# CHAPTER I

# INTRODUCTION

Ointments are semisolid preparation intended for application to the skin with or without inunction. They may be oleaginous (e, g., White Ointment); they may be entirely free of oleaginous substances (e.g., Polyethylene Glycol Ointment), or they may be emulsions for fatty or waxlike materials containing relatively high proportions of water (e.g., Hydrophilic Ointment). Besides serving as vehicles for topical application of medicinal substances they also function as lubricating agents (emollients) for the skin and as protectives to prevent contact of the skin surface with aqueous solutions and skin irritants.

A topically applied preparation may produce a physicochemical effect. Almost all medicated and non-medicated topical vehicles influence the skin in one way or another by virtue of their physicochemical properties. Vehicles containing constituents with low boiling points will cool the skin, through evaporation; an occlusive covering such as an oil will warm the skin by preventing normal evaporation of the sweat and retarding radiation of heat; the same type of covering will make the skin more supple due to hydration of dry skin;an organic solvent will make the skin less supple, due to defatting and/or dehydration.

In dermatologic therapy, the vehicle rarely undergoes a specific biochemical reaction with the skin, and physiologic and allergic reactions to the vehicle are rare. However physicochemical changes which depend to a large extent on the vehicle do occur. These changes may be and important part of the over-all action of the therapeutic agent.

## Ideal Base

According to Beeler (26), various authors have described the

ideal ointment base in terms of its physicochemical properties as follows.

1. Stable ;
2. Neutral in reaction ;
3. Nongreasy ;
4. Not degreasing in action
5. Nonirritating ;
6. Nondehydrating ;
7. Nonhygroscopic ;
8. Water removable ;
9. Compatible with all medication ;
10. Free from objectionable odor ;
11. Nonstaining
12. Capable of serving as a medium for medicaments soluble in either fat or water
13. Efficient on dry, oily or moist skins ;
14. Capable of stock preparation for extemporaneous use ;
15. Composed of readily available ingredients of known chemical composition ;
16. Capable of holding at least 50 percent of water
17. Easily compounded by the pharmacist,
18. Melting or softening at body temperature.

An ointment base may posses several of these properties, depending on the type of base and its end-use. For example, an anhydrous absorption base is capable of absorbing a large quantity of water but is not readily removed from the skin with water. It is a stable base, neutral in reaction and non hygroscopic. When a water-containing absorption base is used as a skin emollient, the lack of ease of removal with water is a desirable property, since the base forms an occlusive film on the skin and thus prevents water loss through evaporation. On the other hand, this would be an undesirable property if the ointment were to be used on a hairy region such as the scalp.

Classification of Bases (5,10)

Ointments can be classified best according to type (based on composition) :

I. Oleaginous Ointment Base. Petrolatum and white ointment,which is petrolatum with 5% beeswax, are typical of this class of hydrophobic vehicles. The most commonly used raw material in ointment vehicles is petrolatum because of its consistency, its bland and neutral characteristics, and its ability to spread easily on the skin. These bases are difficult to wash off the skin and may be used as occlusive coverings to inhibit the normal evaporation of moisture from the skin. A thin film of petrolatum produces a sentation of warmth on the skin because the insensible moisture does not evaporate. Very little water can be incorporated into these greasy bases without the addition of - other substances.

2. Absorption Ointment Base. The absorption bases are formed by the addition of substances miscible with hydrocarbons and possessing polar groupings, such as the sulfate, sulfonate, carboxyl, hydroxyl,or an ether linkage, Lanolin, lanolin isolates, cholesterol, lanosterol and other sterols, acetylated sterols, or partial esters of polyhydric alcohols (e.g., sorbitan monostearate or mono-oleate) may be added to make the hydrocarbon bases hydrophilic. The absorption bases are of two types : the anhydrous form and the emulsion form. Anhydrous lanolin and hydrophilic petrolatum are examples of anhydrous vehicles that absorb water to form water-in-oil emulsion.

