

AN ABSTRACT OF THE THESIS OF

NORMAN FREDRICK BILLUPS for the Doctor of Philosophy in
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Title PREPARATION AND PROPERTIES OF BENTONE[®] OINTMENT BASES

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Abstract approved _____
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A study has been made of ointment bases prepared from mineral oil thickened with Bentone 38 gellant.

The experimental work was divided into two distinct parts: (1) the development of ointment bases using the Bentone gellants, and (2) subsequent comparison of these bases with White Petrolatum, Plastibase Hydrophilic, and other bases in common use.

Three different hydrophilic, water-absorbing ointment bases were prepared from Bentone 38 gellant and mineral oil. Two of the bases were W/O emulsion bases. The third was an anhydrous or "grease type" base.

In evaluating these bases, experimental data are presented for: (1) physical and chemical stability, (2) body

and consistency, (3) drug release properties, and (4) handling and manufacturing characteristics.

PREPARATION AND PROPERTIES
OF BENTONE[®] OINTMENT BASES

by

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DEDICATION

This work is dedicated to my wife, Shirley, for her continuous encouragement during the preparation of this manuscript. Her patience, understanding and ability to make sacrifices have made this thesis possible.

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STATEMENT OF PROBLEM

It has been shown in the lubrication industry that gelled oils have certain advantages over both natural petroleum and soap-base greases (49, p.11). Among these advantages are: (1) greater resistance to viscosity change with changes in temperature, (2) better spreadability (pumpability) at lower temperatures, (3) better lubricating and adhesive characteristics under excessive heat, (4) more oxidation resistance, (5) superior mechanical and chemical stability, (6) less tendency to bleed, (7) increased adherence to metallic and other surfaces, (8) greater resistance to the washing action of water, and (9) ability to take up water by absorption or emulsification without loss of consistency.

Among the few substances which have been developed to gel oils are the organic derivatives of bentonite, known as Bentones[®].

The purpose of this thesis is: (1) to formulate ointment bases with Bentones[®], (2) to compare these bases with other bases in common use, and (3) to determine whether any of the above mentioned advantages in lubricating greases,

or any other advantages, also apply to pharmaceutical ointment bases.

Among the criteria for the evaluation of the experimental bases would be: (1) physical and chemical stability, (2) body and consistency, (3) drug-release properties, and (4) handling and manufacturing characteristics.

INTRODUCTION

HISTORICAL

The original concept of ointments included only mixtures of fatty substances, and references to the use of such preparations for the treatment of skin conditions are found in early Egyptian, Roman and Grecian writings (44, p.101). The fat of animals and man (and mixtures of such fats with powdered herbs, waxes, resins and minerals) were among the earliest drugs employed by man (45, p.407). The fat of animals, as well as that of man, was believed to have some special power.

In addition to fats, other dermatological vehicles were used in ancient Babylon-Assyria and Egypt. Honey, gums, resins, and waxes were among the early vehicles employed for medicinal purposes. Balsams and mucilages from various plant sources were frequently mixed with oils and waxes to form the ointments of the day. The trend to use such substances persisted through most of the eighteenth century.

By the turn of the nineteenth century, however, scientific study stimulated new ideas and many new ointment bases were developed. Lard was used in the early 1800's and became the chief ingredient in the first official

ointment which appeared in the first edition of the Pharmacopeia of the United States (U.S.P.) in 1820. Benzoinated Lard, a product possessing a pleasant odor and stimulating and antiseptic properties, replaced lard because of its stability and resistance to rancidity. In 1858 Schacht introduced glycerite of starch as a new ointment base (45, p. 407). In 1873 Miller introduced petrolatum under the name of "Cosmoline", as still another ointment base (45, p.407). Both of these products were included in the Sixth Revision of the U.S.P. in 1880. The rediscovery of lanolin, in 1885, by Liebrich, brought official recognition of Adeps Lanae Hydrous (lanolin) in the Seventh Revision of the U.S.P. in 1893 and, subsequently, Adeps Lanae (anhydrous lanolin) was added to the Eighth Revision of the U.S.P. in 1905.

The ability of wool fat and lard to absorb or emulsify significant amounts of water led to the investigation of other hydrophilic ointment bases. During recent years, the trend has been to develop hydrophilic ointment bases. Hydrophilic ointment bases more readily release their active ingredients than the traditional hydrophobic bases (45, p.408; 48; 59; 66, p.110).

It may be ascertained from the preceding discussion

that early ointments were considered to be semisolid preparations of a greasy or fatty nature intended for external application. This concept has been markedly changed in recent years, as evidenced by the variety of substances on the market (87). Today's concept of ointments includes preparations of widely varying chemical composition and of such consistency as to be readily applied to the skin by inunction.

SURVEY OF LITERATURE

Definition Of Ointments

Ointments are defined by Skauen as "soft, unctuous, semisolid preparations usually containing medicinal agents and intended for application to the skin with or without rubbing" (44, p.101). From this definition, an ointment may be seen to be made up of two parts, the base and the medicinal or active ingredient. Since the base acts as a carrier or vehicle for the active ingredient(s), "the base may be said to be the ointment without a medicament" (60). This modern concept of ointments is in agreement with Zopf (42, p.246), Jenkins (30, p.338), Wurster (87), Martin and Cook (45, p.407) and others.

Further examination indicates that ointments can be

subdivided into different variations or groups. Jenkins lists creams, pastes, cerates and jellies as the possible prototypes of ointments used in modern prescription practice, and has indicated a definition for each of these classes (30, p.338). Creams are considered to be soft, thin ointments having a lighter body and softer consistency than true ointments. Creams are commonly used on irritated and sensitive areas. Pastes are stiff, thick ointments which do not ordinarily melt at body temperature. Pastes are popular in the field of dermatology where they are used to form protective coatings over various areas of the body. Cerates, are stiff fatty ointments containing a high percentage of wax. Cerates melt at elevated temperatures and for this reason have not been used extensively in recent years. Jellies are thin, almost liquefied ointments containing low melting point fats and oils. Jellies are used chiefly as medicinal bases and for lubricating purposes. Washable jellies frequently have bases of gums, mucilages or suspending agents.

Classification Of Ointments

There is much controversy today concerning the various schemes proposed for the classification of ointments.

Among the more common methods of classification are: (1) those based upon the therapeutic properties as determined by penetration and (2) those based upon the general pharmaceutical properties of the ointment base as influenced by its composition (30, p.339).

Penetration. Based upon penetration, Goodman has divided ointments into the following three classes (19):

1. Epidermic ointments, those which demonstrate little or no ability to penetrate into the skin. Since these ointments are not absorbed, they may be used as carriers for drugs which produce local and topical effects. Protectives, antiseptics, astringents, counterirritants and parasiticides are examples of epidermic ointments. The bases most commonly used to form these ointments are waxes, petrolatum and their combinations.
2. Endodermic ointments, those which release medication that penetrates into, but not through, the skin. Since these ointments are partially absorbed, they are used as emollients, anodynes, stimulants and local irritants. Vegetable oils, lard, wool fat, lanolin and their combinations are the bases most frequently used to form this class of ointments.
3. Diadermic ointments, those which release medication that passes through the skin, thus offering an opportunity for systemic absorption of the medicament. Ointments of this type are not common, however, since drugs are rarely used topically to produce systemic or constitutional effects. The more common diadermic bases of this group are those containing wool fat, lanolin and theobroma oil. Water-soluble and emulsion bases also belong to this class.

Classification based upon drug penetration is not well accepted today. Polano et al. have shown that various degrees of absorption can occur from all types of ointment bases (59). Michelfelder and Peck have shown that the amount of damage to the epidermis and the degree of loss of normal skin barriers are more important than the vehicle in determining the penetration through the epidermis (46). Thus, a classification, based upon penetration or absorption, is not sound since absorption depends not only upon the composition of the base but also on the condition of the skin (42, p.247; 66, p.110).

Composition. Classification by composition is based upon the "type of ointment base" used in preparing the finished ointment. Zopf has placed ointments into the following four general classes according to the particular "type of ointment base" present (42 p.247):

1. Oleaginous Ointment Base
 - Anhydrous
 - Nonhydrophilic
 - Insoluble in water
 - Nonwashable

2. Absorption Ointment Base
 - Anhydrous
 - Hydrophilic
 - Insoluble in water
 - Most are nonwashable

3. Emulsion Ointment Base
 - W/O Emulsion Base
 - Hydrous
 - Hydrophilic
 - Insoluble in water
 - Nonwashable
 - Water-in-oil emulsion
 - O/W Emulsion Base
 - Hydrous
 - Hydrophilic
 - Insoluble in water
 - Washable
 - Oil-in-water emulsion
4. Water-Soluble Ointment Base
 - Anhydrous
 - Hydrophilic
 - Soluble in water
 - Washable
 - Greaseless

It is generally agreed that ointments are best classified by this method (30, p.340; 42, p.247; 44, p.103; 45, p.408).

Qualities Desired In Ointments

The qualities desired in an ointment are many and varied, and depend upon the basis of judgement of the group making the evaluation.

The dermatologist evaluates an ointment from the standpoint of therapeutics. He is especially concerned with the ability of the base to release the medicaments while not

causing irritation to the skin or retardation of the normal healing process.

The patient may "judge an ointment on such points as ease of extrusion from a tube, ease of spreading, odor, staining properties, removal from the site of application, and other similar factors falling within the realm of elegance" (48 p.212).

The pharmacist is concerned with the storage properties of the ointment, the range of compatibility of the base with various medicaments, and the stability of the finished product. In addition, the pharmacist prefers a base which is a good levigating agent and is easily handled.

The manufacturer is concerned with all of these factors in order to produce a successful product. In addition, the manufacturer considers the handling and manufacturing characteristics of the base.

Selection Of Proper Ointment Bases

A large number and variety of ointment bases are available today, and the process of selecting the proper base to compliment a particular ointment formulation is becoming increasingly exacting (37). Mutimer (48), Skauen (44), and Jenkins (30) have suggested some factors to consider in

selecting the proper ointment base for a given formulation.

Mutimer et al. indicate that the "selection of the base for an ointment should be made only after comparative evaluation of many factors" (48 p.212). The general properties which they use in evaluating and selecting ointment bases are: (1) those which exert an effect on the therapeutic manifestations of the active ingredient, (2) those which have an effect on the patient acceptance of the finished product, (3) those which control the stability aspects, and (4) those affecting the compounding and manufacturing of the finished product.

Skauen proposes that the following fundamental qualities be considered in selecting the appropriate ointment base (44, p.101): (1) the base must be physically and chemically compatible with the medicinals to be incorporated into it, (2) the base must neither destroy nor inhibit the therapeutic action of the drug, (3) the base must release the drug at the site of action, and (4) the type of film desired is governed by the particular base selected (occlusive, nonocclusive or washable film).

Jenkins suggests that the following factors be considered in selecting the proper ointment base (30, p.339):

(1) the nature of the medicament (liquid or solid), (2) the stability of the medicament, (3) the therapeutic action desired (local or systemic), (4) the characteristics of the skin (dry or oily, dark or light, hairy or glabrous, dry or serous lesions present), (5) the chemical effect of the vehicle on the medicament, and (6) the properties of the ointment (appearance, texture, o/w or w/o emulsion base, consistency, homogeneity, and irritability).

In the present study an attempt will be made to measure and compare a number of these properties for Bentone[®] ¹ ointment bases with those of various other bases.

Basis For Using Bentone Products In Ointments

An increasing need for more efficient ointment bases is evidenced by the voluminosity of literature in this area of investigation. A review of the literature indicates that the water miscible or hydrophilic ointment bases are in increasing demand (11; 18; 31; 33; 34; 42; 45; 53; 87).

Bentonite U.S.P. has been used successfully as an ingredient in several ointment bases (5, p.13). Ointments

¹ Bentone[®] is a registered trademark for a class of products of the National Lead Co., 105 York Street, Brooklyn, N.Y.

prepared from bentonite do not encourage mold growth and have the advantage of not spreading to the hair when applied to the scalp. Hollander and McClenahan have prepared a base containing bentonite which is compatible with a wide range of drugs, shows few allergic reactions and is reported to have therapeutic value when used alone (27). The chief disadvantage of ointments prepared from bentonite and water is the formation of a hard, dry crust that cracks and shrinks, is slightly drying and is unstable upon standing.

Bentone products have been employed in industry for a variety of uses (49; 50; 51). They have been used by: (1) the petroleum industry to thicken oils into greases, (2) the oil drilling industry to form oil-emulsion-type drilling fluids, (3) paint manufacturers in paint products because of their thixotropic properties (one of the main uses today), (4) textile manufacturers as lubricant emulsions, and (5) paint manufacturers in mastics for improving particle wetting, enhancing homogeneous composition and in increasing long-term storage stability. Mastics are a general class of compounds that include such materials as putty, caulking compound and wood fillers.

Regardless of these diversified uses, however, no mention of the application of Bentones to pharmaceutical or medicinal dosage forms has been made.

Since Bentone products are chemically related to bentonite (33; 34; 35), it would seem likely that the former would exhibit the advantages of the latter when incorporated into ointments. Bentone causes the formation of water-in-oil emulsions, unlike bentonite which forms oil-in-water systems, and it is thought that this property would overcome the drying, shrinking, cracking, and crust formation apparent in bentonite ointment bases.

PROPERTIES OF BENTONITE AND BENTONE

The discussion of the properties of bentonite and Bentone will be divided into two distinct phases: (1) the physical and chemical properties of bentonite, and (2) the preparation, the physical and chemical properties, the polarity as a basis of selection and the toxicology of Bentone products.

BENTONITE

Bentonite U.S.P. is "a native, colloidal hydrated aluminum silicate" found in the midwestern United States and Canada (56 p.81).

Physical Properties Of Bentonite

Bentonite is a fine, odorless powder that has a slight earthy taste. This pale buff to cream-colored powder is free from grit, has a specific gravity of 2.75 and is slightly harder than talc. The U. S. Geological Survey defines bentonite as "a transported stratified clay formed by the alterations of volcanic ash shortly after decomposition" (45, p.1329).

Bentonite particles are reported by Rogers to be about 44 microns in maximum dimension and will pass through a #325 mesh sieve (69, p.470). One cubic inch of bentonite

is estimated to contain 9500 billion particles which have a total surface area of more than one acre. Each of these particles is a crystalline plate of less than microscopic dimensions in thickness and of colloidal dimensions in breadth. It is this fact that accounts for the extreme swelling that occurs when bentonite is placed in water, since water penetrates between and surrounds each of these platelets (69, p.471).

The physical composition of Bentonite, obtained from the National Lead Company property at Clay Spur, Wyoming, has been analyzed extensively by thermal, petrographic and X-ray diffraction methods (17; 21; 33; 34; 35;). X-ray analysis indicates that aside from a relatively small proportion of accessory nonclay material, bentonite is essentially pure montmorillonite (34, p.1196). "Montmorillonite is a hydrous magnesium silicate, with a micaceous structure and an exceptionally small ultimate particle size. It occurs customarily as the salt of a moderately strong acid." (17, p.13).

Montmorillonite has been shown by several researchers to consist of one gibbsite sheet between two sheets of silica tetrahedral groups (17; 21, p.55; 63; 23, p.917; 29).

A schematic representation of the montmorillonite structure is presented in Figure 1.

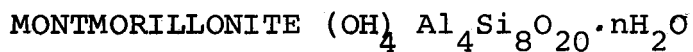
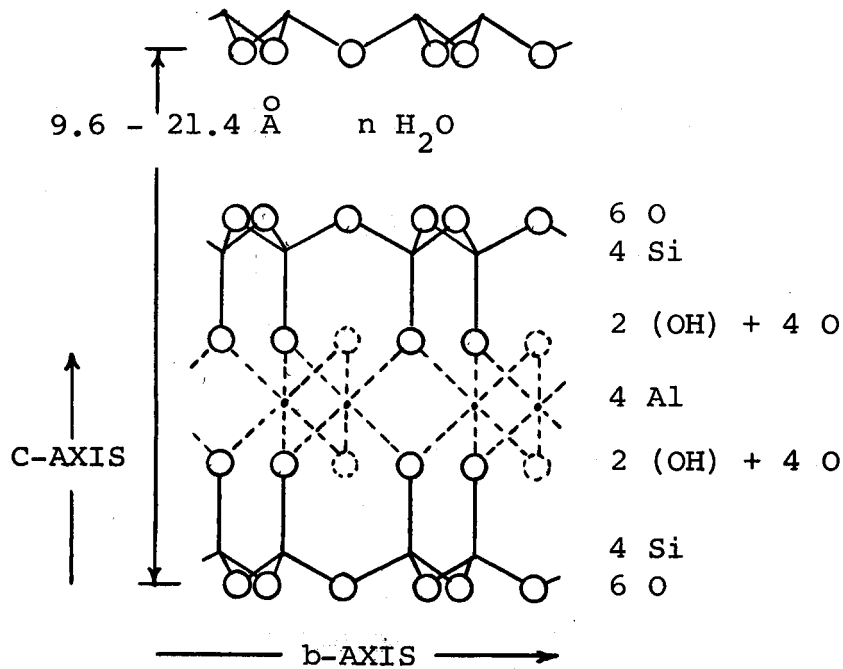


Figure 1. Schematic Representation of Montmorillonite*.

*After Finlayson and McCarthy (17).

