CHAPTER - FIVE

EFFECT OF ADDITIVES ON SULPHACETAMIDE OINTMENTS

CHAPTER - 5

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RESUME

Five different formulations of sulphacetamide sodium ointment was prepared using different ointment bases. Formulation II, showed certain degree of stiffness when applied on to the skin. The other formulations namely Formulation I, III, IV, and V, showed good spreadability characteristics. There was no visible signs of irritancy from any of the formulations. Rank correlation with respect to release rate studies are Formulation V > Formulation II > Formulation IV >Formulation I > Formulation III.

INTRODUCTION

The vehicle or bases provide convenient means of maintaining the drug at or close to the topical absorption site. It is doubtful if vehicles used for dermatological preparation can promote the absorption of drugs that are not themselves absorbable, but the composition of the vehicle can markedly affect the release and absorption of absorbable drugs(50).

The vehicle controls the drug activity, the rate of diffusion in the vehicles and partition coefficient between the vehicle and skin. A high affinity of the bases for the drugs is not desirable. Drugs that complex or bind to components of the vehicle are released into the skin very slowly. Release of the drug is favoured by using a vehicle that is a poor solvent for the drug. A high stratum corneum - vehicle partition coefficient encourages the process of transfer of drug into the epidermis. The partition coefficient may be altered by including various solvents (such as alcohol and propylene glycol) in the vehicle. Hydrocarbon ointment vehicles have an occlusive action on the skin, but emulsion bases are less occlusive. Insoluble powders such as zinc oxide reduce the occlusive properties by their uptake of water and by providing a large surface area for evaporation(104).

It has been shown that emulsion type bases have an effect on the degree of percutaneous absorption from results noted in studies of

ointment vehicles containing sulfonamides(108). There are two general approaches to the development of vehicles that may increase penetration. Once is to include agents into the vehicle that affect the barrier function of the epidermis so as to promote the peneteration of the therapuetic compound(107). The other is to alter the physical characteristics of the vehicle and thus effect the diffusion of the drug from the vehicle into the skin(108). It was pointed out that thermodynamic considerations can help explain varied results with sulfanilamide used as tracers in dermatalogical research. The activity coefficient of these tracers and their thermodynamic activities at a given concentration in the various vehicles would be expected to vary widely just on the basis of the nature of the vehicles and tracers employed in these studies(110).

Although the various factors that influence percutaneous absorption of drugs are becoming better understood, it is not yet possible to select the best vehicle for a drug solely from a knowledge of their respective physicochemical properties. The vehicle is chosen on the basis of practical experience with selected formulations using a quantitative or semiquantitative measurements of drug peneteration.

EXPERIMENTAL

Materials :

Sulphacetamide Sodium (I.P.), Liquid Paraffin (I.P.), Yellow Soft Paraffin (I.P.), Methyl Paraben (I.P.), Propyl Paraben (I.P.), PEG 4000 (B.P.), PEG 400 (B.P.), Paraffin Wax (I.P.), White Petroleum Jelly (I.P.), Anhydrous Lanolin (I.P.), White Petrolatum (I.P.), Anhydrous Lanolin (I.P.), White Petrolatum (I.P.), Stearyl Alcohol (B.P.), Propylene Glycol (I.P.), Sodium Lauryl Sulphate (I.P.).

Equipment :

Mortar and pestle, temperature controlled Oven, Baush and Lomb, Spectronic 20 - Spectrophotometer. Sartorius dissolution and absorption Simulator SM 15703, Artificial Epidermis Barrier Kit. SM 16754. Ointment chamber for absorption simulator.

Formulation :

General preparation method of ointments :

Large and small scale production of ointments are either prepared by the method of Incorporation or Fusion.

Incorporation :

Components are mixed together by various means until a uniform preparation has been attained (a) Mortar and Pestle (b) May employ a spatule and an ointment slab (a large glass or porcelain plate) to rub the ingredients together. Generally the ointment bases is placed on one side of the working surface and the powder components, previously reduced to fine powders and thoroughly blended in a mortar on the other side. Then a portion of the powder is mixed with a portion of the base until uniform and the process is repeated until all portions of the powder and base are combined and thoroughly blended.

Fusion :

All or some of the components of an ointment are combined by being melted together and cooled with constant stirring until congealed. Those components not melted are generally added to the congealing

mixture as it is being cooled and stirred. Insoluble powders generally levigatid with a portion of the base.

On small scale fusion process may be conducted in a porcelain dish or glass beaker. Once congealed, the ointment may be rubbed in a mortar to ensure uniform texture.