3. Emulsion Ointment Base

3.1 Emulsion Ointment Base W/O

3.2 Emulsion Ointment Base O/W

Products coming under this classification are also known as hydrophilic or water - removable ointment base. Though it is possible

to incorporate additional water into these preparations, and water removable as used here refers to the ease with which these bases and resulting ointments can removed from the skin and clothing with water. The availability of a number of newer organic compounds for use as wetting agents, dispersing agents, emulsifiers, penetrants, emollients, detergents, hardeners, preservatives, etc., has given a much greater degree of flexibility to ointment formulation.

Hydrophilic Ointment U.S.P. is an emulsified base possessing a relatively high degree of compatibility and therapeutic efficiency as proved by in vitro and in vivo tests.

4. Water-Soluble Ointment Base. Water-soluble vehicles are prepared from mixtures of high and low-molecular-weight polyethylene glycols, which have the general formula; $HOCH_2(CH_2OCH_2)_n\ CH_2OH$. The low-molecular-weight glycols in this category are liquids; those with a moderately higher molecular weight are somewhat unctuous; and the higher molecular weight polyethylene glycols are solids. Suitable combinations of high-and low-molecular-weight polyethylene glycols yield products having ointment-like consistency which soften or melt when applied to the skin. No water is required for their preparation. They are water-soluble because of the presence of many polar groups and ether linkages.

The "water-soluble" base are also known as greaseless ointment bases. The compatibility of this base with drug substances and their release rate must be evaluate for each class of drugs.

Percutaneous Absorption.

Medicaments may penetrate into and through the skin by the following avenues:

1. Between the cells of the stratum corneum.
2. Through the walls of the hair follicles.
3. Through the sweat glands.
4. Through the sebaceous glands.
5. Through the cells of the stratum corneum.

These regions are shown in Fig I.

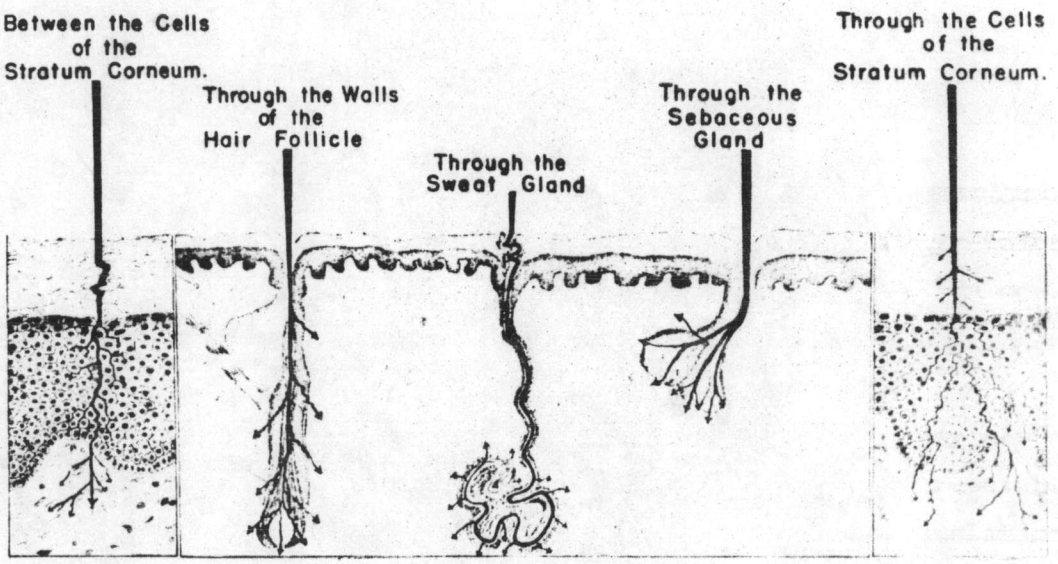


Figure 1 Possible avenues of penetration into and through the unbroken skin

The structure of human skin is very complex. This discussion is limited to the following parts of the skin and their effect on absorption.