The thickness of a montmorillonite platelet is approximately 9.6 Angstrom units (\AA) or about one millimicron (21, p. 56). In the other dimensions, the size is approximately 20 millimicrons (17). The particle is thus a platelet of very small size with a large number of inorganic cations on each

surface. In addition, some cations are held by the broken bonds at the edges of the platelets. According to Hendricks about 80% of the exchange positions of montmorillonite are on the basal plane surfaces with the remainder on the edge of the flakes (24).

The outstanding feature of the montmorillonite structure is that "water and other polar molecules can enter between the unit layers, causing the lattice to expand in the c-axis direction. The c-axis direction of montmorillonite is, therefore, not fixed but varies from $9.6 \overset{\circ}{\text{A}}$, when no polar molecules are between the unit layers, to substantially complete separation of the individual layers in some cases" (21, p.56).

When wetted with water, the montmorillonite flakes cleave apart. The cleavage occurs mainly along the basal planes (5A). "The tops and bottom of the plates are the basal planes, and the thickness (longest plane) is scientifically referred to as the c-dimension" (5A). "When montmorillonite is dispersed in water, the platelets separate to their ultimate particles, and each platelet orients water molecules about it in a hexagonal configuration" (17). It is this action that gives rise to the formation of

thixotropic gels. Repeated wetting and drying of montmorillonite does not alter the physical properties. Dilutions with water as great as 1:5000 do not settle out upon standing (69, p.471). Ewing et al. have reported that a good specimen of montmorillonite (in this instance montmorillonite is used as a general group name for a series of related bentonite clays) will swell in water 12 to 14 times its original volume (14).

A review of the literature indicates that considerable research is being conducted on the rheology of montmorillonite systems (28; 38; 39; 82; 83).

Chemical Properties Of Bentonite

According to Rogers, bentonite is chiefly an aluminum silicate containing SiO_2 , Al_2O_3 , Fe_2O_3 , CaO , MgO , sodium and some potassium. Sodium is the primary exchangeable ion (69, p.471). The most common type of bentonite is Volclay bentonite. Volclay is a trade-name for a commercial bentonite material from Wyoming "which is known to contain finely divided quartz and appreciable silica" (24). "Volclay bentonite is composed of approximately 90% montmorillonite, a clay mineral of unique characteristics" (14). The remainder is mostly feldspar. Other bentonites differ chemically

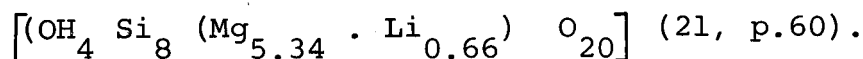
from Volclay bentonite, depending upon the geographical area in which they are mined.

The chemical composition of bentonite and other related silicates and aluminum compounds can be summarized as follows:

1. Bentonite is a colloidal, hydrated, aluminum silicate $[Al_2O_3 \cdot 4SiO_2 \cdot H_2O]$ plus other mineral impurities (56, p.81; 45, p.1329). "Analysis shows it to be an alumino-silicate containing SiO_2 , Al_2O_3 , Fe_2O_3 , CaO , MgO and some sodium and potassium (69, p.471).
2. Feldspar is any of a group of minerals, principally alumino-silicates of potassium, sodium and calcium (2; 21). The general formula for feldspar is:

$$[K_2O \cdot Al_2O_3 \cdot 6SiO_2]$$
 (69, p.470).
3. Gibbsite is a "hydrated aluminum oxide $[Al_2O_3 \cdot 3H_2O]$, occurring in whitish or grayish crystals and masses" (2; 21).
4. Hectorite is a member of the montmorillonite group of clays obtained from the Hector deposit in California (16). "It is essentially the magnesium end member of this group, and the almost total

absence of Al_2O_3 , the presence of Li_2O , and the dominance of F over OH have established hectorite as a distinct mineral species from montmorillonite itself" (5A). The formula for hectorite is listed as:



5. Kaolin is a weathered aluminum silicate (weathered feldspar) plus other mineral impurities. This fine white clay has had many of the impurities weathered out (2; 69, p.472). "Kaolin is a native hydrated aluminum silicate, powdered, and freed from gritty particles by elutriation" (1, p.186). The approximate composition is $2\text{H}_2\text{O} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2$ and it is believed that other bases, if present, represent impurities (21, p.29).

6. Montmorillonite is a hydrous aluminum silicate

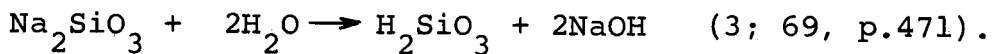
$\left[\text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot 2\text{H}_2\text{O} \right]$ with isomorphous replacement of aluminum by other cations (13, p.2). A second formula indicating some of the impurities is:

$\left[\text{H}_2\text{O} \cdot (\text{Al}_2\text{O}_3 \cdot \text{Fe}_2\text{O}_3 \cdot 3\text{MgO}) \cdot 4\text{SiO}_2 \cdot n\text{H}_2\text{O} \right]$ (14). An empirical formula has been proposed as:



consists of flake-like units of exceptionally small particle size (49, p.2).

Bentonite is insoluble in water and organic solvents, but when mixed with water will swell to produce a slightly alkaline gel resembling petrolatum. In acidic solutions the metallic ions are exchanged for hydrogen ions, and for this reason bentonite is not readily maintained in acidic media (3). Using sodium silicate, the reaction in water may be illustrated as:



Since silicic acid is nonionized, the highly ionized sodium hydroxide maintains an alkaline medium with a pH of 8.5 to 10.

Clay materials have the property of carrying cations that may be exchanged stoichiometrically for other cations by treatment with an aqueous solution of the second cation (21, p.128). "This process of cationic exchange does not alter the structure of the clay but is a very important factor in influencing its properties" (5A). Barr indicates that not all cations have the same affinity for the clay particle, and lists the order of preference as $\text{Ca} > \text{Mg} > \text{K} > \text{H} > \text{Na} > \text{Li}$ (5A). Thus calcium dominates and will

replace any of the other bases below it in the list (4). Barr and Guth noted that the cation content of bentonite influences the degree of swelling, the intensity of the brownish tan color and the pH of the bentonite bases (5). The degree of swelling is influenced by cations in the order of $\text{Na} > \text{K} > \text{Mg} > \text{Ca} > \text{H}$. The ability of the cations to influence the intensity of the brownish-tan color is in the order of $\text{Na} > \text{K} > \text{Mg} > \text{Ca} > \text{H}$. The cations were found to influence the pH of the bases in the order of $\text{Na} > \text{K} > \text{Mg} > \text{Ca} > \text{H}$, with sodium bentonite being the most alkaline.

Rogers states that all dispersions of bentonite are affected by electrolytes (69, p.471). He further indicates that the higher the valence of the cation, the greater the effect. In addition, the order of mixing is important when combining an electrolyte with bentonite. When the electrolyte is added to a suspension of bentonite, no noticeable change is evidenced. If dry bentonite is added to a solution of an electrolyte, however, the suspension is usually thinner than if pure water were used.

In adjusting the pH of bentonite bases by means of buffer mixtures, Darlington and Guth have shown that the buffering effect is less transient in the acid range (11).

In addition to the pH effect, they indicate that a desirable property of bentonite is its avid "sorption" for other substances, both inorganic and organic. They have shown that the activity of medicinals is increased by using an acid-buffered bentonite base, and believe that this increase is due to the medicinal substance being carried by the large number of microscopic particles.

Ointments Prepared From Bentonite

Bentonite has been frequently mentioned in the literature as an active ingredient in ointment bases (5; 9; 11; 20; 27; 70; 79). Ointments prepared from bentonite and water are found to be slightly drying and unstable upon standing. The addition of a humectant such as glycerol or sorbitol in amounts up to 10%, however, will retard this action. The consistency of ointments prepared from bentonite may be regulated by varying the amount of water added. Ointments prepared from bentonite do not encourage mold growth. In addition these ointments have the advantage of not spreading to the hair when applied to the scalp.

Hollander and McClenahan have described a hydrophilic base, containing bentonite, which is compatible with a wide range of drugs and when used alone is reported to have

therapeutic value (27). The formula for this base is presented in Figure 2.

Petrolatum	32.0 Gm.
Bentonite	13.0 Gm.
Sodium Lauryl Sulfate	0.5 Gm.
Water	54.0 Gm.
Methylparaben	0.1 Gm.

Figure 2. Hollander and McClenahan Base.

Allergic reactions to this base have been shown to be rare. Petrolatum was incorporated into this base to prevent the formation of a hard dry crust that cracks and shrinks as is the case with bentonite alone.

Barr and Guth have used five cation saturated bentonites (Na, K, Ca, Mg, and H bentonites) and Volclay bentonite (containing all five cations) as major constituents in preparing six bentonite ointment bases (5). When used as vehicles for anti-infective drugs, ointments prepared from these bases were shown to have greater antibacterial activity in vitro than their respective U.S.P. and N. F. (National Formulary) ointments. The H bentonite base was found to give the greatest activity for sulfathiazole, phenol, and ammoniated mercury. The Ca and Mg bentonites were shown to exhibit only slight swelling properties.

BENTONE

Bentone is a registered trademark of National Lead Company, "applied to a class of products resulting from cation exchange reactions between organic bases and suitable minerals such as montmorillonite. The individual products of this class are identified by a number following the mark Bentone" (50, p.1). The three most widely used gellants are Bentone 34, Bentone 38, and Bentone 27.

"The Bentone products are finely divided, light cream-colored powders. They have a very low chemical reactivity, and are readily stored and handled without difficulty. They are nonhygroscopic and do not lose their effectiveness during long (periods of) storage" (50, p.4).

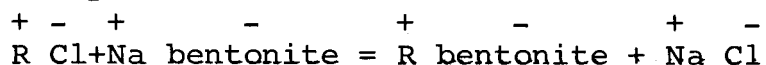
Bentonite is used to stabilize emulsions of organic material in water. Conversion of bentonite to the organophilic condition, as in Bentone products, reverses this situation to form a gellant capable of emulsifying water-in-oil (35). Bentone products are thus capable of forming thixotropic gels in organic liquids (50, p.1).

Preparation Of Bentone Products

Bentone products are formed by replacing the inorganic cations of a clay mineral lattice with organic cations

(50, p.1). The organic chains are attached to the inorganic platelet by means of ion exchange reactions (34; p. 1206; 35). Finlayson and McCarthy indicate that "Bentones are reaction products of bentonite, or more accurately, montmorillonite and various organic cations" (17). The montmorillonite used for the production of Bentone products is the Wyoming type in which the cation is predominantly sodium (17).

The reaction for the commercial preparation of various Bentone products is shown to be one of the simple replacement (13; 16; 17; 33; 34; 35; 49; 50; 68). During commercial preparation "solutions of organic ammonium or onium salts are mixed with centrifuged aqueous bentonite dispersions in the ratio of approximately 100 meq. of organic salt to 100 Gm. of clay" (33, p.295; 34, p.1196; 35). The montmorillonite, previously hydrated in a very dilute dispersion to separate the unit particles, is purified by super centrifugation to achieve complete removal of the non-clay impurities (17). The chemical reaction which takes place is expressed by Jordan and Williams (35) and Slabaugh (68). Using R as an organic ammonium or onium cation, the reaction is expressed as follows:



The reaction product is in most cases a readily filtered flocculent precipitate which is washed to remove salts, dried in an air circulating oven, and pulverized in a hammer mill (33, p.295). Flow sheets illustrating various steps in the commercial production of these materials are presented by Eickhoff et al. (13, p.2) and the National Lead Company (49, p.4).

By varying the organic salts, represented by the RCl group in the above equation, a wide variety of bentonite complexes (Bentone products) can be obtained (33; 34; 35). The specific trade products used in this research, and their equivalent organic substituents, have been identified and are presented in Figure 3.

TRADE PRODUCT	BENTONE COMPLEX
Bentone 27	dimethyl dialkyl* benzyl ammonium hectorite (16; 84).
Bentone 34	dimethyl dialkyl* ammonium bentonite (16) -or- dimethyl dioctadecyl ammonium bentonite (15;16; 49, p.2)
Bentone 38	dimethyl dialkyl* ammonium hectorite (16; 84).

*"Alkyl groups as in the fatty acids of tallow. This is a mixture of C₁₈ and C₁₆ alkyl groups in the ratio approximating 70 to 30 respectively" (16).

Figure 3. Bentone Products and Their Equivalent Bentonite Complexes.

Physical Properties Of Bentonite

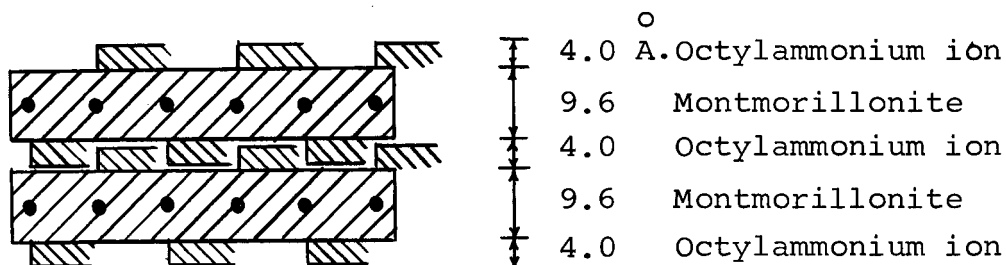
Particles of Bentonite have been shown by Jordan and Williams to "resemble those of the original material (bentonite) and that the organic ions attached to the clay laminae surfaces by ion exchange reaction merely increases the overall thickness of the platelets" (35). This has been demonstrated by X-ray diffraction data showing a plate thickness of approximately $4 \overset{\circ}{\text{A}}$ for each layer of hydrocarbon amines having 10 or fewer carbon atoms (33, p.295; 34, p.1198; 35). This increase in size, which represents the effective van der Waals thickness of a methyl group or hydrocarbon chain, is more or less completely occupied by the amine chains (34, p.1198; 32). This experimental measurement correlates well with the effective diameter of the methyl group listed by Pauling as $4 \overset{\circ}{\text{A}}$ (55, p.262).

For the relatively simple normal primary aliphatic amine reacted with bentonite, "the step-wise separation of the plates by units of $4 \overset{\circ}{\text{A}}$ has been taken to indicate that the hydrocarbon chains lie flat along the surface with the plains of the zig-zag chains parallel to the mineral" (33, p.296). This is especially true where the organic molecules on the top surface of one lamina may fit into the

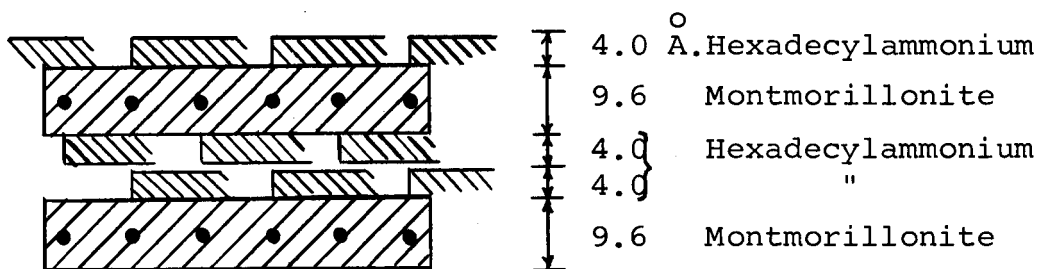
gaps between those on the bottom surface of the lamina directly above it, so that the resulting separation of the two laminae is only the thickness of one hydrocarbon chain, or 4 \AA . Where the chains are longer than 10 carbon atoms and occupy more than 50% of the surface area, however," it is obvious that adjacent flakes will be unable to approach any more closely than the thickness of two hydrocarbon chains or 8 \AA " (33, p.296). This fact is illustrated two-dimensionally by the sketches in Figure 4.

The discussion to this point has involved the bentonite salts of single chain primary amines of less than sufficient size to coat the mineral platelets completely with a single layer of hydrocarbon chains. Other factors which influence the spacing of the platelets are: (1) the addition of branched chain amines, and (2) the degree of saturation of the base-exchange capacity of the platelets (33). An increased plate separation is noticed when dimethyldidodecyl ammonium, a branched chain amine, is reacted with bentonite. On the basis of X-ray data, Jordan observed 9 \AA space for the organic molecules and postulated that the two long chains lie flat on the surface (32). "Since a 12-carbon-atom chain occupies only about 60% of the available

LESS THAN 50% COVERAGE BY AMINE



50 - 100% COVERAGE



MORE THAN 100% COVERAGE

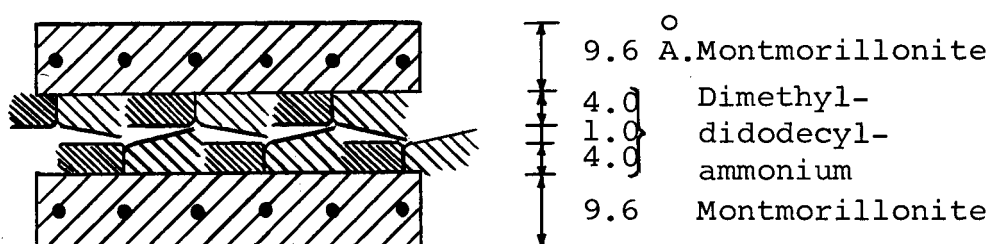


Figure 4. Diagrammatic Edge View of Montmorillonite Platelets Having Organic Ammonium Compounds Attached by Base-Exchange Reaction.*

*After Jordan (33, p.298).

space, the second chain can almost accommodate itself to the vacant area remaining, with a minor proportion overlapping and giving rise to the increased separation over and above 8 \AA . If the chains were to extend more or less perpendicular to the surface, there would be a basal plane spacing of about 29 \AA " (33, p.303).

