are:

IN-VITRO METHODS:

Tests are carried out to know the performance of the products. These tests also help in evaluating new product concepts. Various instruments have been developed by the investigators to know the effect of temperature and humidity on the skin. Since, the softness of skin is directly related to water content present in it.

Various Techniques Or Instruments Involved In In-Vitro Method Are:

Tensile Strength Tester:

This method is useful for determining the tensile property of the excised stratum corneum of the skin. It provides information on the water content present in stratum corneum and also act as screening device for moisturizing ingredients. The stress or strain characteristics of stratum corneum obtained from various sources can study by using this instrument.

Hargen's Gas Bearing Electro Dynamometer (GBE):

This instrument is helpful in determining and monitoring the viscoelastic behavior of the skin. It also helpful in determining the effects on the skin by passing it through various

treatments. It is used in both as in-vitro and in-vivo test.

Occlusive Potential Of Ingredients:

The occlusive potential of the raw materials or ingredients used in the formulation of skin creams are determining by knowing the water diffusion rate. Membrane used in this method can be stratum corneum of neonatal rat or artificial membrane.

Gravimetric Analytical Method:

This method is helpful in establishing relationship between water content present in stratum corneum and relative humidity. This is done by suspending of callus in different dilutions of sulfuric acid. Then the weight of the sample is determined by using sensitive electro balance. This weight of the sample is taken after it reaches an equilibrium state one week. After this, the water content is determining by subtracting dry weight of the tissue and weight of the sample which has attained equilibrium state. This method is also useful in determining sorption and desorption phenomena which takes place in test stratum corneum passing through various treatments.

Thermal Analytical Method:

Various thermal analytical methods like scanning calorimetry, thermo-mechanical analysis, and thermo gravimetric analysis are used. They are used in order to provide information about the effect of temperature which cause change in stratum corneum.

Electrical Methods:

Various electrical properties such as capacitance and dielectric constant are measured by electrical methods which provide information about the variations in the water content present in the stratum corneum.

IN –VIVO METHODS:

In-vivo methods are helpful in providing information on hydration or moisturization process of the skin.

Transpirometry:

This method helps in measuring Trans Epidermal Water Loss of the skin which helps in providing information on moisturizing potential. In this method skin surface of fore arm is used. To this surface, a collection chamber is attached through which nitrogen of stream of air of known humidity is introduced

.the water vapour leave the surface of the skin and enters into the collection chamber .then the gas present in the chamber carries water vapour to suitable detection devices like dew point, hygrometry, thermal conductivity or gas chromatography. This method is useful in detecting three sources of water i.e., eccrine sweat transepidermal water loss and stratum corneum water desorption and also detect the water supplied by cosmetic products.

Scanning Electron Microscopy:

Skin replicas are used in this method to know the effect of topical preparations on skin conditions i.e., dry and rough skin. Polyethylene beads are melted on the surface in order to get impression on skin on the silicon rubber. This rubber is analyzed under microscope.

Optical Microscopy and Microphotography:

With the help of low magnification photography. Stereomicroscopic tests, biopsies of skin surface and micrographs, the changes in the dry and rough are observed before the after application of moisturizers. They also provide information on moisturizing potential preparations.

Skin Friction:

Damp means slightly wet skin has high friction surface compared to wet and dry skin. Investigation of friction surface shows the effect of hydration on stratum corneum and process of moisturization. Frictional properties are also related to elastic nature of skin and help in evaluating the performance of the product.

Sensitivity Tests:

Day Cumulative Irritancy Patch Test:

In this test the test material is applied daily on the same site i.e. fore arms of 24 subjects under the occlusive tapes. Then scores are recorded daily. This test is carried out until the irritation is produced on the fore arm. The irritation is noted as maximum score. The score ranges from 0-4 where 0 indicates redness of skin due to dilation and congestion of capillaries and 4 indicates edema and vascular erosion.

Draize-Shelanski Repeat-Insult Patch Test:

This test is carried out on 100 individuals to measure to measure the extent of sensitization and irritation caused by the product to a skin. The test material is repeatedly applied on the same site under occlusion for 10 alternate days. After a gap of 7 days, the test material is again applied to a new site for 24 hours. The scores are again recorded after 24 hours and scores ranges from 0-4 [12].