Epidermis. The external or outer surface of the skin, the epidermis, is the site of application of medications. The epidermis varies from a thickness of about 1 mm on the palms of the hands and soles of the feet to about 0.1 mm on parts of the face and body. It is covered with a discontinuous surface film of emulsified lipids. This lipid film usually has a pH on the acid side, from about 4.5 to 6.5 depending on the region tested. The epidermis is usually devided into five layers :

1. Stratum corneum (horny layer).
2. Stratum lucidum "barrier zone".
3. Stratum granulosum (granular layer).
4. Stratum mulpighii (prickle cell layer).
5. Stratum germinativum (basal cell layer).

Stratum Corneum. This horny layer is made up of several layers of flattened, keratinized cells which are constantly being replaced by the cornification of the cells moving up from the lower layers. The barrier function of the skin resides almost entirely in the stratum corneum, a thin membranous layer which varies in thickness from 10-15 μ in some parts of the body to a maximum of 600-800 μ on the soles and palms. Its composition is approximately 85% protein, 7-9% lipid (saturated and unsaturated free acids and esters, triglycerides, and cholesterol), and 6-8% of mucopolysaccharides, carbohydrates, mucins, lipo amino acids, etc.

Several investigators have shown that the rate of penetration of variety of liquids applied to the skin surface in vitro were inversely related to the thickness of the epidermis, so that the soles and palms were less permeable than the skin in other parts of the body. (5) Follicle-rich site such as the scalp, the forehead, and the area behind the ear, had a fourfold greater penetration than the forearm, indicating that the skin appendage may be an important parthway for absorption.

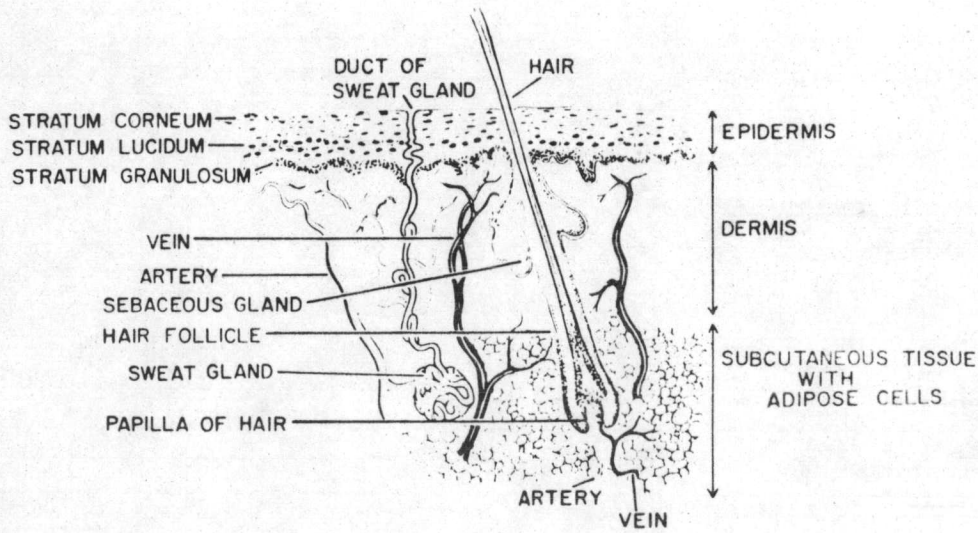


Figure 2 Cross section of human skin

Stratum Lucidum. This is a thin, membrane-like layer which has been called a "barrier zone" since it is reported to act as a barrier to the transport of water across the skin. The sulfur-containing amino acids are probably utilized in this area in the synthesis of keratin. It seems likely that the entire keratin layer provides the skin barrier, with the lower layers of the epidermis offering more resistance to the penetration of medicaments due to the denser packing of the cells in this layer . For most molecules the entire stratum corneum represents the major barrier to penetration.