It is due to the spatial characteristics, that gelation is attained best when C_{12} to C_{18} groups are substituted on the clay platelets (34, p.1199). Typical bentone products containing C_{12} to C_{18} groups "are flat-like particles having average dimensions on the order of $1 \times 150 \times 150$ millimicrons" (51).

The reaction of bentonite with appropriate organic ammonium salts has been shown to convert hydrophilic clays to the organophilic condition (10; 33, p.295). Jordan et al. indicate that "a bentonite originally exhibiting high swelling in water will, after base-exchange reaction with certain organic ammonium salts, show a decided aversion to water and a remarkable tendency to swell in various organic liquids" (34, p.1196). In fact, they indicate that "the treated clay will swell to a much greater extent in some organic systems than will its untreated counterpart in water" (34, p.1196).

Once Bentone compounds have been properly gelled, they are stable on prolonged exposure to temperatures of 300° F. (15; 17; 49; 50; 51). At higher temperatures some yellowing begins to occur, apparently due to the splitting off of minute quantities of the organic component (50, p.5). Bentone gellants have been used at temperatures as high as 400° F. to 550° F. where color is not a factor of importance (49, p.2).

Bentone products are reported to be insoluble in all aqueous or organic liquids within the range of pH 4 to pH 10. Properly gelled Bentone compounds, however, "consist of particles which are considerably less than one micron in their maximum dimension, so that a colloidal gel is obtained in which no particles are discernible" (50, p.4).

"The equilibrium moisture content of Bentone products is less than 3% by weight. From 1% to 2% water is closely held in the Bentone crystal lattice, and this amount of moisture is necessary for optimum gelling properties" (50, p.4). Removal of this associated water from the Bentone compound prior to gelation has been found to detract seriously from its gelling efficiency. For this reason

Bentone products should never be stored at temperatures above 140° F. to 150° F. (50, p.4).

Due to the long hydrocarbon chains about each unit, the dry Bentone particle is resistant to wetting by water. Bentone gels can be emulsified by the use of sufficient shear force. Once emulsified, a mechanically stable emulsion results, especially in cases where the aqueous portion is the internal phase of the emulsion (50, p.5).

Chemical Properties Of Bentone

"The Bentone compounds are chemically neutral; their presence does not affect the pH of an organic liquid. Bentone gellants are resistant to the action of dilute acids and alkalis in a working range of pH 4 to pH 10, and maintain gel stability over extended storage periods in this range. It should be noted, however, that prolonged contact at lower or higher pH values may cause decomposition of the Bentone gellant with consequent reductions of gel strength" (50, p.4).

Polarity As A Basis For Selecting Bentone Gellants

The National Lead Company has shown that the degree of polarity of a particular liquid is an excellent basic guide to use in selecting the most effective Bentone gelling

agent. A selection fan and table for use in choosing the proper Bentone gellant have been prepared by the National Lead Company (50, p.8-9). They recommend Bentone 38 as the gelling agent of choice for use in low and intermediate polarity compounds. Bentone 38 thus appears to be the most effective gelling agent for liquid petrolatum, the oil to be used in this study.

Toxicological Properties Of Bentone

A "Toxicological Examination Of Bentone 34" was made by the Food Research Laboratories, Incorporated, Long Island City, New York, in reports of January 30, 1953 and October 28, 1953 to the National Lead Company of Houston, Texas. These reports were released by the National Lead Company in "Research and Development Laboratories Technical Release No. G-11-53" (52). "These tests proved conclusively that Bentone 34 could be regarded as a highly inert material insofar as its topical or systemic effects on the animal organism are concerned" (52). "Since it was shown that direct contact with Bentone 34 produced no irritation to membranes or to skin surfaces, Bentone 34 may be judged to be safe for handling in manufacturing operations. The above reports have been filed with the Food and

Drug Administration and approval has been obtained for the use of Bentone 34 in cosmetic and drug products intended for topical application" (50, p.5).

The following general conclusions are presented from the report on the "Toxicological Examination Of Bentone 34" (52):

1. The oral LD50 (Median Lethal Dose) for rats of dimethyldistearylammonium chloride was found to be 4.44 Gm. per kg. body weight, or 6.35 Gm. per kg. expressed as Arquad 2HT. Bentone 34 was too innocuous to permit the ingastric administration of a dose large enough to establish an LD50.
2. Bentone 34 was inert when applied to the intact or abraded skin of rabbits or when instilled in the form of a suspension into their eyes.
3. Bentone 34 was nonallergenic when injected intracutaneously into guinea pigs.
4. Bentone 34 caused no significant impairment of growth, food utilization, hemoglobin level, or red or white blood cell count, when fed at the dietary levels as high as 25%. A slight reduction in efficiency of food utilization at the highest test level may be explained to generally lower nutrient intake. Gross autopsies and weights of the livers and kidneys gave no indication of a toxic reaction at these test levels.
5. Bentone 34 may be regarded as a highly inert material insofar as its topical or systemic effects on the animal organism are concerned.

"Separate studies have not been made on Bentone 38 and Bentone 27 as such. Their closely related compositions,

with respect to both mineral and organic components, however, would seem to indicate that a comparably low order of toxicity should be expected" (50, p.5; 84).

EXPERIMENTAL PROCEDURES AND RESULTS

The experimental work was divided into two distinct parts: (1) the development of ointment bases using the Bentone gellants, and (2) the subsequent comparison, of these bases with others in common use, for physical and chemical stability, body and consistency, drug release characteristics, and handling and manufacturing characteristics.

PART I - DEVELOPMENT OF BENTONE OINTMENT BASES

The first phase of investigation involved the formation of several ointment bases prepared from mineral oil, Bentone gellants, Alcohol U.S.P.² and water. A review of the literature, preliminary tests, and a series of specific studies were conducted to find the optimum amount of each of these agents necessary to form stable ointment bases. The formulas for each of these bases, the method of mixing, and some of the properties of each base will be discussed.

² Alcohol U.S.P. contains not less than 92.3% by weight of C₂H₅OH (56, p.25) and will be referred to in this paper by the official name "Alcohol".

Standardization Of Ingredients And Methods

To minimize experimental error, the following measures were taken during manufacturing of the ointment bases:

1. Five gallons of Liquid Petrolatum U.S.P. was pooled into a single container to be used throughout this research. Shell Ondina Oil 27 brand having a Saybolt_o Universal Viscosity of 185-195 seconds at 100° F. was used.
2. Purified Water U.S.P., prepared by a distillation process, was used throughout this study.
3. Alcohol U.S.P. was used as the polar additive. All of the Alcohol used in this study was taken from the same commercial container.
4. The Bentone 38 was randomly taken from a 50-pound commercial package supplied by the manufacturer.
5. All of the Span[®] 85³ used in this research was taken from the same commercial container.
6. The length of time and speed of mixing were regulated closely during the preparation of each ointment base. The time was regulated to + 1 second with a stop watch. The speed of mixing was controlled with a Powerstat⁴ brand of rheostat attached to a high-speed dispersator⁵. The Powerstat was calibrated for r.p.m. with a Strobotac⁶.

³ Span[®] 85 courtesy of Atlas Chemical Industries Incorporated, Wilmington 19, Del.

⁴ Powerstat[®] Type 3PN117 variable 10 amp. rheostat, Superior Electric Co., Bristol, Conn.

⁵ Premier Dispersator Unit Type SDD, Premier Mill Corporation, Reading, Pa.

⁶ Strobotac[®] Type 631B electric tachometer, General Radio Co., Cambridge, Mass.

7. All of the ointment bases were prepared the same day and stored under the same conditions.

Preliminary Studies

Preliminary studies were conducted to determine the relative quantities of the following ingredients necessary for the production of a satisfactory ointment base:

Liquid Petrolatum U.S.P. (mineral oil)
Bentone gellant
Alcohol U.S.P. (polar additive)
Purified Water U.S.P.

Since only one of these ingredients could be changed at a given time, a systematic plan was devised to permit study of each component while holding the remainder of the substances constant.

Because Bentone products tend to form water-in-oil emulsion systems, it was thought that the percentage of oil should be greater than that of water. This was justified by the fact that the internal or dispersed phase of emulsion systems is generally present in smaller amounts than the external or nondispersed phase. Previous work in the paint industry indicates that approximately 1% to 6% W/W⁷ Bentone gellant is sufficient to thicken various oil base paint

⁷ Unless otherwise indicated, all percentages will be expressed on a weight basis.

formulations (50, p.12). Preliminary studies indicated that 6% Bentone gellant was sufficient to gel mineral oil.

The preparation of a gel with Bentone gellants requires mechanical shear action to aid in breaking the strong attractive forces which hold the tiny Bentone platelets together (35). This is readily overcome by the controlled absorption of small polar molecules. The amount of polar additive to "trigger" gel formation has been suggested to be about 30% methyl alcohol or 45% Alcohol based on the weight of the Bentone product (50, p.12). The object is to provide a monomolecular layer of alcohol covering the entire surface area of the bentone mineral platelet (50, p.12). The alcohol aids in dispersing the platelets by penetrating between adjacent flakes to force them apart "in order that a hull of liquid may form around each particle in the production of a gel" (35).

In preparing various ointment bases, the order of mixing the ingredients was found to be particularly important. The following conclusions are proposed from studies by the author on approximately 150 different ointment bases:

For Emulsion Bases (water present)

1. The Bentone gellant should be pre-wetted with oil before the other ingredients are added.

2. Water and Alcohol are then added in either order.
3. If Alcohol is added before oil to the Bentone gellant, it is then more difficult to incorporate the water (using the dispersator). In addition, the possibility of forming lumpy gels is reduced. This is especially true "where stirring equipment is the only mechanical treatment given to the Bentone mixture" (50, p.12).
4. From the standpoint of commercial preparation or even laboratory production, the most rapid method is to first pre-wet the Bentone gellant with oil before the addition of Alcohol and water.

For Anhydrous Bases (no water present)

1. The Bentone gellant should be pre-wetted with Alcohol (the polar additive) before the other ingredients are added.
2. Oil is then added to the Bentone-Alcohol mixture to produce the desired ointment base.
3. Considerable quantities of water can be added to this type of base. The addition of water, however, is best achieved with a mortar and pestle rather than the high speed dispersator.

Specific Laboratory Studies

Specific laboratory studies were next conducted to determine:

1. The Bentone product best able to gel mineral oil into a water-in-oil emulsion-type ointment base.
2. The optimum ratio of water and oil to produce the most desirable ointment base.
3. The optimum amount of Bentone gellant to use for gel formation.

4. The effect of polar additives on the gelling efficiency of these products.

A study was conducted on three montmorillonite derivatives (Bentone 27, Bentone 34, and Bentone 38)⁸ and Bentonite to determine: (1) the agent most satisfactory in gelling mineral oil, and (2) the optimum amount of mineral oil to use in preparing the ointment bases. The investigation of this problem was carried out by incorporating 6% of each gellant into various water and oil combinations. A 3% concentration of Alcohol was added as the polar solvent necessary to "trigger" gel formation. The remainder of the base was composed of purified water. The order of mixing the ingredients was the same as that described "for emulsion bases". Experimental results from this study are presented in TABLE I. The data in TABLE I indicate that Bentone 38 is the most effective of the four agents tested in forming water-in-mineral oil emulsions. This finding is in general agreement with data published by the National Lead Company (50, p.8).

Results from TABLE I further indicate that 50%-70%

⁸ Bentone products were obtained through the courtesy of the National Lead Company, Baroid Division, Houston, Texas.

TABLE I
 RATING* OF OINTMENT BASES** USING BENTONITE AND BENTONE GELLANTS WITH
 VARIOUS PERCENTAGES OF OIL

GELLANT	PERCENT MINERAL OIL								
	10	20	30	40	50	60	70	80	90
BENTONITE	++s	++s	+s	0	0	0	0	--	---
BENTONE 27	---	---	---	--	-	--	--	--	--
BENTONE 34	---	---	--	-	++	+	-	-	-
BENTONE 38	---	---	-	++	+++	++	++	+	-

*Ratings are designated as follows:

- +++ very good base - thick and creamy
- ++ good base - slightly thin or stiff (s)
- + fair base - slight creaming; thin or stiff (s)
- 0 poor to fair - oily; considerable creaming; stiff and gritty
- poor base - grainy but shakable; very thin
- unsatisfactory - some phase separation; nonshakable
- unsatisfactory - extensive separation; nonshakable

** Each ointment base contained: (a) 6% gellant, (b) 3% Alcohol U.S.P., (c) various amounts of oil, (d) distilled water to make a total of 100%.

mineral oil forms the most stable ointment bases with Bentone 38. Less than 40% oil was observed to cause excessive phase separation and cracking while excessive creaming was observed when more than 80% oil was used. The best products were formed from 50% mineral oil.

Having found Bentone 38 to be the gellant of choice, it was next necessary to determine the optimum amount of Bentone 38 to use for gel formation. Accordingly, ointments were prepared containing 1/2% to 20% Bentone 38 using 50% mineral oil in each instance. The amount of Alcohol added to "trigger" gel formation was again based on 50% of the weight of the Bentone product. The remainder of the base was purified water. The order of incorporating the ingredients was similar to that described "for emulsion bases". Data from this study are presented in TABLE II. Analysis of these data indicates that 6% Bentone 38 is the minimum amount of gellant required to produce a thick emulsion-type ointment base that is stable upon standing.

A study was next conducted to determine the exact amount of Alcohol (polar additive) required to "trigger" gel formation. A value of approximately 45% Alcohol based on the weight of the Bentone gellant was suggested in the

TABLE II
EFFECT ON OINTMENT BASES* BY VARYING THE
PERCENTAGES OF BENTONE 38 AND ALCOHOL U.S.P.

PERCENT BENTONE 38	EVALUATION OF OINTMENT BASE	
	Rating	Basis for Rating
0	0	Separation into 2 immiscible layers
1/2	0	Curdled - Separated into 3 layers
1	1	Thin, white emulsion - creamed 15% to 20% in 24 hours
1 1/2	3	
2	5	Medium consistency emulsion - some creaming in 24 hours
3	7	White emulsion - 1% creaming in 96 hours
4	8	
5	9	
6	10	Semisolid ointment formed - trace creaming in 96 hours
7	10	
8	10	
9	9	Further increases in gellant increased solid content of base - excess of solids not warranted for optimum gelation
10	9	
12	9	
14	9	
16	8	
18	8	
20	8	

* Each ointment base contained: (a) 50% mineral oil, (b) various amounts of Bentone 38, (c) 50% Alcohol U.S.P. based on the weight of the Bentone gellant, (d) distilled water to make a total of 100%.

literature (50, p.12). For convenience, 50% Alcohol based on the gellant weight, was used in all preliminary studies prior to this time. Experimentally 50% mineral oil, 6% Bentone 38 and 0% to 25% Alcohol were incorporated into a series of ointment bases. The remainder of each base was made up to the final weight with purified water. The order of mixing the ingredients was similar to that described "for emulsion bases". The results from this study are shown in TABLE III. These data indicate that 50% Alcohol (based on the weight of Bentone gellant) thickened the water-in-oil emulsion to a semisolid ointment base. Smaller quantities of Alcohol produced proportionately thinner ointment bases. Small additional amounts of Alcohol did not appear to change the consistency of the emulsion. When quantities of Alcohol from 200% to 250% of the weight of the gellant were added, however, it was not absorbed but remained uncombined in the container. From this study, 50% Alcohol (based on the weight of Bentone gellant) appeared to be the optimum amount required to "trigger" gel formation.

Proposed Ointment Bases Using Bentone 38 Gellant

Two general types of ointment base formulations are to be considered in this work: (1) a W/O emulsion-type

TABLE III
EFFECT ON OINTMENT BASES* BY VARYING THE
PERCENTAGES OF ALCOHOL U.S.P.**

PERCENT ALCOHOL U.S.P.	EVALUATION OF OINTMENT BASE	
	Rating	Basis for Rating
0	5	Medium consistency, white emulsion-type liquid
1/2	6	Thick, white emulsion-type liquid
1	7	Thin, white ointment
1 1/2	7	
2	9	Medium consistency, white ointment
2 1/2	10	Thick, ultra white, creamy ointment
3	10	
3 1/2	10	
4	10	
5	10	
6	9	Further increases in alcohol had effect of thinning base slightly - excess amount of alcohol not warranted for optimum gelation
8	9	
10	8	
12	7	
14	6	
15	5	Maximum amount of alcohol that could be added to this formulation
20	0	Additional alcohol remained standing uncombined in container
25	0	

* Each ointment base contained: (a) 50% mineral oil, (b) 6% Bentone 38, (c) various percentages of Alcohol based on the total ointment weight, (d) distilled water to make 100%.

** Alcohol U.S.P. was the polar additive.

ointment base, and (2) an anhydrous ointment base. The formulas for each of these bases will be presented and their method of preparation, properties, and appearance will be discussed.

Using data obtained from earlier studies, the ratio of ingredients which produced the most satisfactory W/O emulsion-type ointment base is presented in Figure 5. This ointment base will be designated as Bentone Base #1.