PASTE

INTRODUCTION:

Paste is ointment which contains a high proportion of powder dispersed in a fatty base. Typical powder ingredients include zinc oxide, starch, calcium carbonate, talc, salicylic acid. Pastes are stiffer than parent ointment. Paste may be more successful in absorbing noxious chemicals such as ammonia which bacteria liberate from the urine. Because of their consistency, paste is useful for localizing the action of an irritant or stinging material to circumscribed areas of skin. Paste lay down a thick, unbroken, relatively impermeable film on the skin that can be opaque and act as an efficient sun filter and blocker.

DIFFERENCES BETWEEN PASTES AND OINTMENTS:

- Pastes generally contain a large amount (50%) of finely powdered solids. So they are often stiffer than ointments.
- When applied to the skin pastes adhere well, forming a thick coating protects and soothes inflamed and raw surfaces and minimizes the damage done by scratching in itchy conditions such as chronic eczema. It is comparatively easy to confine pastes to the diseased areas whereas ointments, which are usually less viscous, tend to spread on to healthy skin, and this may result in sensitivity reactions if the preparations contain a powerful medicament such as dithranol.
- Because of the powder contents pastes are porous; hence, perspiration can escape. Since the powders absorb exudates, pastes with hydrocarbon base are less macerating than ointments with a similar base.
- They are less greasy than ointments but since their efficacy depends on maintaining a thick surface layer they are far from attractive cosmetically.
- Most of the pastes are unsuitable for treating scalp conditions because they are difficult to remove from hair.

BASES OF PASTE:

Hydrocarbon Base:

Soft paraffin and liquid paraffin are commonly used bases for the preparation of paste.

- Compound Zinc Paste B.P.
- Compound Zinc & Salicylic acid Paste B.P.
(Lassar's Paste).
- Coal tar paste
- Dithranol paste compound
- Aluminum paste B.P.C.
(Baltimore Paste)

Water Miscible Base:

- Resorcinol & sulfur Paste B.P.C.
- Zinc & Coal tar Paste
- Magnesium sulfate paste B.P.C. (Morison's paste)
- Titanium dioxide paste B.P.C.

Water Soluble Bases:

Water soluble bases are prepared from mixtures of high and low molecular weight polyethylene glycols.

- Water soluble dental pastes

METHODS OF PRAPERATION:

Like ointment, pastes are prepared by triturating and fusion methods. Trituration method is used when the base is liquid or semisolid. Fusion method is used when the base is semisolid and/or solid in nature.

Type of Preparation:

Paste with semi-solid base prepared by fusion and trituration. Zinc oxide and starch powder are passed through No. 180 sieve. Soft paraffin is melted on a water bath. The required amount of powder is taken in a warm mortar, triturated with little melted base until smooth. Gradually rest of the base is added and mixed until cold.

Type of Preparation:

Paste with semi-solid base prepared by fusion.

PROCEDURE:

Method-I:

Emulsifying wax is melted in a tared dish (700C). The coal tar is weighed in the dish. Stirred to mix. Soft paraffin is melted in a separate dish (700C) and about half is added to the tar-wax mixture; stirred well. Remainder is added; stirred again until homogeneous. Allowed to cool at about (300C) and zinc oxide (previously passed through 180 mesh) and starch, in small amount with constant stirring. Stirred until cold.

Method-II:

Wax and paraffin melted together, mixed well and stirred until just setting. Powders are mixed on a slightly warm tile and the tar is incorporated. This method eliminates risk of overheating.

GEL**INTRODUCTION:**

Gels are transparent or translucent, non-greasy, semisolid preparation generally applied externally. They are used for medication, lubrication and some miscellaneous applications.

TYPES OF GELS:**Medicated Gels:**

Water soluble drugs like local anesthetics, spermicides and antiseptics are suitable for incorporation in the gels. They are easy to apply and evaporation of the water content produces a pleasant cooling effect. The medicinal film usually adheres well and gives protection but is easily removed by washing when the treatment is complete e.g. ephedrine sulfate jelly - used to arrest bleeding from nose. Pramoxine HCl, a local anesthetic - relieves discomfort of pruritis and hemorrhoids. Phenyl mercuric nitrate - as spermicidal contraceptive.

Lubricant Gels:

Catheters, items of eletrodiagnostic equipment, such as cyst scopes, and rubber gloves or finger stalls used for rectal and other examinations require lubrication before use. The lubricants must be sterile for articles inserted into sterile regions of the body, such as urinary bladder. For painful investigations a local anesthetic may be included as in Lignocaine.

