CHAPTER I

INTRODUCTION

Ointments are soft, semi-solid preparation intended for application to cutaneous tissue with or without inunction. They are used in dermatologic therapy for three purposes(5,6)

1. as lubricating agents (emollients)

2. as vehicles in which to incorporate drugs required to treat skin disorders.

3. as protective coverings to prevent contact of the skin surface with chemicals, aqueous solutions and some organic solvents.

Classification of Ointments.

Ointments are usually classified according to their composition and/or their therapeutic action, based on their degree of penetration on application to the skin.

Based on composition, ointments can be classified as follows (5,6,33)

1. Oleagenous Ointment Base or Hydrocarbon Base : White Ointment U.S.P. XIX.

   1.1 anhydrous

   1.2 nonhydrophilic

1.3 insoluble in water

1.4 not water removable

2. Absorption Ointment Base : Hydrophilic Petrolatum U.S.P.XIX

2.1 anhydrous

2.2 hydrophilic

2.3 insoluble in water

2.4 not water removable

3. Emulsion Ointment Bases

3.1 Emulsion Ointment Base W/O : Rose Water Ointment NF.XIV.

3.1.1 hydrous

3.1.2 hydrophilic

3.1.3 insoluble in water

3.1.4 not water removable

3.1.5 water in oil emulsion

3.2 Emulsion Ointment Base O/W : Hydrophilic Ointment U.S.P. XIX

3.2.1 hydrous

3.2.2 hydrophilic

3.2.3 insoluble in water

3.2.4 water removable

3.2.5 oil in water emulsion.

4. Water Soluble Ointment Base : Polyethylene Glycol

Ointment U.S.P.XIX

4.1 anhydrous

4.2 hydrophilic

4.3 water soluble

4.4 water removable

4.5 greaseless.

Based on their degree of penetration on application to the skin as (5,6,33)

1. Epidermatic Ointments, or those with demonstrate little or no power of penetration into the skin. This group includes the oleagenous and the hydrocarbon bases.

2. Endodermatic Ointments, or those which posses some power of penetration into the skin. Lard, lanolin, and vegetable oils are included in this group.

3. Diadermatic Ointments, or those which penetrate the skin permitting or encouraging systemic absorption of active constituents incorporated in the base. Emulsion type and water soluble bases belonging to this class.

This classification is not sound because absorption can occur from any ointment base depending on the solubility of the medicant, the extent of hydration and the condition of the skin (cut, abraded, eczematous etc.)

Ideal Ointment Bases (33)

Ideal ointment bases in terms of its physicochemical

properties

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 medicaments
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 penetration 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 serveral 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 nonhygroscopic. 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.

Percutaneous Absorption (6,13)

Drugs 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.

It is generally recognized that an ointment base may affect drug penetration by modifying the permeability of the skin barrier phase and by releasing the drug to the skin in adequate amounts at a sufficient rate. A series of physicochemical factors both pertaining to the drug and to the vehicle, appear to be involved in the latter process(7)

In the case of a membrane separating the donor and

receptor phases, the release process may obey two different kinetic laws, depending on the resistance offered by the membrane to drug penetration. The relevant mathematical relationships have been developed and mainly investigated by T. Higuchi (11), W.I. Higuchi (12), and their coworkers. When the membrane offers little resistance to drug penetration (as may occur with injured skin or with some artificial membranes), large concentration gradients develop in the donor phase, and diffusible migration of drug with in the ointment bases constitutes the slowest step in the release process. The following equations derived from Fick's law, have been found to describe the rate of release of drugs from ointment bases under these conditions. (7)

The first equation refers to Emulsion-type ointments (2,7,11,12) (The emulsion type ointments may be oil in water or water in oil emulsions. Anionic and nonionic surfactants 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.)

$$Q = q/A = 2C\sqrt{Dt/\pi} \quad \text{.....(1)}$$

where Q is the amount of drug (q) released to the sink at time t per unit area (A) of contact, D is the diffusion coefficient

of drug in the vehicle, and C is the initial concentration of drug in the vehicle, expressed in units per milliliter.

The second equation refers to Suspension -type ointments (2,7,11,12) (Ointments in which a finely divided medicinal solid is uniformly dispersed. The medicinal compound is the dispersed phase, and the ointment 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).

$$Q = q/A = \sqrt{Dt(2C-C_s)\ C_s} \quad \text{.....(2)}$$

where C is the total drug concentration, and C_s is the solubility of drug in ointment, both values are expressed in units per milliliter.

Equations 1 and 2 predicted that plots of the amounts of drug released with $\sqrt{t}$ will give straight lines passing through the origin. The origin as intercept may not be observed in some cases because of the lag time phenomenon.

The preceding model is based on a series of simplifying assumptions : (7)

1. only a single drug species is important in the base
2. the diffusion coefficient is constant with respect to both times and position in the base.
3. the drug alone is allowed to diffuse out of the base.

4. the drug is rapidly removed upon reaching the base-membrane interface and the receiving phase is a perfect skin.

5. the percent drug released is not too large ($<30\%$) in the case of solutions.

6. C is substantially greater than C_S in the case of suspensions.

The assumption that D must be constant with respect to both time and position is a serious limitation, because in many situation.

Factors Affecting Percutaneous Absorption (13)

The absorption of drugs depends on the physiologic state of the skin and the physicochemical properties of the drug and to vehicles in which the drug is incorporated(6)

1. Skin Condition. Intact skin is one of the most important factors preventing absorption, but injurious skin will increase permeability. Additionally, the polar solvents such as acetone, alcohol, and hexane greatly increased the penetration of water into the skin. Excised stratum corneum is virtually opened by delipidization by holding with mixture of a polar and nonpolar solvents at the lipid fraction of the stratum corneum and makes holes or artificial shunts in the membrane.