Mineral Oil	50 Gm.
Bentone 38	6 Gm.
Alcohol U.S.P. (polar additive)	3 Gm.
Purified Water U.S.P.	41 Gm.
TOTAL	100 Gm.

Figure 5. Hydrophilic, Water Absorbing, W/O Emulsion Base (Bentone Base #1).

The order of mixing was similar to that described "for emulsion bases". Bentone 38 and oil were mixed with a high speed dispersator at 2400 r.p.m. for three minutes, using a Powerstat operated at a setting of 90 units⁹. Water was added next to the Bentone-oil suspension and allowed to mix

⁹ The dispersator unit was calibrated for r.p.m. at various Powerstat settings by the Department of Mechanical Engineering, Oregon State University.

for two minutes at 2400 r.p.m. to form a thick, white emulsion. Alcohol was then added to "trigger" gel formation. Mixing was continued for three additional minutes at 2400 r.p.m. A thick, semisolid, slightly granular, off-white ointment base was formed.

A second ointment base was developed by adding 10% Span 85 to Bentone Base #1, to increase the water absorbing properties (see Figure 6). This base will be designated as Bentone Base #2.

Mineral Oil	50 Gm.
Bentone 38	6 Gm.
Alcohol U.S.P. (polar solvent)	3 Gm.
Purified Water U.S.P.	41 Gm.
Span 85	10 Gm.
TOTAL	110 Gm.

Figure 6. Hydrophilic, Water Absorbing, W/O Emulsion Base (Bentone Base #2).

The actual laboratory method of preparing Bentone Base #2 consisted of mixing 10% Span 85 with 90% Bentone Base #1 at 2400 r.p.m. for three minutes. Incorporation of Span 85 produced a glossy, nongranular, thick, ultra-white ointment base having an improved appearance over Bentone Base #1.

The third ointment developed was an anhydrous or "grease-type" base containing no water. The formulation of

the anhydrous ointment base is presented in Figure 7. This base will be designated as Bentone Base #3.

Mineral Oil	91 Gm.
Bentone 38	6 Gm.
Alcohol U.S.P. (polar solvent)	3 Gm.
TOTAL	100 Gm.

Figure 7. Hydrophilic, Water Absorbing, Anhydrous, "Grease-type" Base (Bentone Base #3).

The method of preparing Bentone Base #3 was similar to that discussed "for anhydrous bases" and consisted of pre-wetting the Bentone 38 gellant with Alcohol for two minutes. Oil was then added and the mixture was dispersed at 2400 r.p.m. for three minutes. A thick, translucent, pale yellow ointment base was formed.

Preparation Of Bentone Bases For Evaluation

Using the formulas given in Figures 5, 6, and 7, and the order of mixing discussed under each of these monographs, the three Bentone bases were prepared and labeled for evaluation.

To aid in eliminating individual lot errors caused during preparation, 15 separate 200 Gm. lots were pooled into a single 3000 Gm. batch. A 3000 Gm. batch of ointment was prepared for each of the three Bentone ointment bases.

PART II - COMPARATIVE EVALUATION OF BENTONE OINTMENT BASES

The second phase of investigation involved a comparison of the three Bentone bases with other bases in common use. Before any qualities could be evaluated, however, it was necessary to determine a rational basis for the selection of different ointment bases to be compared with the three Bentone bases. Because of numerous replications involved in obtaining statistically significant data, the research program was designed to employ several different testing methods on a small number of bases, rather than to use a limited number of testing methods on a wide variety of bases. If a specific test in the series showed special merit, the particular test could then be repeated using a larger number of bases.

White Petrolatum U.S.P. (56, p.518) and Plastibase Hydrophilic[®] 10 were selected as the reference ointment bases to be compared with the three Bentone bases. White Petrolatum was selected since it is a major ingredient in many current official and nonofficial ointment formulations. This substance is "probably the most commonly used

¹⁰ Plastibase Hydrophilic[®] courtesy of E. R. Squibb and Sons, 745 Fifth Avenue, New York 22, N. Y.

of all ointment bases" (47). White petrolatum, a purified mixture of semisolid hydrocarbons, is considered to have properties like Bentone Base #3, the anhydrous hydrocarbon-Bentone 38 mixture. Plastibase[®] 11 and Plastibase Hydrophilic are ointment base formulations that have been reported favorably by several investigators (18; 31; 43; 48; 73; 87). Both Plastibase and Plastibase Hydrophilic are plasticized hydrocarbon gels composed of polyethylene and mineral oil (73, p.5). Plastibase Hydrophilic differs from Plastibase, however, in that a Hydrophilic agent, glyceryl mono-oleate, has been added to enable the base to absorb considerable quantities of water. The water is reported to form an o/w emulsified preparation (73, p.5). Because of its water absorbing properties, Plastibase Hydrophilic was selected to compare with the three Bentone bases and White Petrolatum.

Using the three Bentone bases, White Petrolatum and Plastibase Hydrophilic, experimental data are presented for: (1) physical and chemical stability, (2) body and consistency as defined by the effect of temperature on spreadability, capacity for solids, water absorbing properties,

¹¹ Plastibase[®] Type 30W courtesy of E. R. Squibb and Sons.

cone penetrometer readings, (3) drug release characteristics, and (4) handling and manufacturing properties.

Physical And Chemical Stability

The stability of ointments is of particular importance to the manufacturer. The manufacturer is especially interested in stability over extended periods of time, and the ability of an ointment to withstand extremes of temperature in shipment and during storage. Although the average life of a product from manufacturer to consumption is less than one year, it is often longer (6). In the present study, the physical and chemical stability was determined by evaluating the following: (1) the breaking temperature of the Bentone ointment bases, (2) the stability of the Bentone bases to cold, (3) the compatibility of Bentone and other common ointment bases with selected medicinal agents, and (4) aging tests (30, 60 days) employing the Bentone bases and other common ointment bases with selected medicinal agents.

Breaking Temperature. The maximum temperature to which an ointment base can be heated and retain the original properties upon cooling is termed the breaking temperature (31). The breaking temperature was determined for the three

Bentone ointment bases by placing 20 Gm. of each base in a crucible, heating in a sand bath and cooling to room temperature. The results from this study are shown in TABLE IV.

TABLE IV - BREAKING TEMPERATURE OF BENTONE OINTMENT BASES

OINTMENT BASE	BREAKING TEMPERATURE ° C.
Bentone Base #1	100° C. *
Bentone Base #2	100° C. **
Bentone Base #3	180° C. **

* These bases can be heated in excess of 100° C. for short periods of time. Longer periods of time drive off water.

** At 180° C. the ointment took on a slight charred odor. At 230° C. the base turned light yellow.

Results from TABLE IV indicate that the Bentone bases are stable to relatively high temperatures, and are considered to be stable during the highest temperatures encountered during shipping and storage. Bentone Base #3 is especially stable to high temperature and could be used in ophthalmic preparations where sterilization with heat is necessary.

Stability Of Bentone Bases To Cold. The stability to cold was determined for the three Bentone bases by cooling 20 Gm. of each base in open and sealed ointment jars to 0° C.

for six months. Examination of the bases indicated that all were stable.

Compatibility. The compatibility of an ointment base with a wide variety of drugs is desirable if the base is to be useful. In this study several substances used in present day dermatologic practice were incorporated into the three Bentone bases. Using several drops of liquid petrolatum as the levigating agent, the following is a partial list of substances that can be incorporated readily into each of the Bentone bases:

Benzoic acid	Penicillin
Salicylic acid	Thimerosal
Boric acid	Iodine-potassium iodide
Tannic acid	Ichthammol
Zinc oxide	Camphor
Ammoniated mercury	Menthol
Sulfur	Methyl salicylate
Sulfisoxazole	Liquefied phenol

Since the Bentone bases are largely hydrocarbon in composition, and are therefore relatively chemically unreactive, few chemical incompatibilities were encountered. Bentone Bases #2 and #3 were compatible with a wider range of drugs than Bentone Base #1.

Aging Studies. A series of aging studies was conducted with seven of the above drugs to determine both the initial compatibility, and the stability over extended periods of

time at 22.5° C. The drugs tested were ichthammol, iodine-potassium iodide, liquefied phenol, sulfisoxazole, zinc oxide, thimerosal and ammoniated mercury. The ointment bases used were Plastibase Hydrophilic, White Petrolatum, and the three Bentone bases. Evaluations were made on each ointment for: (1) separation, (2) texture, and (3) spreadability, initially and at the end of 30 and 60 days. Phase separation and texture were determined by visual examination of the ointment base, initially and after working with a spatula on a pill tile. Spreadability was judged visually only, pending further study to be described later using the spreadability machine (See Figure 8 to be presented later). Data from this study are presented in TABLE V.

Results from the aging study indicate:

1. Phase separation was more common with ointments prepared with Bentone Base #1. The remainder of the ointments tested were stable or showed only traces of bleeding.
2. The texture of the finished ointments was smooth and homogeneous in every instance except those with Bentone Base #1 and certain drugs.
3. The spreadability was found to vary among the different ointments. White Petrolatum, normally thick at room temperature, became even less spreadable when solid substances were incorporated into it. Bentone Base #1 became more spreadable with the incorporation of certain drugs. The spreadability of Bentone Bases #2 and #3 remained

TABLE V

AGING STUDIES OF OINTMENT BASES CONTAINING VARIOUS MEDICINALS AT 22° C.

OINTMENT BASES	PROPERTY	DRUGS INCORPORATED																							
		10% Ichthammol			4% I 4% KI			2% Liquefied Phenol			10% Sulfi-soxazole			20% Zinc Oxide			0.5% Thimerosal			5% Ammoniated Mercury			CONTROL		
BENTONE BASE #1	S	5	0	0	8	3	3	7	6	6	10	9	9	8	8	8	10	7	7	10	7	7	10	10	10
	T	5	0	0	8	4	4	8	6	6	10	9	9	10	10	10	10	10	10	10	10	10	10	10	10
	Sp	5 ^t	0	0	7 ^t	0	0	9 ^t	6	6	10	10	10	8 ^t	8	8	8 ^t	8	8	10	9	9	10	10	10
BENTONE BASE #2	S	10	9	9	10	8	8										10	9	9						
	T	10	10	10	10	10	10	10*			10*			10*			10	10	10	10*			10*		
	Sp	10	10	10	10	10	10										10	10	10						
BENTONE BASE #3	S																								
	T		10*		10*			10*			10*			10*			10*			10*			10*		
	Sp																								
PLASTIBASE HYDROPHILIC	S													10	10	10									
	T		10*		10*			10*			10*			10	10	10	10*			10*			10*		
	Sp													9 ^s	9	9									
WHITE PETROLATUM	S	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	T	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	Sp	5 ^s	5	5	5 ^s	5	5	5 ^s	5	5	3 ^s	3	3	3 ^s	3	3	5 ^s	5	5	5 ^s	5	5	5 ^s	5	5
Days after Manufacture		0	30	60	0	30	60	0	30	60	0	30	60	0	30	60	0	30	60	0	30	60	0	30	60

S = Separation - 10=homog. & creamy; 9=trace bleeding; 8=bleeding; 7=creamed; 3-6=some separation; 0=cracked.

T = Texture - 10=smooth & homogeneous; 4=grainy and/or lumpy; 0=unsatisfactory.

Sp= Spreadability - 10=spreadable; 4-9=stiff (s) or thin (t); 3=very stiff or thin; 0=unsatisfactory.

* All values were 10.

approximately the same after the addition of medicaments.

4. Bentone Bases #2 and #3 and Plastibase Hydrophilic had the best overall stability, texture and spreadability of all bases tested. Bentone Base #3 was the best base tested in the aging study.

Bentone bases containing no medicinal ingredients were subjected to storage conditions of 0° C. and 47.5° C. for three months. Results indicate that Bentone Bases #2 and #3 were stable at both high and low temperatures. Bentone Base #1 was stable at lower temperatures but discolored slightly and creamed at elevated temperatures.

Body And Consistency

The therapeutic effectiveness, utility, and patient acceptance of an ointment base depends largely upon its consistency. Skauen et al. indicate that softer ointments show a greater release of active ingredients (67). Mutimer et al. indicate that it is important for an ointment to spread easily if the product is to gain patient acceptance (48). Ease of spreading is important where ointments are to be applied to painful areas. This is especially true when the ointment must be rubbed in well to ensure maximum contact. For these and other reasons, the composition of ointment bases consisting of greasy, stiff, hydrophobic,

semisolid products is no longer consistent with modern day thinking. The current concept of ointments has rather been expanded to include soft, unctuous, hydrophilic preparations, frequently in an emulsion form.

Although the body and consistency of ointments have been evaluated frequently as stiff or spreadable on the basis of "feel", it has been only in the last few years that specific tests have been devised to yield numerical values for these properties. In this study, the measurement of body and consistency was determined by: (1) the effect of temperature on spreadability, (2) capacity of ointment bases for solids, (3) water absorbing properties of ointment bases, and (4) cone penetration measurements.

Spreadability. An ointment that spreads easily, without the need for excessive pressure upon application, will be less irritating to painful areas. Mutimer et al. have devised a method to measure the spreadability of various ointments (48). This method is based on the theory that for an ointment to spread well it should behave like a good lubricant, exhibiting a minimum of "drag" and a maximum of "slip". In this method, a glass microscope slide is covered with a uniform film of ointment base and pressed flat

against the surface of a second slide. The spreadability of the ointment base is measured by the time required for a standardized force to draw one slide over the other.

In the present study a spreadability apparatus was constructed, tests were conducted, and spreadability times were recorded for seven ointment bases at 10° C., 22.5° C., 35° C. and 47.5° C. The drugs used in this study were the three Bentone bases, Plastibase Hydrophilic, White Petrolatum, Plastibase and Wool Fat. The apparatus used in taking these spreadability measurements was patterned after Mutimer et al. (48, p.216) and is shown in Figure 8. In making the tests, an excess of ointment, previously standardized to the appropriate testing temperature for 24 hours, was placed between two slides. A 1000 Gm. weight was placed on each slide for five minutes to expel air between the sides and to provide a uniform film of ointment. Excess ointment was carefully removed from the edges of the slides. The slides were handled on their edges to prevent warming by the fingers. The bottom slide was anchored and the ointment-containing slides were allowed to remain on the apparatus for an additional five minutes to ensure equilibrium temperature. The top slide was then subjected to a

pull of 80 Gm. The time in seconds required to separate completely the two slides was noted at 10° C., 22.5° C., 35° C. and 47.5° C. The 10° C. temperature was maintained in a previously regulated industrial-type walk-in cold room. The 22.5° C., 35° C. and 47.5° C. temperatures were maintained in an oven¹². Although the oven was equipped with a thermometer, additional thermometers were placed into each container of ointment base in order to make certain that the base remained the same temperature after opening the oven door. The data obtained from this study are presented in TABLE VI and Figure 9.

Results from the spreadability tests indicate:

1. The three Bentone bases and Plastibase demonstrated good spreadability at 10° C., indicating that they had good body and consistency at this temperature. Plastibase Hydrophilic had intermediate spreadability at 10° C. Wool Fat and White Petrolatum were not spreadable at 10° C., and are considered to be too stiff for use as ointment bases at this temperature.
2. At 22.5° C. the three Bentone Bases, Plastibase and Plastibase Hydrophilic demonstrated the best spreadability, indicating that they would be satisfactory bases at this temperature. Wool Fat and Petrolatum offered some resistance to spreadability at 22.5° C. Wool Fat was the least

¹² Aloe Scientific Oven No. 400, Labline, Inc., Chicago Surgical and Electric Co., Chicago 22, Ill.

TABLE VI

EFFECT OF TEMPERATURE ON SPREADABILITY OF OINTMENT BASES AT 10° C., 22.5° C., 35° C. AND 47.5° C.

OINTMENT BASES	Time in Seconds Required to Separate Slides at 10° C., 22.5° C., 35° C. and 47.5° C.									
	10° C.			22.5° C.			35° C.			47.5° C.
BENTONE	2.9	2.8	2.7	2.5	2.6	2.3	1.1	1.1	1.0	
BASE #1	2.8	3.0	<u>2.8*</u>	2.2	2.5	<u>2.4</u>	1.0	1.0	<u>1.0</u>	<u>1.0</u>
BENTONE	5.3	5.4	5.4	3.9	4.1	3.7	3.2	3.9	2.6	
BASE #2	5.8	5.5	<u>5.5</u>	3.8	3.9	<u>3.9</u>	3.1	2.8	<u>3.1</u>	<u>1.0</u>
BENTONE	8.4	8.0	7.9	4.6	4.7	4.9	4.0	3.8	4.2	
BASE #3	8.2	7.6	<u>8.0</u>	4.5	4.7	<u>4.7</u>	3.9	4.1	<u>4.0</u>	<u>1.0</u>
PLASTIBASE	24.2	20.4	21.8	7.5	8.9	7.3	3.5	3.6	3.6	
HYDROPHILIC	23.6	21.0	<u>22.2</u>	7.9	8.2	<u>8.0</u>	3.7	3.8	<u>3.6</u>	<u>1.0</u>
WHITE	1 hr.	1 hr.	1 hr.	52.5	63.8	58.8	4.7	3.8	4.8	
PETROLATUM	1 hr.	1 hr.	<u>1 hr.</u>	57.5	64.2	<u>59.4</u>	4.3	4.1	<u>4.3</u>	<u>1.0</u>
PLASTIBASE	2.6	2.3	2.6	2.1	1.9	2.1	0.8	0.9	1.0	
	2.1	2.4	<u>2.4</u>	2.3	2.2	<u>2.1</u>	1.1	0.9	<u>0.9</u>	<u>1.0</u>
WOOL FAT	1 hr.	1 hr.	1 hr.	286.7	302.8	299.2	4.2	4.3	4.6	
	1 hr.	1 hr.	<u>1 hr.</u>	328.1	315.5	<u>306.4</u>	4.1	4.1	<u>4.3</u>	<u>1.0</u>

*The underlined numbers represent an average of the five recorded values.