Many medicated ointment bases containing such components as beeswax, paraffin, stearyl alcohol and high molicular weight P.E.G. which do not lend themselves well to mixture by incorporation are prepared by fusion. In preparing an ointment with these types of materials by fusion, it is generally found that the melting points of the individual component are quite varied, therefore the temperature required to achieve fusion may also vary from formula to formula. In a given formula, if the item having the highest melting point is melted first and the other components are added to this hot liquid, all of the components will be subjected to high temperature. Therefore, melting all of the components together very slowly a lower temperature is usually sufficient to achieve fusion. This is apparently due to the solvent action exerted by the first melted component on the other component and if the process is allowed to proceed by using only slowly rising temperatures, the fusion process does not generally require to melt the individual component having the highest melting point. Chemical antimicrobial preservative to inhibit the growth of contaminating micro organisms are added here namely methyl

paraben and propyl paraben. The ingredients for formulation I is listed in Table-20.

FORMULATION I :

Method :

Melt yellow soft Paraffin. Add liquid paraffin Filter the hot mixture through a coarse filter paper, placed in a heated funnel. Sterilize by dry heat. The base is allowed to coal. Sulphacetamide Sodium is triturated with small portion of melted base until mixture is smooth. Gradually add the remainder of the melted base and continue trituration until the onitment is cool.

The ingredients for Formulation II is listed in Table-21.

FORMULATION II :

Method :

Heat PEG 4000, and PEG 400 on a water bath to 65°C. Allow to cool and stir until congealed. The drug is then triturated with small portion of the melted base until mixture is smooth. Gradually add the remainder of the melted base and continue trituration until an ointment is formed.

TABLE - 20

FORMULATION I

Ingredients	Quantity
Sulphacetamide Sodium	5%
Liquid Paraffin	9.5 g
Yellow Soft Paraffin	85.5 g
Methyl Paraben	0.025%
Propyl Paraben	0.015%

TABLE - 21

FORMULATION II

Ingredients	Quantity
Sulphacetamide Sodium	5%
PEG 4000	37.0 g
PEG 400	58.0 g
Methyl Paraben	0.025%
Propyl Paraben	0.015%

The ingredients for Formulation III is listed in Table-22.

FORMULATION III :

Method :

Melt the white wax in a suitable dish on a water bath, add the white petrolatum warm until liquified. Then discontinue heating and stir the mixture, until it begins to congeal. Triturate the drug with small portion of melted base until mixture is smooth. Gradually add the remainder of the melted base and continue trituration until the ointment is cool.

The ingredients for Formulation IV is listed in Table-23.

FORMULATION IV :

Method :

Melt together the anhydrous landlin and the yellow soft paraffin. Add liqud paraffin, filter the hot mixture through a coarse filter paper placed in a heated funnel and allow to cool. Triturate the drug with small portion of melted base until mixture is smooth. Gradually add the remainder of the melted base and continue trituration until the ointment is cool.

TABLE - 22

FORMULATION III

Ingredients	Quantity
Sulphacetamide Sodium	5%
Paraffin Wax	2.0 g
White Petroleum Jelly	93.0 g
Methyl Paraben	0.025%
Propyl Paraben	0.015%

TABLE - 23

FORMULATION IV

Ingredients	Quantity
Sulphacetamide Sodium	5%
Liquid Paraffin	9.0 g
Yellow Soft Paraffin	77.0 g
Anhydrous Landlin	9.0 g
Methyl Paraben	0.025%
Propyl Paraben	0.015%

The ingredients for Formulation V is listed in Table-24.

FORMULATION V :

Method :

Melt the stearyl alcohol and the white petrolatum on a steam bath and warm to about 75°C. Add the other ingredients previously dissolved in water and warmed to 75°C. Stir the mixture until it congeals.

Ointment Properties :

Formulations were checked for the following quality control measures :

(a) Leak test
(b) Spreadability with check on particle
(c) Content Assay
(d) Release rate from bases

(a) **Leak Test :**

Select 10 tubes of the ointment, with seals applied. Thoroughly clean and dry the exterior surfaces of each tube with an absorbent cloth. Place the tubes in a horizontal position on

TABLE - 24

FORMULATION V

Ingredients	Quantity
Sulphacetamide Sodium	5%
White Petrolatum	25.0 g
Stearyl alcohol	25.0 g
Propylene glycol	12.0 g
Sodium lauryl sulphate	1.0 g
Purified Water	32.0 g
Methyl Paraben	0.025%
Propyl Paraben	0.015%

a sheet of absorbent blotting paper in an oven maintained at a temperature of 60 ± 3°C for 8 hours.