Patch Testing:

Here the gel is the vehicle for allergens applied to the skin to detect sensitivity. Several allergens may be applied on one person. The viscosity of the jelly and it leaves on drying help to keep the particles separate.

Electrocardiography:

To reduce electrical resistance between the patient's skin and electrodes of the cardiograph, an electrode jelly may be applied. This contains NaCl to provide good conductivity and often pumice powder which, when applied onto the skin, removes part of the horny layer of the epidermis, the main layer of electrical resistance.

FORMULATION:

Pharmaceutical gels are usually prepared by adding a thickening agent such as tragacanth or carboxy methylcellulose (CMC) to an aqueous solution in which drug has been dissolved. The mass is triturated in a mortar until a uniform product is obtained. For the preparation of gels whole gum is preferred rather than powdered gum because the former gives a clear preparation of uniform consistency.

The following gelling agents are used for the preparation of gel.

Tragacanth:

The main hydrophilic component of tragacanth that gels in water has been named bassorin - hence, tragacanth jellies are sometimes called bassorin paste. The amount of gum required for a preparation varies with its use:

- For lubricating jelly 2 to 3%.
- For dermatological vehicles about 5%.
- For incorporation of ichthamol, resorcinol, salicylic acid and other medicaments, about 5% is generally used. All formulations contain alcohol and/or glycerol and/or a volatile oil to disperse the gum and prevent lumpiness when water is added.
- They vary in viscosity, due to the natural origin of the gum and variations in milling and storage.
- The film left on the skin tends to flake.
- Viscosity is rapidly lost outside the pH range of 4.5 to 7.0; for example if benzoic acid is used as the preservative.
- They are susceptible to microbial growth.

Sodium Alginate:**Uses:**

- As lubricant - 1.5 to 2 % is used.
- As dermatological vehicle - 5 to 10 % is used.
- A trace of Ca - salt (CaCl₂) may be added to increase the viscosity and most formulations contain glycerol as a dispersing agent.
- Advantage: Sodium alginate has an advantage over tragacanth that is available in several grade or standardized viscosity.

Pectin:

Pectin is a very good gelling agent and is used in the preparation of many types of gels including edible gels. Glycerin is used as a dispersing agent and humectants in dermatological gels. Gels must be packed in well-closed containers because they lose water rapidly by evaporation and this loss is increased by the susceptibility of pectin gels to syneresis (i.e. exudation of the aqueous phase as a result of contraction of the gel).

Starch:

Starch in combination with gelatin and glycerin is commonly used for preparations of gels. Glycerin in 50% may act as preservative. Medicaments are incorporated in the cold gel by triturating.

Gelatin:

Insoluble in cold water but swell and soften in it. It is soluble in hot water. Hot solution contains 2% gelatin forms a jelly on cooling. Very stiff (15%) gels are melted before used and after cooling to desired temperature are applied with a brush to the affected area. The area is covered with bandage and the dressing may be left in place for several weeks. Zinc-gelatin jelly (Unna's paste).

Cellulose Derivative:

Methyl cellulose and sodium carboxy methyl cellulose produce neutral gels of stable viscosity. Have good resistance against microbial growth. Clear due to freedom from insoluble impurities. Produce strong film after drying on the skin.

Clays:

Gels containing 7 to 20 % of bentonite can be used as dermatological bases.

PRESERVATION OF GELS:

Although some bases like clays and cellulose derivative(s) resist microbial contamination but since all the jellies contain large amount of water, therefore must be suitably preserved. e.g. Methyl paraben 0.1 to 0.2 % is commonly used. Loss of water can quickly lead to skin formation on jellies and to prevent the hygroscopic substances, e.g. glycerol, propylene glycol or sorbitol solution may be added. Bases and medicaments sensitive to heavy metals are sometimes protected by a chelating agent e.g. (EDTA) [13].

EVALUATION OF VARIOUS SEMI-SOLID DOSAGES FORM :

Semi-solid dosages forms are generally evaluated for the following parameters:

Bioavailability and Bioequivalence:

Evaluation of the bioavailability or bioequivalence of dosage forms applied to the skin is generally done for one of three reasons:

- The manufacturer wishes to demonstrate that the dosage form proposed for marketing, and produced on large scale has an acceptable bioavailability when compared the dosage form that was employed in the clinical trials conducted to support the new drug application.
- The manufacturer wish to demonstrate that a proposed will yield product that can be expected to perform identically with the dosage form that is approved through the NDA process.