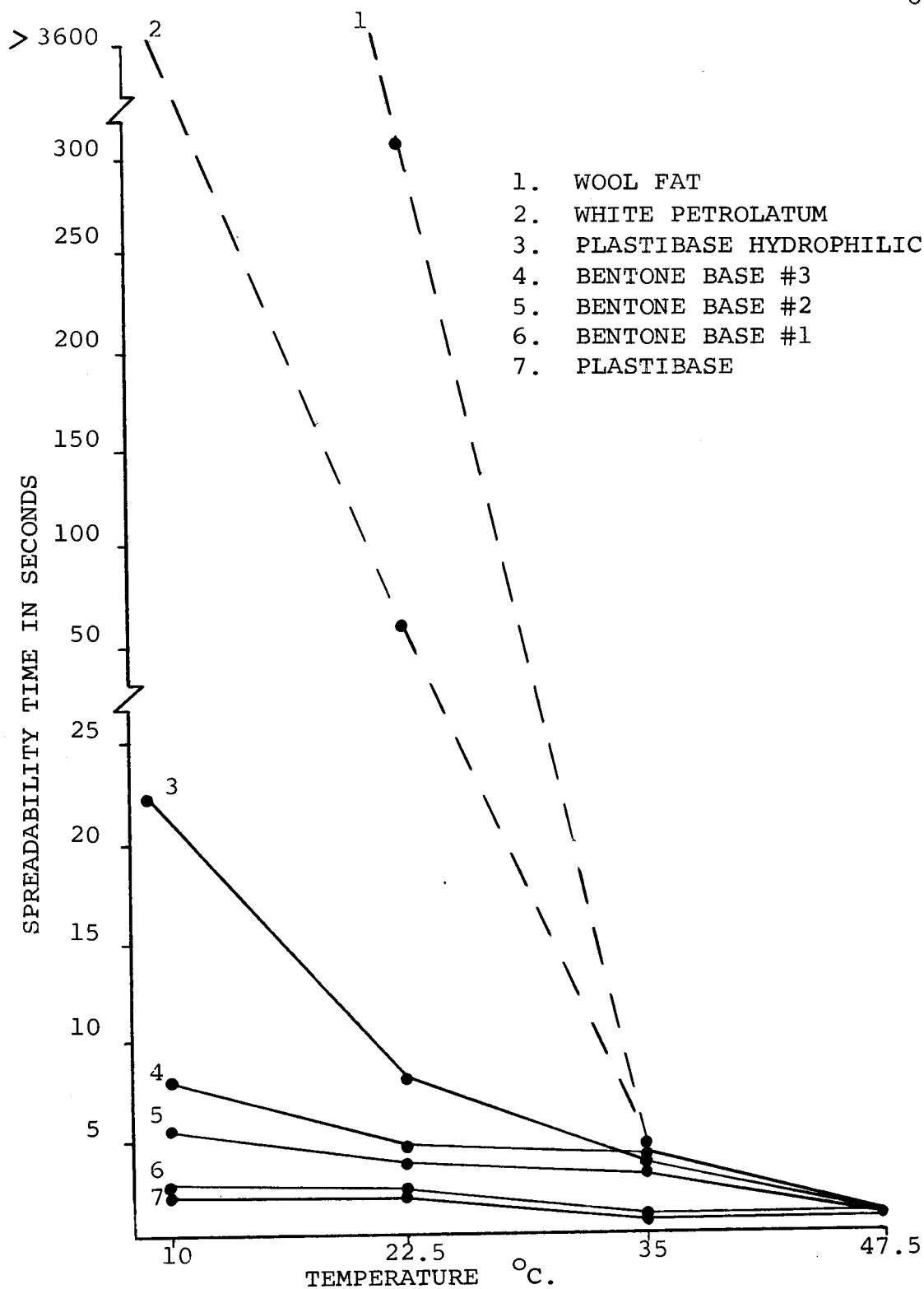


Figure 9. Spreadability of Ointment Bases at 10° C., 22.5° C., 35° C. and 47.5° C.

spreadable base tested at 22.5° C.

3. All of the bases were readily spreadable at 35° C. Plastibase and Bentone Base #1 were especially thin at 35° C., however, and are considered to be of little value at this temperature.
4. At 47.5° C. Bentone Bases #2 and #3, Plastibase Hydrophilic and White Petrolatum were spreadable but retained their body and consistency. Plastibase, Bentone Base #1 and Wool Fat were especially thin and are considered to be of little value at 47.5° C.
5. Changes in temperature affected the spreadability of Bentone Bases #2 and #3 and Plastibase Hydrophilic the least, and on this basis these bases are considered superior to the other bases included in this study.

Capacity for Solids. Although the consistency of an ointment base is important, the consistency of finished ointments prepared from the base is of even greater importance. Ointment bases which maintain good consistency, even with a high solid content, are more versatile than those which become hard when similarly loaded with solids. To measure the capacity for solids, increments of 5% to 20% of zinc oxide were added to Bentone Base #2 and White Petrolatum, and spreadability measurements were taken at 10° C., 22.5° C. and 35° C. Bentone Base #2 and White Petrolatum were chosen since they represented extremes of spreadability in the various studies (see Figure 9). Results obtained

from this study are presented in TABLE VII and Figure 10.

These data indicate:

1. Bentone Base #2 was able to maintain good consistency at all temperatures tested, even with a high content of solids.
2. White Petrolatum became hard when loaded with solids, and was very difficult to manipulate at 10° C. and 22.5° C. At 35° C. White Petrolatum was thin, runny and separated from the zinc oxide.
3. Bentone Base #2 was superior to White Petrolatum in its ability to maintain desirable body and consistency when loaded with solids.

In addition to these quantities of solids, concentrations of 30% and 50% zinc oxide were incorporated into Bentone Base #2 and White Petrolatum. A concentration of 30% zinc oxide in White Petrolatum was very stiff and unmanageable. A concentration of 50% zinc oxide in Bentone Base #2 was heavy but still easily manipulated. The results from this study indicate that Bentone Base #2 was more versatile than White Petrolatum as an ointment base for solid medicaments.

Water Absorbing Properties. Since liquids are frequently incorporated into prescriptions written for ointments, the ability of an ointment base to "take up" liquid substances is essential to the stability of the finished product. One method for measuring the ability of ointment

TABLE VII

CAPACITY OF BENTONE BASE #2 AND WHITE PETROLATUM FOR SOLIDS AT 10° C., 22.5° C. AND 35° C.

OINTMENT BASES	TEMPERATURE	Spreadability Time in Seconds for Bases Containing Zinc Oxide**											
		5 %			10 %			15 %			20 %		
BENTONE BASE #2	10° C.	81.3	72.2	71.5	139.5	127.5	132.2	182.5	174.6	193.0	312.7	298.1	292.3
		78.5	68.5	<u>74.4*</u>	140.0	143.3	<u>136.5</u>	190.2	171.5	<u>182.4</u>	287.5	308.8	<u>299.9</u>
WHITE PETROLATUM	10° C.	1 hr.	1 hr.	1 hr.	1 hr.	1 hr.	1 hr.	1 hr.	1 hr.	1 hr.	1 hr.	1 hr.	1 hr.
		1 hr.	1 hr.	<u>1 hr.</u>	1 hr.	1 hr.	<u>1 hr.</u>	1 hr.	1 hr.	<u>1 hr.</u>	1 hr.	1 hr.	<u>1 hr.</u>
BENTONE BASE #2	22.5° C.	9.2	11.1	8.9	15.2	16.0	14.2	26.8	34.4	35.6	87.2	100.6	89.1
		11.3	9.6	<u>10.0</u>	18.1	19.0	<u>16.5</u>	37.7	34.9	<u>33.9</u>	95.3	81.3	<u>90.7</u>
WHITE PETROLATUM	22.5° C.	63.3	63.8	66.2	82.0	76.9	88.2	101.8	90.0	88.3	114.8	91.5	87.9
		72.4	61.7	<u>65.5</u>	79.8	67.6	<u>78.9</u>	85.8	108.4	<u>94.9</u>	110.2	105.1	<u>101.9</u>
BENTONE BASE #2	35° C.	6.3	5.8	5.5	11.5	11.2	14.1	22.2	19.8	19.0	50.1	59.1	41.5
		7.1	5.8	<u>6.1</u>	12.2	13.3	<u>12.5</u>	21.6	18.2	<u>20.2</u>	46.7	52.7	<u>50.0</u>
WHITE PETROLATUM	35° C.	4.8	4.9	4.6	6.2	6.1	5.9	8.2	6.9	7.1	9.1	9.9	9.7
		5.1	4.8	<u>4.8</u>	6.1	5.9	<u>6.0</u>	7.1	7.5	<u>7.4</u>	8.9	8.2	<u>9.0</u>

*The underlined numbers represent an average of the five recorded values.

**See Table VI for bases with 0 % zinc oxide.

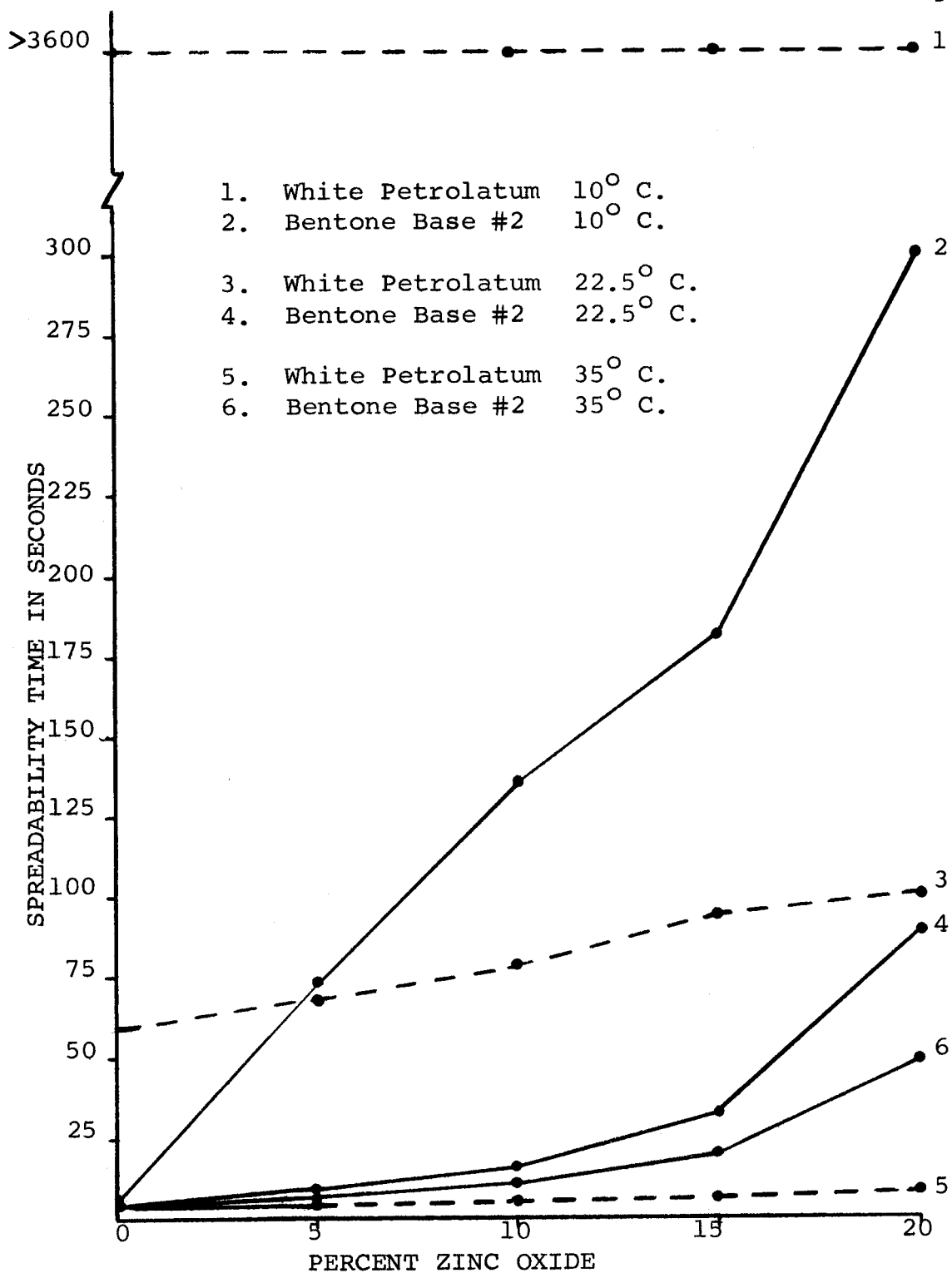


Figure 10. Capacity For Solids of Bentone Base #2 and White Petrolatum at 10° C., 22.5° C., and 35° C.

bases to absorb water is by the computation of their "water numbers" (7; 8; 22; 45, p.412). The "water number" for a system has been defined by Casparis and Meyer as the largest amount of water which 100 Gm. of an ointment base or fat will hold at normal temperature, 20^o C. (7; 8). In determining the "water number", different experimental designs and methodology have been employed, depending upon the "type" of ointment base (i.e. emulsion, anhydrous, etc.) to be evaluated. Using two entirely different methods, Halpern and Zopf have shown that comparable "water numbers" could be obtained for certain bases (22). They found, for example, that the "water number" of White Petrolatum was 9.0 by one method and 9.5 by a second method, while the "water number" of Yellow Petrolatum was 10.2 and 10.8 respectively. This work correlated well with that earlier reported by Casparis and Meyer (7; 8).

The method for determining the "water number" in the present study was similar to the second method of Halpern and Zopf (22) and is described as follows:

1. Preliminary studies were made on a 10 Gm. portion of base.
2. A 100.0 Gm. portion of ointment was then triturated in a mortar, with water delivered from a burette 0.5 cc. at a time.

3. When no more water was taken up, the mixture was chilled for one hour in an ice bath.
4. The ointment was then allowed to warm to room temperature and was levigated on an ointment tile.
5. If water was exuded by levigation the process was repeated with a fresh sample, using 0.5 ml. less of water. This was repeated until a level was reached at which no water could be exuded by levigation.
6. The "water number" was calculated in the following manner:

$$\text{Water Number} = \frac{\text{ml. water absorbed}}{\text{Gm. base used}} \times 100$$

In the present study the "water number" was obtained for the three Bentone bases, Plastibase Hydrophilic, White Petrolatum, Plastibase and Hydrophilic Petrolatum by the method outlined above. The results of this study are presented in TABLE VIII.

Results from the water absorption study indicate:

1. Bentone Base #1 had better texture than Plastibase, but was inferior in consistency to the other bases used in this study.
2. Bentone Bases #2 and #3 did not separate when considerable quantities of water were incorporated, but formed stable, homogeneous bases.
3. Bentone Bases #2 and #3 had a smooth glossy texture even after the incorporation of large quantities of water.
4. Bentone Bases #2 and #3 maintained better body and consistency than the other bases tested, even after the incorporation of large amounts of water.

TABLE VIII

WATER NUMBER OF BENTONE BASES AND OTHER COMMON BASES

BASE	WATER NUMBER	EVALUATION* OF SATURATED BASES FOR SEPARATION, TEXTURE AND SPREADABILITY		
		S	T	Sp
Bentone Base #1	30 s	9 oil	8 grainy	5 t
Bentone Base #2	100 ns	10	10	10
Bentone Base #3	120 ns	10	10	10
Plastibase Hydro- philic	120 ns	10	10	7 t
White Petrolatum	10 s	10	10	5 s
Plastibase	30 s	8 water	5 bubbles	5 t
Hydrophilic Petro- latum	40 s	9 water	10	5 s

ns = not saturated, but additional water is added with considerable difficulty.

s = saturated with water.

*S = Separation----- 10=homogeneous and creamy;9=trace bleeding;8=bleeding;0=cracked.

*T = Texture----- 10=smooth and homogeneous;5=grainy and/or lumpy;0=unsatisfactory.

*Sp= Spreadability - 10=good consistency;5-9=stiff (s) or thin (t); 0=unsatisfactory.

5. Plastibase Hydrophilic absorbed large amounts of water, but in doing so become overly thin.
6. White Petrolatum absorbed little water and remained stiff.
7. In general, Bentone Bases #2 and #3 had water absorbing properties superior to the other bases included in this study.

Cone Penetration. Penetration methods have been reported extensively as a method of determining the body and consistency of ointments and products of ointment-like consistency (15; 17; 18; 48; 78). The method used in the present study is based on the depth of penetration, by a metal cone, into various ointment bases at varying temperatures.