(b) **Spreadability with check on particle :**

Test material was applied on to the skin for check on spreadability and irritancy. The extruded contents of tubes of ointments previously melted in flat bottom petridishes and then allowed to solidify, are scanned under a low - power microscope fitted with a micrometer eyepiece. The requirement are met if the total number of particles in all 10 tubes does not exceed 50 and if not more than 1 tube is found to contain 8 such particles(23).

(c) **Content Assay :**

Preparation of standard. Weigh 50 mg of sulphacetamide sodium and dissolve in 50 ml of distill water. Take 5 ml and dilute it to 200 ml with water. From this take 2 ml for colour development.

Preparation of Sample :

Transfer 1 gm of the sample to a separating funnel. Add 20 ml each of distill water and Ether and shake well. Collect the aqueous layer

and add another 20 ml of water and repeat. Finally make up the volume to 50 ml. Take out 5 ml from this and dilute it to 200 ml with water. From this take 2 ml for colour development.

Colour Development :

To 2 ml of the sample add 0.5 ml of 4 M HCl and 1 ml of 0.1% sodium nitrite. Allow the mixture to stand for 2 min. Add 1 ml of 0.5% W/V ammonium sulphamate. Allow to stand for 15 min. Then add 1 ml of 0.1% solution of N (1-napthyl) Ethylene diamine dihydrochloride. Allow the mixture to stand for 10 min. for complete colour development. Add water to make up the volume to 25 ml.

Blank :

2 ml of water is treated as per the assay.

Finally read the absorbances of standard solution and sample solution at 538 nm against a reagent blank.

Release Rate from Bases :

The release rate studies for sulphacetamide sodium ointment was carried out in vitro using sartorius ointment liberation chamber.

Instruction for the preparation of an artificial double layer membrane :

The artificial double layer membrane for the sartorius ointment liberation chamber consists of a

(a) barrier foil, soaked in water until swollen
(b) membrane filter, type RS, lipid impregnated which are pressed together(11).

Place the swollen barrier foil side (hydrophillic) of the prepared membrane directly onto the ointment in the ointment liberation chamber.

Preparation of the 2 layers of the membrane :

(a) **Barrier Foil :**

Soak foil in distilled water for at least 1 hour and let it completely swell.

(b) **Membrane filter type RS :**

Weigh in 4 g of component N, heated up to approx. 40°C into a petridish.

Determine the weight of the membrane filter and place it into the warm liquid until it becomes completely transparent. Let the membrane drip off and press it slightly with a hand roller between two layers of blotter paper. Repeat this procedure with two fresh blotter pads. Weigh membrane filter to check weight increase. The weight increase should be 90-105% of the filter weight. To prevent congealing, component N from, store lipohil membrane at temperature above 24°C until pressing the two layers of membrane together.

Combine the two layers of the membrane immediately after preparation as follows :

Dry swollen barrier foil (a) with hand roller under slight pressure between two sheets of blotted paper and combine it instantly with the lipohil membrane, (b) just prepared. Place both membrane layers concentrically onto each other and press them with a hand roller between two layers of blotter paper. Insert double layer membrane directly into the liberation chamber with the hydrophillic side (a) on the ointment. This unit is fitted to the Sartorius Absorption Simulator mentioned in Chapter II. Start test immediately. 100 ml of the medium is pipetted into each of the containers of the sartorius absorption simulator. The temperature is maintained at 37°C. After appropriate tube connections are made 1 gm of the ointment is weighed into the sample holder. The sample was moistened to induce hydration. The prepared barrier was placed covering the sample box. The other

half of the chamber was fitted and media was allowed to circulate. Samples were withdrawn at 30 minute intervals and release rate was studies over a period of 3 hours. The samples were analyzed spectrophotometrically at 538 nm.

RESULTS AND DISCUSSION

Sulphacetamide ointments, when subjected to leak test no significant leakage occured during or at the completion of the test in any of the formulations.

Except for Formulation II which showed a certain degree of stiffness when applied on to the skin, the other formulations showed in Tables 20, 22, 23, 24 have general good spreadability characteristics. No visible reaction was seen with regard to irritancy from any of the formulations. Each of the formulations showed to contain 5% of sulphacetamide sodium as indicated in Table 25. The assay method followed the diazotization of the aromatic amino group after acid hydrolysis and coupling with dimethyl alphanapthylamine or the Bratton and Marshall reagent(75).