The effectiveness of semi-solid dosage form, several types of studies may be considered :

- A well controlled clinical trial
- Measurement of pharmacodynamic effect
- Measurement of drug penetration into the skin
- In -vitro methods correlated with a clinical endpoint
- Animal studies

Evaluation Of Physical And Chemical Stability:

Semi-solid systems provide us with two special problems:

- Semi-solids are chemically complex, to a point that just separating drug and adjacent from all other components.
- Semi-solid undergo phase change on heating, one cannot use high temperature kinetic for high stability prediction. Thus stability has to be evaluated at the storage temperature of the formulation, and its take a longtime. Often product yellow or brown with the age as a result of oxidative reactions occurring in base. Change in product pH also indicates chemical decomposition, most probably of a hydrolytic nature. Change in the nature of individual phases or phase separation may results from emulsion breakage, clearly a critical instability. More commonly encountered change in formulation is the evaporative loss of water or other volatile phases from a preparation during storage. This can occur as the result of inappropriate packaging or a flaw made in packaging. Some collapsible tube allows diffusive loss of volatile substances through the container walls.

Evaluation of In-Vitro Skin Permeation:

Determination of Amount Of Drug Deposited Into The Skin:

In-vitro skin permeation method can be used to determine the skin deposition in cases, carrier system and free drug application. In this method the in-vitro drug release study is performed in two stages using diffusion cell at 32°C. In the first stage PBS (pH 6.5) 10 ml is used as the receptor media for a period of 10 hrs and in-vitro permeation is carried out. The second stage uses 50% v/v ethanol as a receptor solution for a further period of 12 hrs and performed without donor phase. During this stage ethanolic receptor will diffuse into skin disrupting the carrier system, which may have penetrated and deposited in tissue and thus releasing both carrier bound and free drug. Use of 50% ethanol as a receptor fluid slightly reduce the barrier nature of the Stratum corneum hence the second stage is performed after removal of the donor to avoid any excess permeation due to enhancing activity of ethanol.

Hairless Mouse Skin:

Hair loss is used predominantly because it is economical, attainable, easy to house and hairless. However, the permeability and lipid composition of hairless mouse skin are very

different to those found in human cadaver skin. Hairless mouse skin tends to be very thin with a small stratum corneum and the permeability of hairless skin in some studies has been found to be 30-40 fold higher than human cadaver skin.

Pig Skin:

Weanling pig skin is recognized as the closest alternative to human cadaver skin in its permeability and lipid composition.

Living Skin Equivalents:

The use of living skin equivalents and epidermal equivalents has become popular for topical/transversal permeation and in-vitro toxicity studies. They consist of dermal and epidermal tissues with the dermis consist from the collagen matrix. Polymeric membrane and other artificial membranes have also been used for topical experiments even through these membrane lack of complex histological structures present in the human skin. The membranes showed higher permeation relative to animal and human skin models.

Evaluation Of Skin Sensitivities:

Draize Test:

In Draize sensitization test, one flank of 20 guinea pig is shaved and 0.05ml of a 0.1% solution of test material in saline, paraffin oil or polyethylene glycol is injected into the anterior flank on day 0. Every other day through day 20, 0.1ml of the test solution injected into a new site the same flank. After a 2 week rest period, the opposite untreated flank is shaved and 0.05ml of test solution is injected into each animal. 20 previously untreated controls are injected at the same side. The test side is visually evaluated 24 hrs and 48 hrs after injection. A larger or more intensely erythematous response than that of controls is considered a positive response.

Evaluation Of Irritation Potential Of Topical Dosages Form:

Draize Type Test:

This test is carried out on 100 individuals to measure to measure the extent of sensitization and irritation caused by the product to a skin. The test material is repeatedly applied on the same site under occlusion for 10 alternate days. After a gap of 7 days, the test material is again applied to a new site for 24 hours. The

scores is again recorded after 24 hours and scores ranges from 0-4.

Non-Draize Animal Studies:

Animal assay to evaluate the ability of chemicals to produce cumulative irritation have been developed. Those assays used often are not as well standardized as Draize-type tests and many variables have been introduced. Repeat application patch tests in which diluted material are applied to the same side each day for 15 to 21 days have been reported using several species. Because the degree of occlusion is an important determinant of percutaneous penetration, the choice of covering materials may determine the sensitivity of given test. A reference material of similar use or one that produces a known effect in humans [14].

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