In the present study a cone penetration assembly apparatus was constructed and cone penetration depths were recorded for several ointment bases at 10° C., 22.5° C., 35° C. and 47.5° C. The ointments tested were the three Bentone bases, Plastibase Hydrophilic, White Petrolatum, Plastibase and Wool Fat. The apparatus developed to make these measurements is shown in Figure 11. In making these tests, the ointment bases were carefully packed into standard 125 ml. conical metric graduates¹³ (manufactured to the

¹³ Phenix brand graduates were obtained from Armstrong Cork Co., Lancaster, Pa.

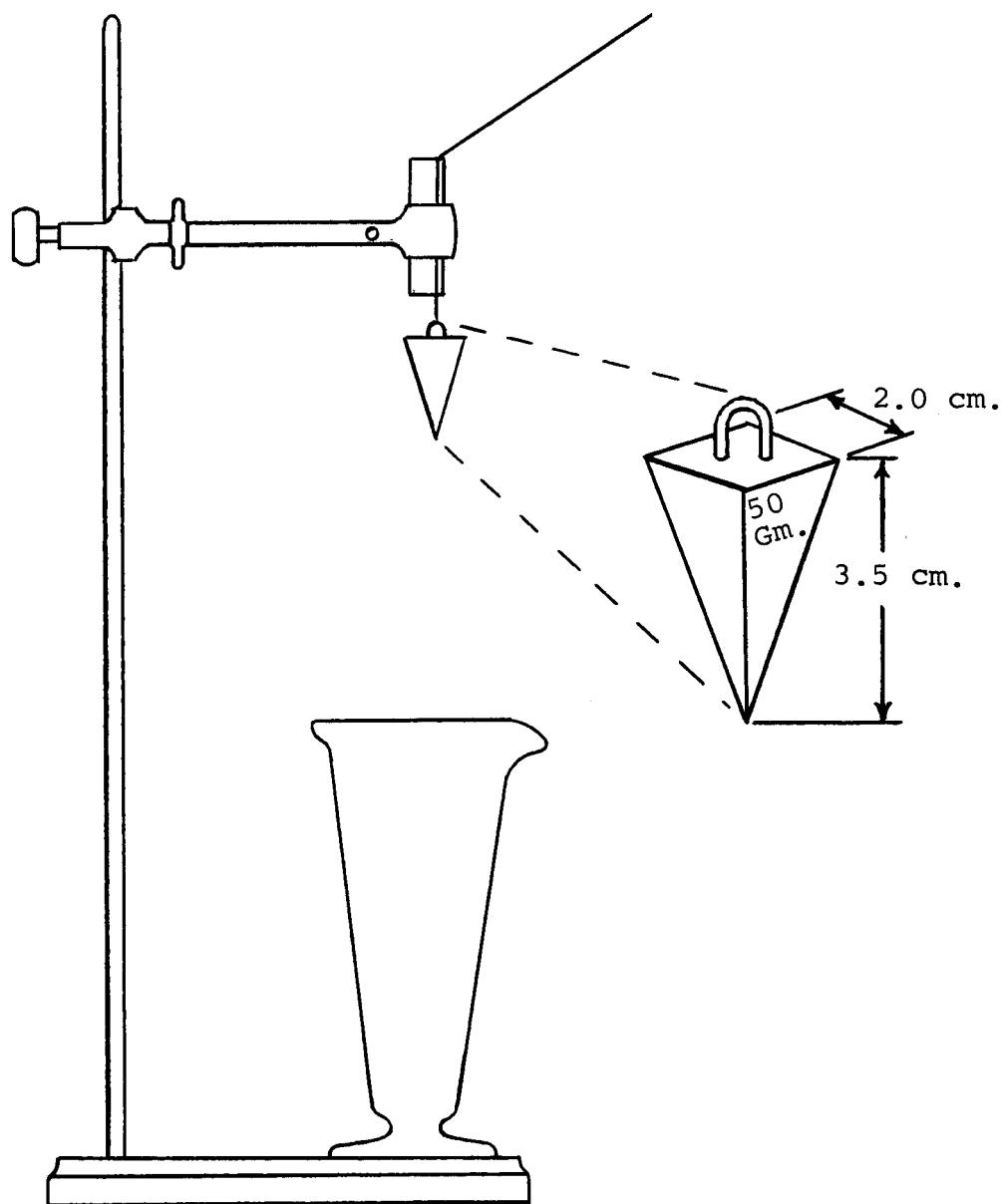


Figure 11. Cone Penetration Assembly for Determining the Body and Consistency of Ointment Basis.

specifications of U.S.P. and U.S. Bureau of Standards). A 50.00 Gm. weight (see Figure 11) was suspended from a nylon thread and dropped a distance of 8.0 cm. into each of seven ointment bases. The distance that the weight penetrated into each base was measured immediately. The tests were conducted in an oven and cold room under temperatures previously described for spreadability tests. The results obtained in comparing the seven ointment bases are shown in TABLE IX and Figure 12.

Results from the cone penetration study indicate:

1. Wool Fat and White Petrolatum offered the most resistance to penetration at 10° C., and their usefulness as ointment bases is seriously questionable at this temperature. Bentone Bases #2 and #3 and Plastibase Hydrophilic were intermediate in consistency and are considered good ointment bases. Bentone Base #1 offered the least resistance to penetration at 10° C., indicating that it could be applied more easily than the other bases tested.
2. Wool Fat and White Petrolatum offered the most resistance to penetration at 22.5° C., the former being exceptionally stiff. Bentone Bases #2 and #3 and Plastibase Hydrophilic were again intermediate in consistency and are considered good ointment bases for use at room temperature. Plastibase and Bentone Base #1 offered the least resistance to penetration, but were not considered to be overly thin.
3. All of the bases were easily penetrated at 35° C. White Petrolatum, Bentone Bases #2 and #3, Plastibase Hydrophilic and Wool Fat maintained the best

TABLE IX

CONE PENETRATION READINGS OF OINTMENT BASES AT 10° C., 22.5° C., 35° C. AND 47.5° C.

OINTMENT BASES	Degree of Penetration in Centimeters at 10° C., 22.5° C., 35° C. and 47.5° C.											
	10° C.			22.5° C.			35° C.			47.5° C.		
BENTONE	6.2	6.2	6.4	9.0	8.9	8.8	9.7	9.7	10.1	10.5	10.1	10.4
BASE #1	6.4	6.3	<u>6.3*</u>	8.8	8.9	<u>8.9</u>	9.8	9.9	<u>9.8</u>	10.5	10.3	<u>10.4</u>
BENTONE	3.5	3.6	3.7	5.1	5.1	5.2	5.9	5.9	5.9	6.8	6.9	6.6
BASE #2	3.8	3.7	<u>3.7</u>	5.1	5.0	<u>5.1</u>	6.1	6.0	<u>6.0</u>	6.7	6.9	<u>6.8</u>
BENTONE	3.1	3.1	3.2	3.3	3.3	3.4	3.4	3.5	3.3	3.7	3.5	3.6
BASE #3	3.2	3.3	<u>3.2</u>	3.4	3.5	<u>3.4</u>	3.5	3.6	<u>3.5</u>	3.7	3.6	<u>3.6</u>
PLASTIBASE	3.0	3.1	2.9	3.8	3.7	3.7	4.1	3.9	4.2	4.1	4.3	4.4
HYDROPHILIC	2.9	3.0	<u>3.0</u>	3.7	3.9	<u>3.8</u>	4.2	4.0	<u>4.1</u>	4.3	4.2	<u>4.3</u>
WHITE	0.4	0.4	0.3	2.5	2.5	2.6	3.4	3.3	3.2	3.4	3.6	3.6
PETROLATUM	0.3	0.3	<u>0.3</u>	2.4	2.5	<u>2.5</u>	3.3	3.2	<u>3.3</u>	3.5	3.6	<u>3.5</u>
PLASTIBASE	4.4	4.2	4.5	8.6	8.8	8.4	9.8	10.0	9.8	10.7	10.5	10.8
	4.3	4.3	<u>4.3</u>	8.5	8.6	<u>8.6</u>	9.7	9.9	<u>9.8</u>	10.6	10.5	<u>10.6</u>
WOOL FAT	0.2	0.1	0.1	0.9	0.8	0.9	4.5	4.6	4.3	11.0	11.1	10.9
	0.1	0.2	<u>0.1</u>	0.8	0.8	<u>0.8</u>	4.6	4.6	<u>4.5</u>	10.9	10.7	<u>10.9</u>

*The underlined numbers represent an average of the five recorded values.

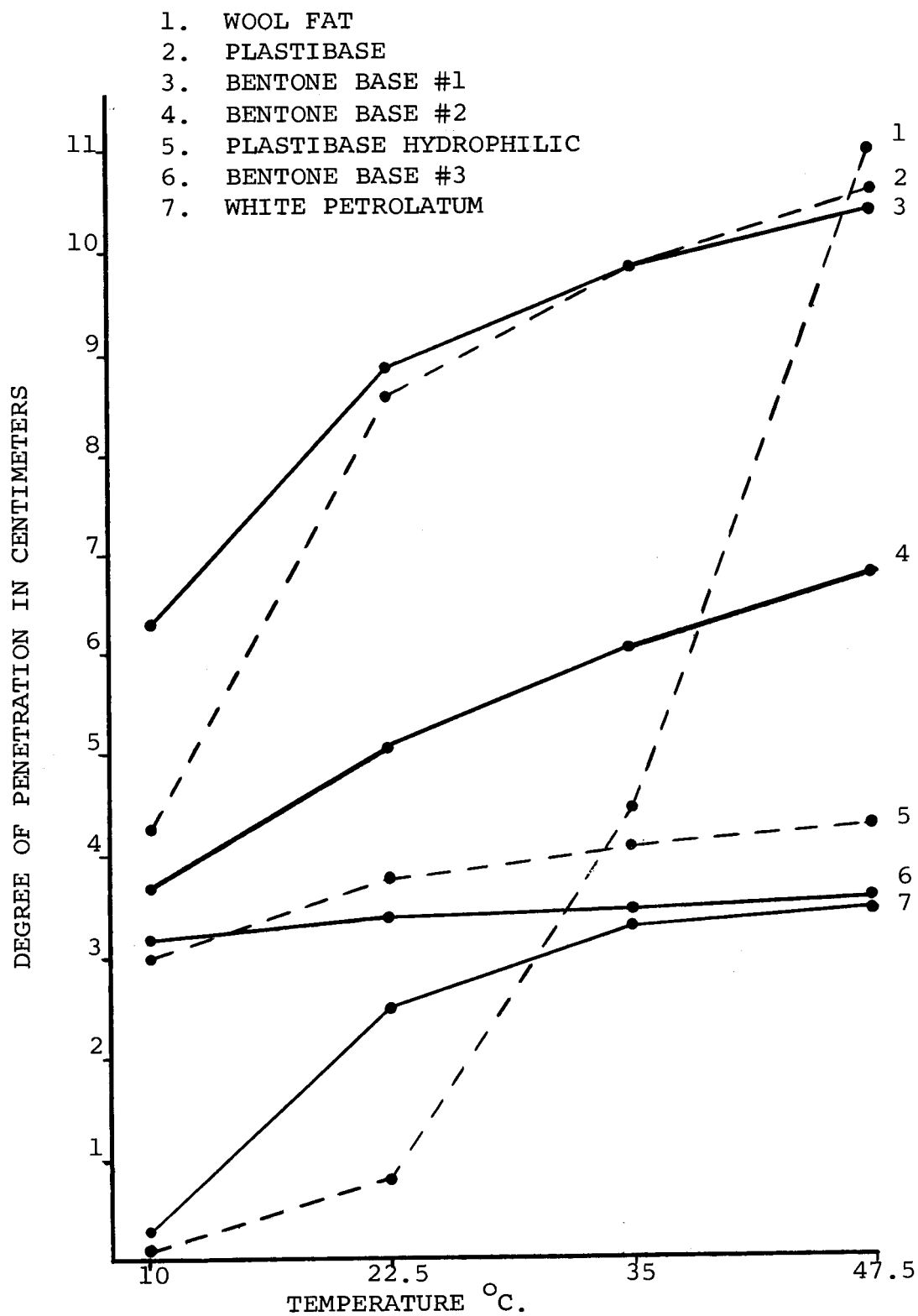


Figure 12. Degree of Cone Penetration Into Ointment Bases at 10° C., 22.5° C., 35° C. and 47.5° C.

body and consistency at this temperature. Plastibase and Bentone Base #1 were easily penetrated at 35° C., and their usefulness at this temperature is questionable.

4. White Petrolatum, Bentone Bases #2 and #3 and Plastibase Hydrophilic were readily penetrated at 47.5° C., but retained their body and consistency. Wool Fat, Plastibase and Bentone Base #1 were especially thin at 47.5° C. and are of little value as bases at this temperature.
5. The degree of penetration in Bentone Bases #2 and #3 and Plastibase Hydrophilic was affected the least by changes in temperature. These bases were readily penetrated when cold and maintained body when warmed. These three bases are considered to be superior to the other bases tested in this study.

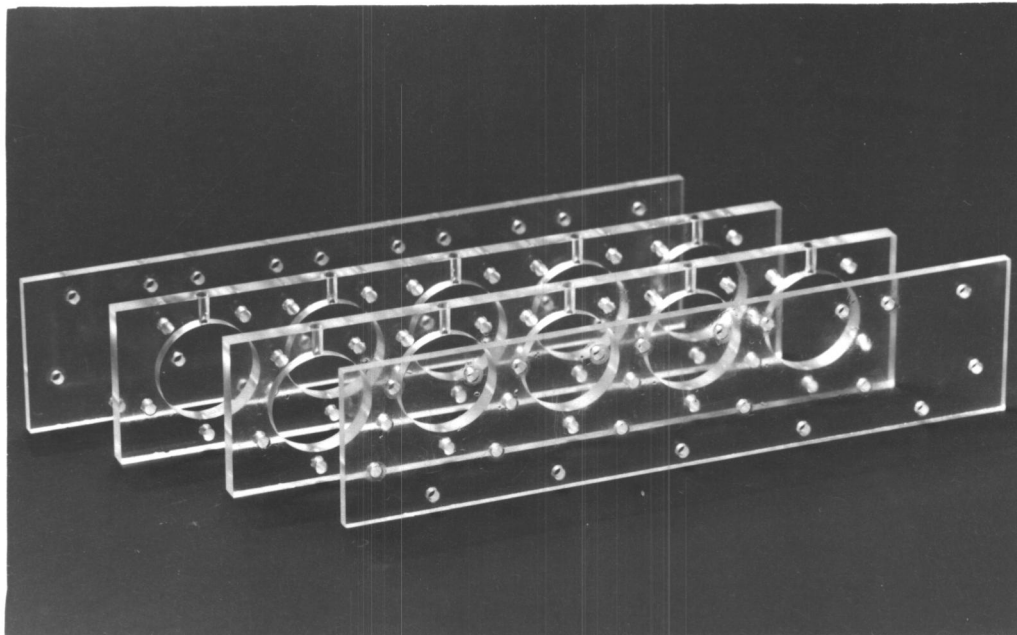
Drug Release Characteristics

"Probably the most important function of an ointment base is the control that it exerts on the release of the medication which it carries" (48). For a drug to be effective, it must first be released from the ointment base. Numerous methods are reported in the literature for measuring the release of drugs from various ointment bases (12; 25; 29; 40; 41; 46; 48; 53; 64; 65; 67; 71; 72; 74; 75; 76). Although many of the in vitro tests enjoy only limited application, they nevertheless have been shown to measure the rate and extent of drug release. In this study a dialysis cell method and a microbiological method were used to evaluate the drug release characteristics of ointment bases.

Dialysis Cell Method. Jurist has described a dialysis cell method for measuring the ion-exchange capacity of a resin incorporated into an ointment base (36). This method is based on the measurement of ion exchange through a semi-permeable membrane, specifically the exchange of hydrogen ions on the resin for sodium ions in a solution of sodium citrate. A modification of this method has been used successfully by Mutimer et al. (48), Wood et al. (86), and other researchers (12).

In the present study a dialysis cell method was employed to determine the extent of drug release from the three Bentone bases, Plastibase Hydrophilic, White Petrolatum and Plastibase. The procedure used in this study was a combination of the methodology employed by Jurist (36) and Mutimer et al. (48), and a diffusion cell patterned according to the specifications reported by Wood et al. (85; 86). The diffusion cell used in this study was the "type for semisolid media" (86) constructed from 3/8-inch plastic, and is shown in Figure 13.