Stratum Granulosum. This layer actively participates in the keratinization process, although the exact mechanism remain obscure. This layer consists of flattened, coarsely granular cells which started out in the germinal layer as columnar, nucleated cells. As they move toward the surface, the germinal or basal cells start losing their columnar shape and become polyhedral in the lower level of the stratum spinosum and increasingly flattened at the higher levels. The stratum spinosum and stratum germinativum are together called the malpighian layer.

The basal cell layer is the innermost layer of the epidermis and consists of regularly outlined columnar cells which form the imaginary base line separating the epidermis from the corium.The function of the basal cells is to reproduce and to form the layers that constitute the epidermis

Dermis (corium), is 3 to 5 mm thick. Its surface projects into undersurface of epidermis and helps connect the two layers of the skin. The dermis is mainly a network of collagen and elastin fibers which - form a network that is responsible for many of the important properties of the skin. The dermis contains blood vessels, lymph vessels, hair follicles, sebaceous glands, sweat glands, muscle and nerve fibers and pacinian corpuscles. In the uppermost region of the corium there are many conelike ridges, or papillae, which form the papillary layer projecting into the epidermis. The papillary layer con-

tains the nerve endings which are affected by changes of temperature and by the application of local anesthetics, as well as by irritants.

The subcutaneous fatty tissue is a specialized layer of the corium which acts as a cushion and heat insulator.

From classification of ointment, oleaginous ointment base, absorption ointment base, and water soluble base may be defined as suspension-type ointment base.

Suspension-type Ointments. Ointment in which a finely divided medicinal solid is uniformly dispersed. The medicinal compound is the dispersed phase, and the base is the dispersion medium in such that sedimentation does not normally occur; however, if the ointment is exposed to heat, it may soften or liquefy so that sedimentation can occur.

Emulsion-Type Ointments. The emulsion type ointment may be oil-in-water or water-in-oil emulsions. Anionic and nonionic surface- active agent are used as emulsifying agent. The nonionic emulsifying agent are usually nonirritating, tolerant to hard water, and compatible with acidic substances. Emulsion type ointments are cosmetically acceptable to the user as they do not feel greasy, they provide a cooling effect as water evaporated, and they are readily washed from the skin and clothing.

Absorption from Emulsion-type-Ointments. The simplest model consists of an ointment in which the drug is initially dissolved. It is assumed that the diffusion coefficient of the drug is constant in the ointment and that components other than the drug do not diffuse out of the ointment. According to the Fick law of diffusion, q.the amount of drug released at the skin-ointment boundary per unit area of application, is

$$q = h\,Co \left\{ 1 - \frac{8}{\pi^2} \sum_{m=o}^{\alpha} \frac{1}{(2m+1)^2} \cdot \exp\left[ \frac{-D\,(2m+1)^2 \pi^2 t}{4h^2} \right] \right\} \quad -(1)$$

where h is the thickness of the applied layer, Co the initial concentration of the drug in the ointment, D the diffusion coefficient of the drug in the ointment and t the time after application, m is an integer. (9)

In terms of f, fraction of the drug released. The equation (1) may be written

$$f = \frac{q}{h C_o} = \left\{ 1 - \frac{8}{\pi^2} \sum_{m=o}^{\infty} \frac{1}{(2m+1)^2} \exp \left\{ \frac{-D (2m+1)^2 \pi^2 t}{4h^2} \right\} \right\} \quad - (2)$$

If f does not exceed 0.3, the equation (2) is approximately

$$q = 2 Co \sqrt{\frac{Dt}{\pi}} \quad - (3)$$

Absorption from Suspension - Type - Ointments. The amount q released at time t per unit area of application of finely divided solid drug from a homogeneous base, does not follow the Fick law of diffusion and may be expressed as

$$q = (2C - C_s) \sqrt{\frac{Dt}{1 + 2(C - C_s)/C_s}} \quad \text{-------(4)}$$

Where C is the concentration of drug, $C_s$ the solubility of the drug in the ointment, and D the diffusion coefficient of the drug molecule in the dispersion phase