2. Skin Ages. Fetal and infant skin appears more permeable than adult skin, so percutaneous absorption of drugs

occur more readily in children than adults.

3. Skin Hydration. Hydration may physically alter the skin tissue and also result in changes both in the diffusion coefficient and activity coefficient of the penetrating medicament, thereby increasing its rate of passage through the skin.

4. Regional Skin Sites. Anatomical differences in penetration rate may depend largely on differing thickness of the layer because of permeation rates were in direct proportion to the area, the penetration across skin, the flux, is inversely proportional to the thickness according to Fick's law (6,13)

$$dq/dt = \frac{(P.C.)(C)DA}{L}$$

where dq/dt is the rate of penetration, P.C. is the partition coefficient, of the penetrant between the vehicle and the barrier of the skin, C is the concentration of the penetrant in the vehicle, D is the diffusion coefficient of drug in skin barrier, A is the area and L is the thickness of skin barrier.

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

6. Species Variation. Human and animals display wide difference in physical, biochemical characteristics such as the

thickness of the stratum corneum, skin reactions with penetrant chemicals. The species variations of barrier permeability have been noted only in the broadest sense, so the relationship between species is not consistent for different substances, but the average permeability order is rabbit > rat > guineapig > human (13)

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. (13)

8. Drug Concentration. Generally, the amount of drug percutaneously absorbed per unit surface area and per unit time interval increases as the concentration of the drug in the vehicle is increased. But the amount of drug released from system of 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. (6)

$$dQ/dt = \sqrt{\frac{ADC_s}{2t}}$$

9. Drug Solubility Characteristics. The lipid/water partition coefficient, as postulated in the Mayer-Overton theory, is actually important for the absorption of substances through the skin. This 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 rate of diffusion through the skin has a comparatively minute value when the compound under study is soluble almost solely in water but increases rapidly as the partition coefficient (between lipid, or lipid solvent, and water) approaches unity. The highest diffusion rates through skin seem to occur with compounds having distribution ratio between lipid(or lipid solvent) and water of between 1 and 2. As the lipid solubility increases further, the diffusion rate through the skin decrease slowly.(13)

10. Molecular Characteristics of Drugs. Such as size and shape must play a part in penetration. Small molecules penetrate more rapidly than large ones, but within a narrow range of molecular size. About polarity, 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 best absorption takes place when the concentration of nonpolar molecule is greatest (9,13)

11. Vehicles. Ointment bases have been classified according to their supposed effect on the penetration of medicaments through the skin. Using the antiwhealing effect as a criterion for absorption of pyribenzamine hydrochloride from various vehicles, it was found that the best results were obtained with water miscible emulsion base. Thus far, the physicochemical properties of the vehicle have been considered in relation to their influence on percutaneous absorption. Formerly, the primary factor influencing penetration through the skin was believed to be the vehicle itself. But now it is indicated that unless an applied material is capable of passage through either the skin barrier or follicles, the vehicle is only of subsidiary importamce. 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 which affect the barrier function of the epidermis so as to promote penetration of the medicament. The other is to alter the physical characteristics of the vehicle and thus affect the diffusion of drug from the vehicle into the skin. For the latter, it is advantageous to select vehicles which do not bind the incorporated drug too strongly, because the drug has to separate from the vehicle before it enters the cells. In vivo and in vitro studies have shown that the release of a

substance will be favored by the selection of vehicles havings 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(3,4,14)

12. Penetration Enhancers. These agents have a direct effect on the permeability of the skin barrier. Some materials may act by a direct chemical insult on the skin, while others may affect the solubility and/or dispersibility of the medicament and/or its delivery system (the vehicles). The most effective is dimethysulfoxide(DMSO). followed by dimethylformamide(DMF), dimethylacetamide(DMA), urea, propylene glycol. Organic solvents like benzene, alcohol and ether have also enhanced the penetration rate of both water soluble and lipid soluble substances which act by removing the lipids from the stratum corneum. The mechanism involved is probably hole formation. However, the action of hydrogen bonding solvents like DMSO, is attributed to membrane expansion and uniform increase in media diffusivity. 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, then increasing skin permeability. (6,10,15,18,23,24)

Statement of Problem.

Successful formulation of ointments is determined by completeness of the release of active ingredients from ointment bases used and subsequent percutaneous absorption of the released ingredient. In general, this release depends upon types of the ointment bases as well as properties of the active ingredient. Moreover, incorporation of some substances into the formula may facilitate the release. Therefore, this study was aimed to search for an ideal ointment base for the active ingredient hexamidine, and to identify species and quantity of cationic surfactants which when added into the formula would facilitate the maximum release of hexamidine without loosing in stability of the formula.

Purpose of Study.

The purpose of this study is to investigate the effects of different ointment bases upon the release of hexamidine, and also to study the effect of cationic surfactants which would facilitate the maximum release of hexamidine.

Experiment Procedure.

Used the diffusion technique which developed by Bottari, F., et al (1974). The amount of hexamidine released from different ointment bases (Hydrophilic ointment, Hydrophilic petrolatum, Polyethylene glycol ointment, White ointment) was determined by spectrophotometer at 265 nm.

The various cationic surfactants(Benzalkonium chloride 1:1000, Cetrimide 1:1000, Cetylpyridinium chloride 1:1000) were added to hexamidine ointment (with best ointment base). The species and quantity of the cationic surfactants that give the maximum release of hexamidine were determined.