From Figure 13 it can be seen that the apparatus consists of four plastic components, the center two each containing five diffusion cell compartments. Each diffusion



ASSEMBLED UNIT

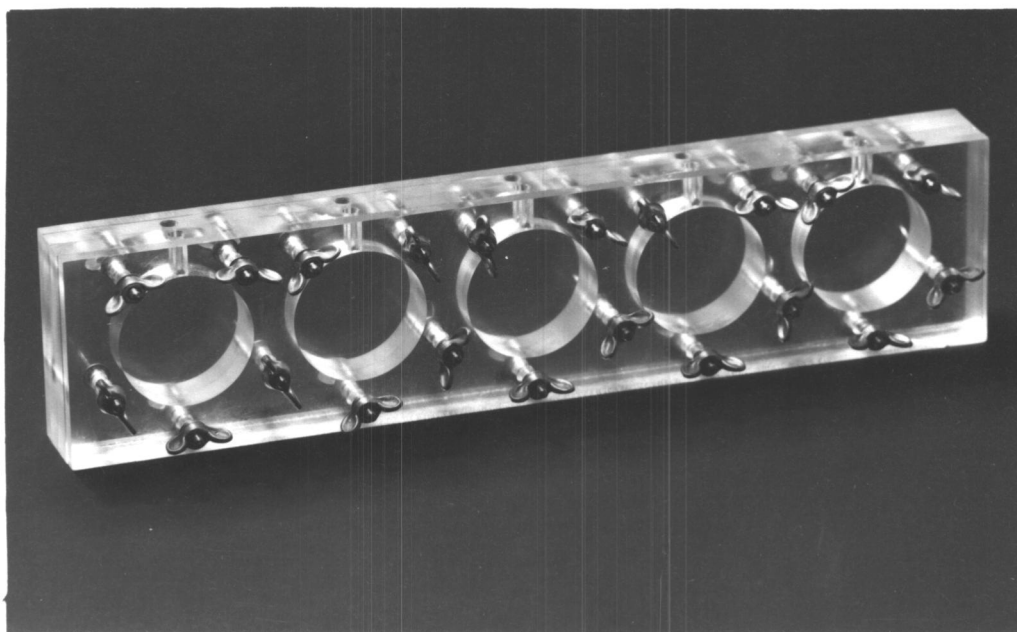


Figure 13. Plastic Diffusion Cell for Measuring the Diffusion of Medicaments From Ointments.

cell compartment is cylindrical in shape with an opening in each section of the cylinder for filling the cell and removing its contents. To assemble the apparatus, cellophane¹⁴ was placed at the center of the four plastic components, and the unit was assembled by tightening the wing nuts on the bolts passing through the unit (See Figure 13). The internal dimensions were such that when completely full, each of the five cell compartments contained 15.5 cc. of ointment and 15.5 cc. of liquid solution separated by the cellophane membrane.

Experimentally, 30.0 Gm. of Amberlite[®] 15 CG-50 AR Type II (200 to 400 mesh) ion exchange resin was incorporated into 170.0 Gm. of each of the three Bentone bases, Plastibase Hydrophilic, White Petrolatum and Plastibase. The ointments were selected for testing one at a time in all five diffusion cell compartments. A portion of the first

¹⁴ Cellophane No. 300 pt, courtesy of E. I. du Pont de Nemours and Co., Wilmington, Del.

¹⁵ Amberlite[®] is a registered trademark of Rohm and Haas Co., Philadelphia, Pa., distributed by Mallinckrodt Chemical Works, St. Louis, Mo. (62). Amberlite CG-50 AR was formerly designated as Amberlite XE-64 (77). This is a weakly acidic, carboxylic type of cationic exchange resin (62).

ointment to be tested was spread evenly in the "donor side" of each of the five diffusion cell compartments and the depression was leveled exactly with a straightedge scraper. The cellophane membrane was installed with care to make good contact with the ointment, and the unit was assembled with bolts and wing nuts to make a watertight seal. Exactly 15.5 ml. of freshly prepared 5.00% w/v aqueous sodium citrate solution (adjusted to pH 11.5 ± 0.05 with sodium hydroxide) was introduced into the "receptor side" of each of the five diffusion cell compartments at successive two-minute time intervals. Precise final adjustments were made in the ointment level so that the 15.5 ml. of sodium citrate solution was exactly at the top of each of the five cell compartments (i.e. pressure was applied or released from the ointment side of the membrane to regulate the final height of the sodium citrate solution in each of the five cell compartments). The assembled cell unit was then immersed almost to the top in a constant temperature water bath at 22.5° C. At 60-minute time intervals, 10.0 ml. of sodium citrate solution was withdrawn from the opening in each of the five diffusion cell compartments by means of a syringe, and pH determinations were made using a Beckman Zeromatic

pH meter¹⁶ previously standardized to pH 8.0 ± 0.05 at 25° C. with pHydrion[®] Buffers¹⁷ powders. The sample was returned in less than one minute to the dialyzer. Readings were recorded to the nearest 0.01 pH unit. However, when taking into consideration the sensitivity of the pH meter, the errors induced by the operator, and the degree of accuracy of the buffer used to standardize the pH meter, the data were considered significant only to the nearest 0.1 pH unit. The results obtained for each of the six ointments are presented in TABLE X and Figure 14.

Results from the dialysis cell study indicate:

1. Bentone Base #2 caused the most rapid reduction in pH of the bases tested. Bentone Base #2 reduced the pH two times more rapidly than the next nearest base, and eight to ten times more rapidly than the remainder of the bases.
2. Plastibase Hydrophilic caused an intermediate reduction in pH of the six bases tested. Plastibase Hydrophilic reduced the pH three times more rapidly than the remainder of the bases.
3. Plastibase, Bentone Bases #1 and #3, and White Petrolatum caused the least rapid reduction of pH. White Petrolatum caused slightly greater pH reductions than Plastibase and Bentone Bases #1 and #3.

¹⁶ Beckman Instruments Inc., Fullerton, Calif.

¹⁷ Registered trademark of Micro Essential Laboratory, Brooklyn, N. Y.

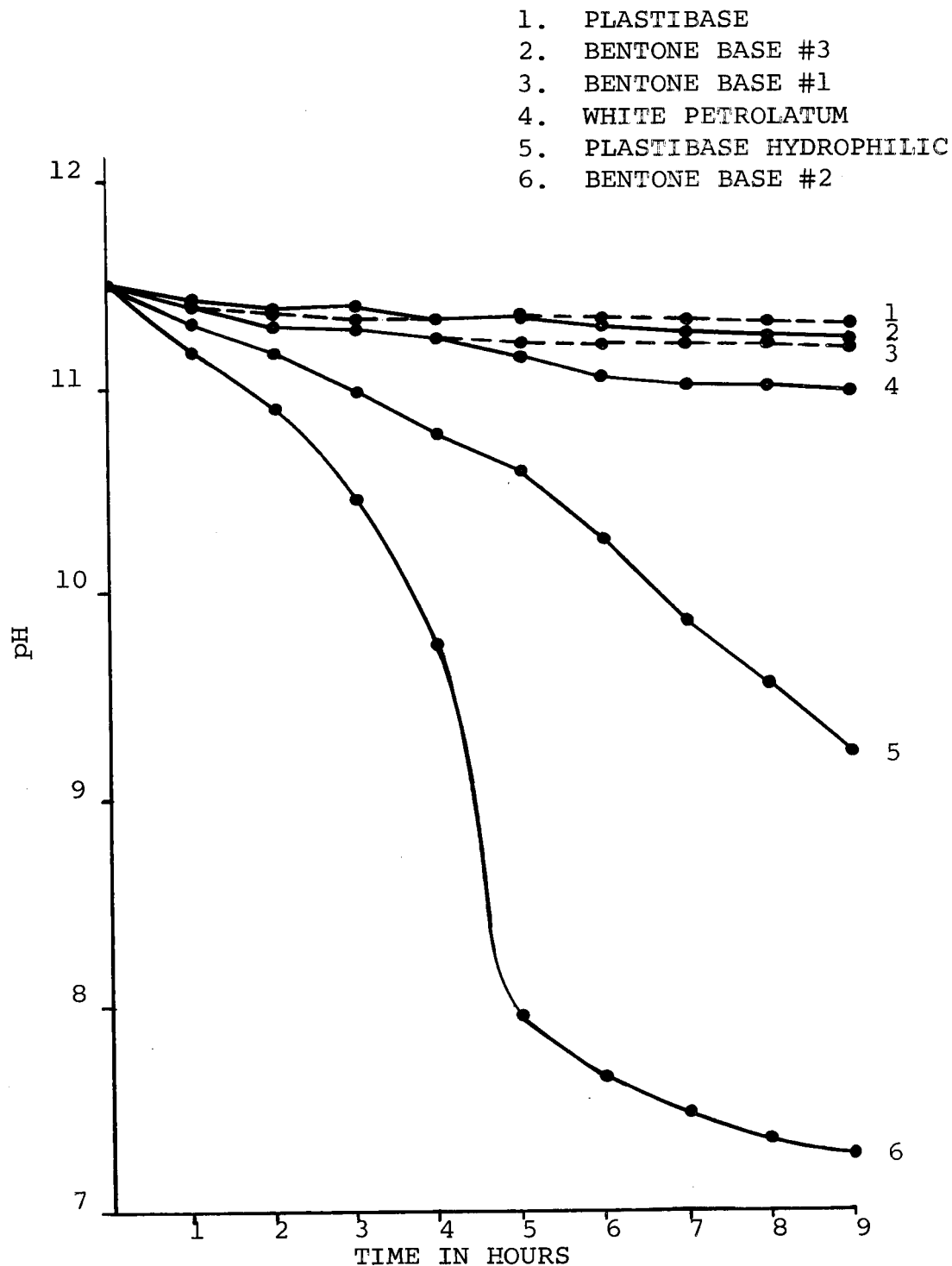


Figure 14. pH of Alkaline Sodium Citrate Solution at Different Time Intervals on Exposure to Ointments Containing 15% Amberlite (CG-50 AR) Resin.

Microbiological "Agar Tube" Method. A microbiological method was used as an alternate method to measure drug release from various ointment bases. The method employed in this study was a variation of the official F.D.A. Agar Cup Plate Method (63) and the methods proposed by Darlington and Guth (11), Barr and Guth (5), Foster et al. (18) and other researchers (12; 57; 58; 61; 63; 78; 81).

The experimental portion of this study was divided into three phases: (1) preparation of media and anti-infective ointments, (2) development of an "agar tube" method to be used in evaluating the release of medicaments from ointment bases, and (3) testing of selected anti-infective ointments for release of medicaments using the "agar tube" unit.

The media and anti-infective ointments were prepared as follows:

1. Brain heart infusion¹⁸ broth was prepared according to the directions suggested by the manufacturer on the package. Broth was prepared in the ratio of 37 Gm. infusion to 1000 ml. of purified water.
2. Agar media was prepared by incorporating 1.5% agar into brain heart infusion broth.

¹⁸

Baltimore Biological Laboratory, Inc., Baltimore, Md.

3. The glassware, brain heart infusion broth and agar media were autoclaved at 121° C. for 20 minutes.
4. Stock cultures of the test organisms Streptococcus zymogens Strain O.S.U.¹⁹ (Streptococcus faecalis variety zymogens), were maintained in brain heart infusion broth at 37° C. and subcultured into broth carrying cultures every 72 hours.
5. Ointments containing 10% Sulfisoxazole²⁰ U.S.P., 0.5% Thimerosal N.F.²¹, 5% Ammoniated Mercury U.S.P. and 2% Liquefied Phenol U.S.P. were prepared in Bentone Base #2 and White Petrolatum. Bentone Base #2 and White Petrolatum were chosen since they represented extremes in ability to lower the pH of alkaline sodium citrate solution in the dialysis study (See Figure 14). Furthermore, it was considered more advantageous in light of the dialysis study to evaluate two bases on four anti-infective drugs rather than to evaluate several bases on one anti-infective agent.

An "agar tube" method was developed to measure the release of medicaments from various anti-infective ointments. In this method a battery of 48 individual "agar tube" units was used. The individual "agar tube" units were made from test tubes cut into two sections as illustrated in Figure 15.

¹⁹ Supplied by the Department of Microbiology, Oregon State University.

²⁰ Supplied as Gantrisin[®] powder courtesy of Hoffman-La Roche Inc., Nutley, N. J.

²¹ Supplied as Merthiolate[®] powder courtesy of Eli Lilly and Co., Indianapolis, Ind.

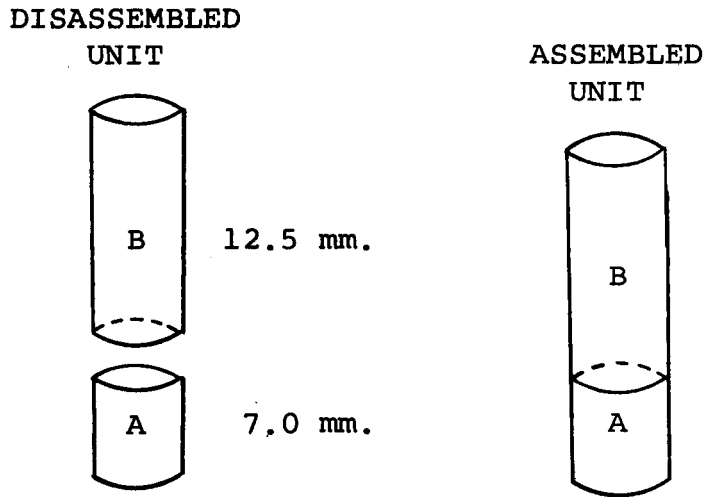


Figure 15. "Agar Tube" Unit Used for Measuring Drug Release.

The testing of the selected anti-infective ointments was conducted as follows:

1. The previously prepared anti-infective ointments were packed into 48 "agar tube A" sections as follows: 12 containing 10% Sulfisoxazole in Bentone Base #2; 12 containing 10% Sulfisoxazole in White Petrolatum; 12 containing Bentone Base #2 and 12 containing White Petrolatum. This procedure was repeated for each anti-infective agent.
2. Saran Wrap[®] was secured about the lower end of each section of the disassembled unit.
3. The test organism, Streptococcus zymogens, was inoculated into the sterile agar media at 47° C.,

using 0.5 ml. of an 8-hour growing broth culture for each 10 ml. of agar media. Care was taken not to exceed 47° C., as exposure to higher temperatures would inactivate the test organism.

4. The inoculated agar medium was poured into the "B" section of the disassembled units previously secured with Saran Wrap, and the cylinders were refrigerated at 4° C. for 10 minutes to ensure complete hardening of the agar.
5. When the agar had solidified, the Saran Wrap was removed and sections "A" and "B" (ointments were earlier packed into section "A") were taped together and incubated at 37° C. until colonies developed.
6. It was found that when the "agar tube" units were refrigerated at 4° C. immediately after assembling, the time could be lengthened for the colonies to develop. This allowed more time for the antibacterial agents to diffuse from the ointments into the agar media, and gave longer zones of bacterial inhibition.
7. Once the colonies had developed, the assembled units were removed from the incubator and the length of the zones of inhibition was measured. The reported values present an average of four readings taken on different sides of each "agar tube" assembly.

Data obtained from the "agar tube" study are presented in TABLE XI and Figure 16. In these tests, "the general order of effectiveness of the anti-infective drugs was taken as the amount of complete inhibition of growth produced by the test organism" (11).

Results from the "agar tube" study for drug release indicate:

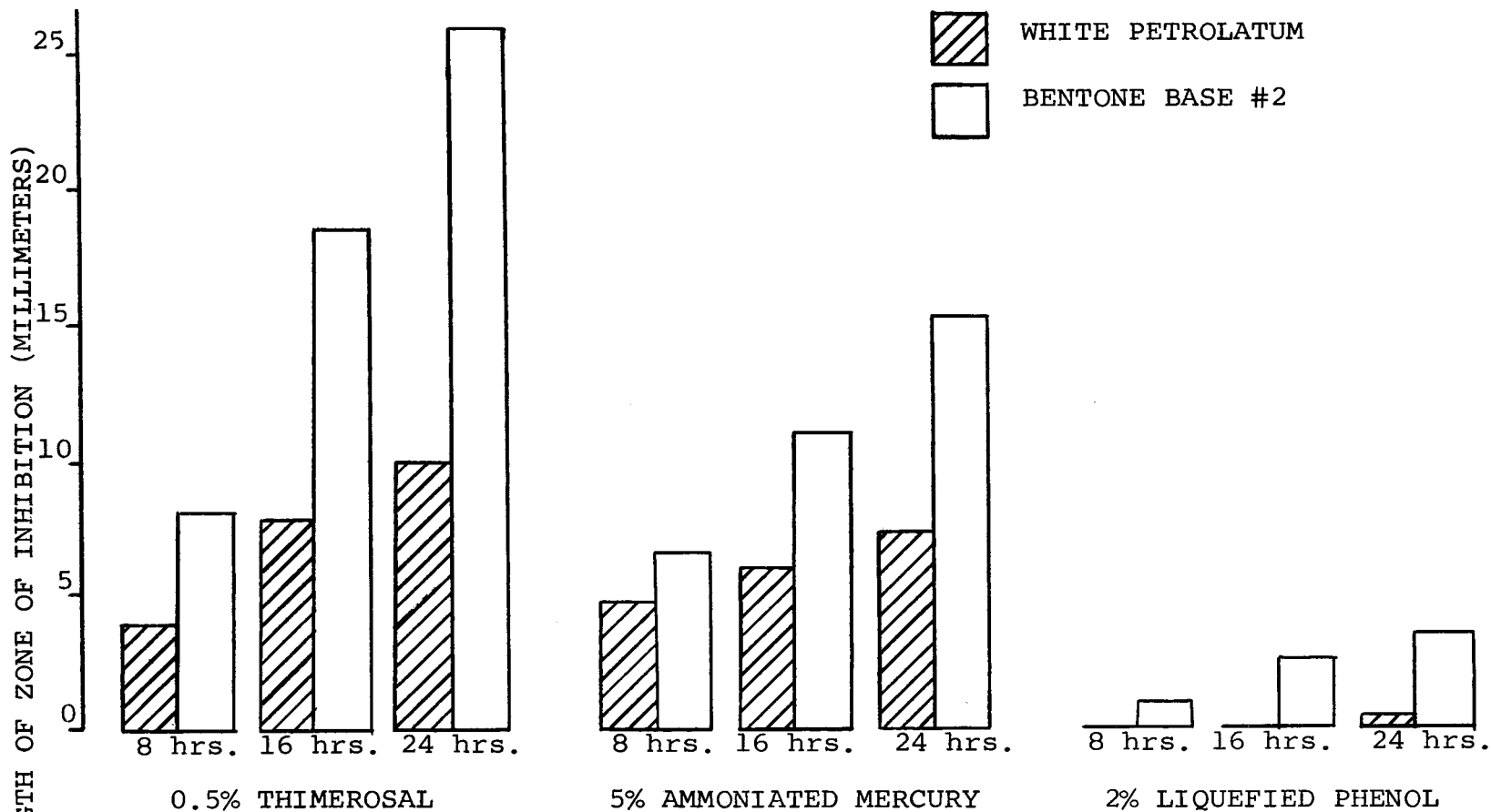
TABLE XI

BACTERIAL INHIBITION STUDY* USING "AGAR TUBE" METHOD ON BENTONE BASE #2 AND WHITE PETROLATUM

OINTMENT BASE	DRUG	LENGTH OF ZONE OF INHIBITION (millimeters)														
		8 Hours					16 Hours					24 Hours				
		1	2	3	4	Ave.	1	2	3	4	Ave.	1	2	3	4	Ave.
BENTONE BASE #2	CONTROL	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	10% SULFISOXAZOLE**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.5% THIMEROSAL	8.0	7.5	8.0	8.0	7.9	18.0	17.5	18.5	18.0	18.0	25.5	26.0	26.0	26.5	26.0
	5% AMM. MERCURY	7.0	6.5	6.0	6.5	6.5	10.0	11.5	11.0	11.0	10.9	15.0	15.0	15.5	15.5	15.25
	2% LIQUEFIED PHENOL	1.0	1.0	1.0	1.0	1.0	2.0	2.5	2.5	2.0	2.25	3.5	3.5	3.0	3.5	3.4
	CONTROL	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
WHITE PETROLATUM	10% SULFISOXAZOLE**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.5% THIMEROSAL	4.0	4.5	4.0	4.0	4.1	8.0	7.5	8.0	7.5	7.75	9.5	10.0	10.0	9.0	9.6
	5% AMM. MERCURY	4.5	5.0	5.0	4.5	4.75	5.5	6.0	5.5	6.0	5.95	7.0	7.5	7.0	7.5	7.25
	2% LIQUEFIED PHENOL	0	0	0	0	0	0	0	0	0	0	0	0	0.5	1.0	0.4
	CONTROL	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	10% SULFISOXAZOLE**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

* Streptococcus zymogens was the test organism used in this study.