Release rate from Formulation V is far more better than from soft paraffin Formulation (I) simple ointment Formulation (III) and absorption ointment Formulation (IV). Formulation V is an hydrophillic ointment. It shows 34% release within 3 hours as per Table 26, Fig.19. It has an emulsion base. Stearyl alcohol and petrolatum comprise an oil phase which renders proper smoothness and comfort to the skin. Stearyl alcohol serves as an adjuvant emulsifier. Petrolatum in the oil phase also contributes to the water holding ability of the overall formulation. Propylene glycol serves as a

TABLE - 25

CONTENT OF SULPHACETAMIDE SODIUM
IN DIFFERENT OINTMENT FORMULATIONS

Formulation	Standard O.D.	Sample O.D.	Content (mg)/5g
I	0.5	0.510	255.0
II	0.5	0.525	262.5
III	0.5	0.515	257.5
IV	0.5	0.510	255.0
V	0.5	0.520	260.0

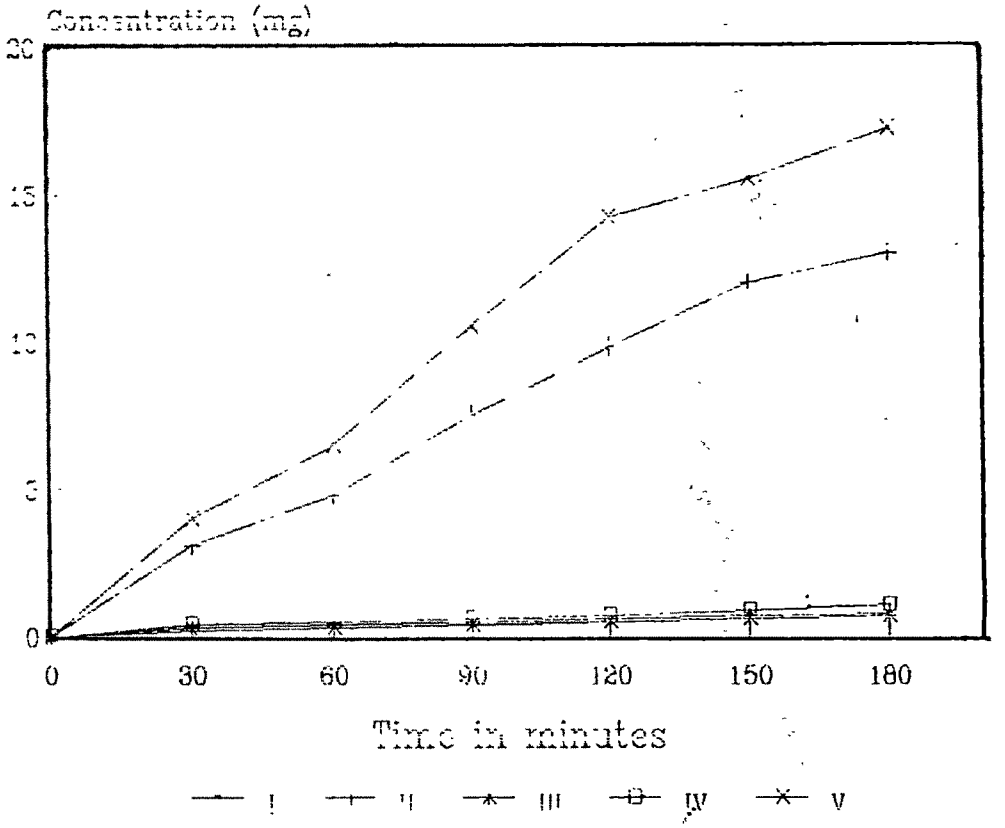
TABLE - 26

RELEASE RATE PROFILE OF SULPHACETAMIDE SODIUM OINTMENT

Formulation	Concentration (mg)					
	Time					
	½ hour	1 hour	1½ hour	2 hour	2½ hour	3 hour
I	0.20	0.31	0.42	0.53	0.58	0.63
II	3.12	4.75	7.52	9.70	11.91	13.07
III	0.10	0.15	0.20	0.26	0.29	0.29
IV	0.31	0.42	0.55	0.69	0.89	1.10
V	4.06	6.60	10.40	14.20	15.40	17.40

Fig. 19

Release rate of Sulphacetamide sodium from different ointment bases



humectant to minimise water loss in the finished composition. It can also fountion as preservative to some extent. Formulation II which is a water soluble phase shows 26% release within 3 hours. Formulation IV shows better release (2%) when compared to Formulation (I) - 1%. This is mainly due to the presence of anhydrous lanolin incorporated in the base. The release rate is only 0.5% from Formulation III which is a hydrocarbon base.