Generally, there are considerably more drug present than required to saturate the dispersion medium, i. e., $C >> C_s$ and the relationship simplified to

$$* q = \sqrt{2CDC_s t} \quad \text{----------(5)}$$

The fraction of the drug released is expressed as

$$f = \frac{q}{hC} = 0.01 \sqrt{\frac{h^2 C^2}{C_s (2C - C_s)} Dt} \quad \text{-----(6)}$$

The amount of drug released from a suspension-type-ointment to a perfect absorber is proportional to the square roots of the amount of drug per unit volume, the diffusion coefficient, the drug solubility and time. In formulating ointments the rate of release can be controlled by regulating these factors. Obviously the concentration of drug can be easily varied. The diffusion coefficient is inversely proportional to the viscosity of the vehicle and may be altered by a change of vehicle. (15)

Factors Affecting Percutaneous Absorption

The absorption of drugs depends primarily on the physiologic state of the skin and the physicochemical properties of the drug and, to a lesser degree, the vehicle in which the drug is incorporated.

1. Skin Condition "Intactness" of the skin is one of the most important factors preventing penetration. Injurious agents such as mustard gas, acids, and alkalies injure barrier cells and increase permeability. When the stratum corneum is damaged, diffusive water loss is increased. In human subjects, 70 - 90% of hydrocortisone - $^{14}C$ penetrates stripped skin sites while only 1-2% was absorbed from areas of normal skin. Pretreatment of the skin with organic solvents has variable effects on permeability. Treatment with ether does not alter the penetration rate of salicylates or surfactants, While the polar solvents acetone, alcohol, and hexane greatly increased the penetration of water into the skin. Excised stratum corneum is virtually "opened" by delipidization of the stratum corneum by holding it in a mixture of a polar and a nonpolar solvent. This procedure removes much of the lipid fraction of the stratum corneum and makes "holes" or artificial shunts in the membrane.

2. Skin Ages. The relationship of age to skin permeability has been rarely investigated. Fetal and infant skin appears more permeable than adult skin. Percutaneous absorption of topical steroids occur more readily in children than adults.

3. Increased Blood Flow. If blood flow through the dermal vessels increases, the rate of clearance of materials should also increases as the concentration decreases. The more rapid removal of material that has penetrated must alter the perfusion gradient across this area.

4. Regional Skin Sites. Anatomical differences in penetration rate may depend largely on differing thickness of the barrier laver . Variations in penetration rates have been demonstrated for full thickness cadaver skin, isolated from different sites, with rates increasing in the following anatomical order : plantar,anterior forearm, instep, scalp and ventral thigh, scrotum, and posterior auricular. These permeation rates may be in direct proportion to the thickness of the area, because the penetration across skin, the flux, is inversely proportional to the thickness. From Fick's law it can be expressed as.

$$\frac{dQ}{dt} = \frac{D\ (PC)\ \Delta\ c}{h}$$

D = Diffusion coefficient of drug in skin barrier

PC = Partition coefficient

h = Thickness of skin barrier

$\Delta c$ = Concentration gradient across the membrane

$$P = \frac{(PC)\ D}{h}$$

P = Permeability coefficient

D = Diffusion coefficient of drug in skin barrier

5. Species Variation. Human and animals display wide differences in physical characteristics such as the number of appendageal openings per unit area and the thickness of the stratum corneum. Furthermore, biochemical differnces between animal and human skin, even when subtle, may significantly alter skin reactions with penetrant chemicals. Species variations of barrier permeability have been noted only in the broadest sense. The skin of common laboratory rodents is more permeable than human skin. The relationship between species is not consistent for different substances, but the average permeability order is rabbit > rat > guineapig > human . (11)