**No zone of inhibition was observed in either base with Sulfisoxazole.



ACTION OF ANTI-INFECTIVE DRUGS AT DIFFERENT TIME INTERVALS

Figure 16. Length of Zone of Bacterial Inhibition Using "Agar Tube" Method on Bentone Base #2 and White Petrolatum Containing Anti-infective Drugs.

1. Bacterial inhibition was not noted in any of the control assemblies.
2. Sulfisoxazole did not inhibit the growth of Streptococcus zymogens when incorporated into White Petrolatum or Bentone Base #2.
3. Thimerosal caused the longest zone of inhibition of all anti-infective agents tested in both bases, followed by Ammoniated Mercury and Liquefied Phenol.
4. Drugs incorporated into Bentone Base #2 were, in general, able to diffuse two to three times further than the same drugs in White Petrolatum.
5. The drugs appeared to diffuse from the ointment bases at a fairly uniform rate. This is evidenced by the linear relationship between the 8-hour, 16-hour and 24-hour time intervals shown in Figure 16.

The results from this study are in general agreement with those of Darlington and Guth (11) and Barr and Guth (5).

Handling and Manufacturing Characteristics

In preparing the Bentone ointment bases to be used in this study, several handling and manufacturing advantages were noted over those of other bases. These advantages are considered to be of even greater importance when applied to the manufacture of quantities of base sufficient for pilot plant and commercial preparation.

An examination of many ointment formulas indicates that the fusion process is frequently used in small scale

production and is practically always involved in large scale manufacturing (48; 60). In preparing ointments from Bentone gellants, however, a cold process may be used. As a consequence, the capital expenditure for equipment is less, since expensive heating and cooling cycles are eliminated.

A milling process is used on many ointments to improve texture and appearance. Production is usually slow by this process and even with large roller mills production is limited to only a few hundred pounds of ointment per hour. In the preparation of Bentone bases, however, the appearance and texture were such that milling was not considered necessary.

The addition of active ingredients to many ointment bases generally involves: (1) the fusion of the base, (2) dispersion of the active ingredient in the melted base, (3) cooling, and (4) milling. In adding powdered drugs to the Bentone bases, however, the drugs were incorporated directly.

In some instances, milling may be required to produce the desired appearance. When milling is required, it is possible to make concentrated dispersions of the solid in the base, because of the large capacity for solids of the

Bentone bases. This represents a considerable saving in time, since only the concentrate is milled. The concentrate is then stirred into the bulk of the base to produce the finished ointment.

Over-all analysis of the handling and manufacturing characteristics indicates that the bentone bases are prepared more easily than other common bases. The advantages in handling and manufacturing Bentone bases are considered to be of even greater importance when applied to pilot plant and commercial production.

SUMMARY AND CONCLUSIONS

The purpose of this study was to prepare ointment bases from mineral oil thickened with Bentone 38 gellant, and to compare these bases with White Petrolatum, Plastibase Hydrophilic and other bases in common use.

Three different hydrophilic, water absorbing ointment bases have been prepared from Bentone 38 gellant and mineral oil. Two of the bases are W/O emulsion bases. The third is an anhydrous or "grease type" base.

In evaluating these bases, experimental data are presented for: (1) physical and chemical stability, (2) body and consistency, (3) drug release characteristics, and (4) handling and manufacturing characteristics.

The Physical and Chemical Stability was determined by evaluating: (1) the breaking temperature of the Bentone ointment bases and the stability of Bentone bases to cold, (2) the compatibility of Bentone and other common ointment bases with selected medicinal agents, and (3) aging tests (30, 60 days) employing the Bentone bases and other common ointment bases with selected medicinal agents. Analysis of the data obtained from these studies can be summarized as follows:

1. Breaking Temperature and Stability to Cold. The breaking temperature and stability to cold were measured for the three Bentone bases (data on other bases are easily obtained in the literature and on commercial packages). Results from these studies indicated that the Bentone bases were extremely stable to high and low temperatures, and are considered to be stable during the most severe temperature changes encountered during shipping and storage. Bentone Base #3 would be especially good in ophthalmic preparations where sterilization with heat is necessary, as this base can withstand temperatures to 180° C.
2. Compatibility With Drugs. Several drugs used in common dermatological practice were incorporated into the three Bentone bases. Analysis of the finished ointments indicated that Bentone Bases #2 and #3 were compatible with a wide variety of medicinal agents. Most substances used in present-day dermatologic practice were readily incorporated into Bentone Bases #2 and #3. Bentone Base #1 was compatible with a smaller range of drugs than Bentone Bases #2 and #3.
3. Aging Studies. Aging studies were conducted on seven drugs to determine both the initial compatibility and the stability over extended periods of time at 22.5° C. Plastibase Hydrophilic and White Petrolatum were compared with the three Bentone bases. Results from the aging studies indicated:
(a) Phase separation was more common with ointments prepared from Bentone Base #1, (b) The texture of the finished ointments was smooth and homogeneous except in those with Bentone Base #1 and certain drugs. (c) The spreadability was found to vary among the different ointments. (d) Bentone Bases #2 and #3 and Plastibase Hydrophilic had the best over-all stability, texture and spreadability of all bases tested. (e) Bentone Base #3 was the best base tested in the aging study.

Over-all results from these studies indicated that Bentone

Bases #2 and #3 and Plastibase Hydrophilic had the best physical and chemical stability under the conditions tested. Bentone Base #3 was more stable to heat and is considered to have better physical and chemical stability than the other bases tested.

Body and Consistency were determined by: (1) the effect of temperature on spreadability, (2) capacity of ointment bases for solids, (3) water absorbing properties of ointment bases, and (4) cone penetration measurements. Data obtained from these studies can be summarized as follows:

1. Effect Of Temperature On Spreadability. A spreadability apparatus was constructed, tests were conducted, and spreadability times were recorded for seven ointment bases at 10° C., 22.5° C., 35° C. and 47.5° C. The seven bases tested were the three Bentone bases, Plastibase Hydrophilic, White Petrolatum, Plastibase and Wool Fat. Results from this study indicated: (a) Wool Fat and White Petrolatum were not spreadable at 10° C., and are considered to be too stiff for use as ointment bases at lower temperatures. (b) The three Bentone bases, Plastibase and Plastibase Hydrophilic demonstrated the best spreadability at 22.5° C. (c) Plastibase, Wool Fat and Bentone Base #1 were especially thin at temperatures above 35° C., and were considered to be of little value in this temperature range. (d) At 47.5° C., Bentone Bases #2 and #3, Plastibase Hydrophilic and White Petrolatum were spreadable but retained their body and consistency. Plastibase, Bentone Base #1 and Wool Fat were exceptionally thin and were considered to be of little value at 47.5° C. (e) Changes in temperature affected the spreadability of Bentone Bases #2 and #3 and Plastibase Hydrophilic the least,

and on this basis these bases were considered superior to the other bases included in this study.

2. Capacity For Solids. The capacity for solids was measured by incorporating 5% to 20% zinc oxide into Bentone Base #2 and White Petrolatum, and taking spreadability measurements at 10° C., 22.5° C. and 35° C. Results from this study indicated: (a) Bentone Base #2 was able to maintain good body and consistency at all temperatures tested even when loaded with solids. (b) White Petrolatum became hard when loaded with solids, and was very difficult to manipulate at 10° C. and 22.5° C. At 35° C. White Petrolatum was thin, runny and separated from the zinc oxide. (c) Bentone Base #2 was superior to White Petrolatum in its ability to maintain desirable body and consistency, and is recommended where large quantities of solid material are to be incorporated into ointment bases.
3. Water Absorbing Properties. The water absorbing properties were determined by measuring the "water number" of the three Bentone bases, Plastibase Hydrophilic, White Petrolatum, Plastibase and Hydrophilic Petrolatum. Results from the water absorption study indicated: (a) Bentone Base #1 was inferior in consistency to the other bases. (b) Bentone Bases #2 and #3 did not separate when considerable quantities of water were incorporated. Bentone Bases #2 and #3 maintained better body and consistency than the other bases tested, even after the incorporation of large amounts of water. (c) Plastibase Hydrophilic absorbed large amounts of water, but, in doing so, became excessively thin. (d) White Petrolatum absorbed little water and remained stiff. (e) In general, Bentone Bases #2 and #3 had superior water absorbing properties to the other bases.
4. Cone Penetration. A cone penetration apparatus was devised and cone penetration depths were recorded for seven ointment bases at 10° C., 22.5° C., 35° C. and 47.5° C. The bases included in this study were the three Bentone bases, Plastibase

Hydrophilic, White Petrolatum, Plastibase and Wool Fat. Results from this study indicated: (a) White Petrolatum and Wool Fat offered the most resistance to penetration at 10° C., and their usefulness at this temperature is seriously questioned. Bentone Bases #2 and #3 and Plastibase Hydrophilic were intermediate in consistency at 10° C. Bentone Base #1 offered the least resistance to penetration at 10° C. (b) White Petrolatum and Wool Fat offered the most resistance to penetration at 22.5° C., the former being exceptionally stiff. The other bases were readily penetrated at 22.5° C. (c) All of the bases were penetrated at 35° C. Bentone Bases #2 and #3, Plastibase Hydrophilic and Wool Fat maintained the best consistency at this temperature. Plastibase and Bentone Base #1 were easily penetrated at 35° C., and their usefulness is seriously questioned at this temperature. (d) Bentone Bases #2 and #3 and Plastibase Hydrophilic retained their body and consistency at 47.5° C. The other bases were especially thin and are considered to be of little use at 47.5° C. (e) The degree of penetration in Bentone Bases #2 and #3 and Plastibase Hydrophilic was affected the least by changes in temperature. These three bases are considered to be superior to the other bases tested.

Over-all results from these studies indicated that Bentone Bases #2 and #3 had the best body and consistency of the bases tested. Plastibase Hydrophilic experienced slightly greater changes in consistency, than Bentone Bases #2 and #3, when water and solids were added. The body and consistency of the remaining bases were influenced considerably by the addition of water, the incorporation of solids, and changes in temperature.

Drug Release Characteristics were determined by the following two methods: (1) a dialysis cell method, and (2) a microbiological "agar tube" method. Analysis of the results obtained from these studies can be summarized as follows:

1. Dialysis Cell Method. A dialysis cell method was employed to determine the extent of drug release from the three Bentone bases, Plastibase Hydrophilic, White Petrolatum and Plastibase. The procedure used in this study was a combination of the methodology employed by Jurist (36) and Mutimer et al. (48), and a diffusion cell patterned according to the specifications reported by Wood et al. (85; 86). The methods of Mutimer and Jurist are based on the measurement of ion exchange through a semipermeable membrane, specifically the exchange of hydrogen ions on the resin for sodium ions in a solution of sodium citrate. Results from the dialysis cell study indicated: (a) Bentone Base #2 caused the most rapid reduction in pH of the six bases tested. Bentone Base #2 reduced the pH two times more rapidly than Plastibase Hydrophilic, the next nearest base, and eight to ten times more rapidly than the remainder of the bases. (b) Plastibase Hydrophilic caused an intermediate reduction in the pH of the six bases tested. Plastibase Hydrophilic reduced the pH three times more rapidly than the remainder of the bases. (c) Plastibase, Bentone Bases #1 and #3 and White Petrolatum caused the least rapid reduction of pH.
2. Microbiological "Agar Tube" Method. A microbiological method was used as an alternate method to measure drug release from ointment bases. The method employed in this study was a variation of the official F.D.A. Agar Cup Plate Method (63) and the methods proposed by Darlington and Guth (11), Barr and Guth (5) and Foster et al. (18). An "agar tube" apparatus was devised, and anti-infective ointments were prepared from Bentone Base #2 and White Petrolatum using 10% Sulfisoxazole U.S.P.,

0.5% Thimerosal N.F., 5% Ammoniated Mercury U.S.P. and 2% Liquefied Penol U.S.P. Bentone Base #2 and White Petrolatum were selected since they represented extremes in the dialysis cell study for drug release. The test organism was Streptococcus zymogens Strain O.S.U. In this study "the general effectiveness of the anti-infective drugs was taken as the amount of complete inhibition of growth produced by the test organism" (11). Results from the "agar tube" study for drug release indicated: (a) Sulfisoxazole did not inhibit the growth of Streptococcus zymogens when incorporated into White Petrolatum and Bentone Base #2. This was probably due to fact that the microorganism was gram positive and Sulfisoxazole is more effective against gram negative organisms. (b) Thimerosal caused the longest zone of inhibition of all anti-infective agents tested in both bases, followed by Ammoniated Mercury and Liquefied Phenol. (c) Drugs incorporated into Bentone Base #2 were, in general, able to diffuse two to three times further than the same drugs in White Petrolatum. (d) The drugs appeared to diffuse from the ointment bases at a fairly uniform rate. This is evidenced by the nearly linear relationship between the 8-hour, 16-hour and 24-hour time intervals shown in Figure 16.

Over-all results from the drug release studies indicated that Bentone Base #2 was superior to the other bases tested. Plastibase Hydrophilic was intermediate in ability to release medicaments. It was observed that the dialysis cell method and the microbiological "agar tube" method, employed in these studies to measure drug release, gave the same trends in effectiveness for the ointments used. The ointments that were the most effective in the first study thus gave the same order of effectiveness when used in the

second study.

The emulsion-type ointment bases were in general found to promote a greater release than the anhydrous hydrocarbon bases. These results are in agreement with DeKay (12) and other researchers (64; 65; 67) who have reported greater release from emulsion and hydrophilic ointment bases. The general effectiveness of Bentone Base #2 over Bentone Base #1 indicated that a surface active agent, when added to an emulsion base formulation, promoted greater release. Other researchers have indicated that surface active agents, when added to ointment bases, promote greater release of medications (12; 54; 74; 76).

The Handling And Manufacturing Characteristics were observed while preparing the Bentone ointment bases to be used in this study. The following handling and manufacturing advantages were noted for the Bentone bases over those of other bases:

1. A cold process was used in preparing ointments from Bentone gellants. This is contrasted with the fusion process required in the manufacture of many ointment bases (48; 60). As a consequence, the capital expenditure for equipment was less, since expensive heating and cooling cycles were eliminated.
2. A milling process was not considered necessary to improve the texture and appearance of the Bentone

ointment bases. Many bases require a time consuming milling process in their production.

3. Due to the large capacity of the Bentone bases for solids, active ingredients were readily added. When milling was required to evenly disperse the medicinal substances, it was possible to make concentrated dispersions of the solid in the base. The concentrate was then stirred into the bulk of the base to produce the finished ointment. This represented a considerable saving of time, since only the concentrate was milled.

Over-all analysis of the handling and manufacturing characteristics indicated that the Bentone bases could be prepared more easily than many other common bases. The advantages in handling and manufacturing Bentone bases were considered to be of even greater importance when applied to pilot plant and commercial production.

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