6. Hydration. Hydration of the stratum corneum is among the most important factors in skin penetration, increasing the rate of passage of all substances that penetrate the skin. Hydration results from water diffusing from underlying epidermal layers or from perspiration accumulating after application of an occlusive vehicle or covering on the surface. Under occlusive conditions, the stratum corneum is changed from a tissue that normally contains very little water (5-15%) to one that may contain as much as 50% water. Permeability increases four to fivefold. Further evidence of the importance of hydration can be found in investigations employing occlusive plastic films in steroid therapy. Here the prevention of water loss from the stratum corneum and the subsequent increased water concentration in this skin layer apparently enhance the penetration of the steroid. There is not only a physical alteration of the tissue due to hydration, but at high water activities there are also changes in both the diffusion coefficient and activity coefficients of the penetrating agent. The important thing is the thermodynamic activity of water in the barrier phase, not just the amount there. (11)

7. Temperature. The temperature of the skin plays significant but secondary roles to hydration. Blank and Scheuplein studied the rate of penetration of ethanol and 1 - pentanol within the 0 - 55° range. The flux, or the amount of alcohol penetrating per unit area in unit time, was an exponential function of the temperature. The energies of activation were determined by Arrhenius plots of the log of the permeability constant against the reciprocal of the temperature (11)

8. Drug Concentration. The amount of drug percutaneously absorbed per unit surface area per unit time interval increases as the concentration of the drug in the vehicle is increased. Also, more drug is absorbed per time interval at a constant drug concentration if the drug is applied to a larger, surface area. The duration of contact with the skin as well as the concentration of the penetrant play important roles in skin diffusion. (5,11)

The amount of drug released from such suspension type ointment is not directly proportional to concentration but is proportional to the square roots of the concentration of drug per unit volume (A), drug solubility, ($C_s$) in the vehicle, diffusion constant (D) of the drug molecule in the vehicle, and time (t). The instantaneous rate of absorption at time t is dQ/dt. (5,11)

$$\frac{dQ}{dt} = \sqrt{\frac{A\ D\ C_s}{2\ t}}$$

For these systems, skin properties are not directly important. The drug concentration in the base, the diffusion coefficient of the drug molecule, and the solubility of the drug in the base are the important factors.

9. Drug Solubility Characteristics. The solubility characteristics of a substance greatly influence its ability to penetrate biological membranes. The lipid-water partition coefficient, as postulated in the Meyer - Overton theory, is actually important for the absorption of substances through the skin. These include the thermodynamic activity of the drug in the vehicle and in the skin barrier phase, and the diffusion coefficient of the drug in the vehicle and skin barrier phase. Drugs that are very soluble in a vehicle will probably exhibit slower rates of penetration than those exhibited by drugs which are less soluble in the vehicle. The highest diffusion rates through skin seem to occur with compounds having distribution rates between lipid (or lipid solvent) and water of between 1 and 2. As the lipid solubility increases further the diffusion rate through the skin decreases slowly. (5,11)

10. Molecular Characteristics of Drugs. Molecular features such as size and shape must play a part in penetration. There are few published reports in which permeability coefficients are correlated with a size of penetrating molecules. Small molecules penetrate more rapidly than large molecules, but within a narrow range of molecular size. The effect of polarity was discussed. As polar group are added to the diffusing molecule, force of attraction between these groups and

polar sites within the stratum corneum increase and the diffusibility of the molecule therefore decrease. The polarity is also affected by the pH. The best absorption takes place when the concentration of non-polar molecules is greatest. (11)

11. Vehicles. The primary requirement for topical therapy is that a drug incorporated in a vehicle reach the skin surface at an adequate rate and in sufficient amounts. At one time, the primary factor influencing penetration through the skin was believed to be the vehicle itself. The bulk of evidence now indicates that unless an applied material is capable of passage through either the skin barrier or follicles, the vehicle is only of subsidiary importance. Hence, there are two general approaches to the problem of the development of vehicles that may increase penetration. One is to include agents in the vehicle that affect the barrier function of the epidermis so as to promote penetration of the therapeutic compound. The other is to alter the physical characteristics of the vehicle and thus affect the diffusion of the drug from the vehicle into the skin. For the latter, it is advantageous to choose vehicles that do not bind the incorporated drug too strongly, because the drug has to separate from the base before it enters the cells In vivo and invitro studies have shown that the release of a substance will be favored by the selection of vehicles having a low affinity for the penetrant or in which the drug is least soluble. This finding is consistent with the view that the rate of the release is governed by the vehicle to receptor phase (stratum corneum), partition coefficient. (5,10,11)



12. Penetration Enhancers (additives).The methods of increasing the rate of absorption of topically applied drugs is to add materials that can combine with, or dissolve in, the structures of substances making up the barrier. These agents have come to be known as accelerants. To increase permeability, the accelerant causes the keratin to swell and leaches out essential structural material from the stratum corneum, thus reducing the diffusional resistance and increasing the permeability. The most effective is dimethylsulfoxide (DMSO) followed

by dimethylformamide (DMF), dimethylacetamide (DMA), urea, propyleneglycol, and surface active agents. Another attributes the effectiveness of penetration enhancers to their ability to lower the barrier properties of the stratum corneum by modifying its natural structure. Organic solvents like benzene, alcohol, and ether, which have been shown to enhance the penetration rate of both water-soluble and lipid soluble substances, may act by removing the lipids from the stratum corneum . The mechanism involved is probably hole formation. Surfactants are also used as penetration enhancers. Evidence regarding the influence of detergents and surfactants on epidermal permeability suggests that the effect of surfactants in lowering the surface tension of water is not an important factor in enhancing penetration of the skin even though skin lipids may be removed when the surface tension of water is decreased. The effect of surfactants as penetration enhancers has been attributed to their ability to bind protein, thereby altering the structure of the stratum corneum. (5,10,11,26)

## Statement of Problem

Dexamethasone is a synthetic glucocorticoid. It has been administered by a variety of routes for example, oral, injection, and topical application. A topical application dispensed in the form of ointment has been widely used in skin disease for eczema, allergic diseases such as urticaria, contact dermatitis, drug reactions, bee stings, angioneurotic edema, and anaphylaxis. In occular diseases, corticosteroids are frequently used to suppress inflammation in the eye. (8,18 22) From the stand point of therapeutics one important attribute of an ointment is ability to release its active ingredient. These are two general approaches to formulation problem of maximizing the absorption of active ingredient from the vehicle. One approach is to include an agent that affects the barrier function of the epidermis and the second is to alter the physical characteristics of the vehicle and the diffusion of the drug from the vehicle to the skin. (3) Therefore this investigation is to find out which additives would give the more release

and what concentration would give the greatest effect without lost in stability. The cationic surfactants used as antiseptic may enhance the release of active ingredient.

## Purpose of Study

The purpose of this investigation is (a) to study the effect of various ointment bases on the release of dexamethasone, and also choose the best vehicle for the drug, (b) to evaluate the effect of various additives such as alcohol, water, and surfactants (c) to determine the type and quantity of additives which give the maximum release of dexamethasone.

The results of in vitro method used in this investigation should bring about knowledge of choosing dexamethasone ointment, which give the maximum release of dexamethasone .

## Experimental Procedure

The amount of the release of dexamethasone from various ointment bases i.e., oleagineous base, absorption base, emulsion base, and water soluble base is determined by a spectrophotometric method

The various additives (penetration enhancers or sorption promoters) such as alcohol, water, and surfactants. i.e., cetylpyridinium chloride, benzalkonium chloride, are added to the base in order to obtained maximum release of dexamethasone. The concentration of the additives that gives the maximum release is determined