Topical Agents

In this chapter, a wide variety of uses will be discussed for an even wider variety of compounds. The term "topical" places the use of these compounds on body surfaces, as opposed to "systemic," which indicates that the compounds are absorbed into the circulatory system and distributed to various organs and tissues. The pharmacological effects of topical compounds are evidenced primarily at the surface to which they are applied. This is not to say that there is no penetration into deeper tissues or absorption into the general circulation. Indeed, this does occur in many instances with resulting beneficial effects—for example, the penetration of an antiseptic compound into the tissues below the exposed area of a wound aids in the prevention of deep infections. On the other hand, systemic effects of many of these compounds may elicit toxic or allergic manifestations depending upon the amounts absorbed, e.g., topically applied mercury-containing compounds. Because of this possibility, general aspects of systemic toxicity will be discussed in association with appropriate compounds. It should be stated further that topical application of drugs may be accomplished within body cavities that open to the outside (e.g., the oral, vaginal, and colonic cavities). This type of application is done with the expectation that the compound will exert local or surface activity. However, it should be noted that systemic absorption from these areas may be more extensive in comparison to the skin. Indeed, drugs are often applied to these areas as a route of systemic administration (e.g., buccal tablets, suppositories, etc.).

The compounds used topically will be divided into broad categories based on their usual action or use. The categories are: (1) protective, and (2) antimicrobial and astringent compounds. These classifications are broad enough to encompass most of the compounds; however, some of the agents have uses extending beyond the limits of the specific category. It may also be noted that there is a tremendous amount of overlap between categories where the particular use will depend on the area of application, the concentration of the agent, the presence of other compounds in the preparation, and the solubility (e.g., insoluble zinc oxide is a protective and soluble zinc sulfate is an astringent).

Protectives

As the term implies, protectives are substances which may be applied to the skin to protect certain areas from irritation, usually of mechanical origin. Those compounds or substances most appropriate for this purpose are insoluble and chemically inert. Insolubility is a desirable property in that this limits the absorption of the compounds through the skin, makes it difficult to wash them off, and diminishes metallic properties on tissue. Compounds which are chemically unreactive are necessary in order to prevent interactions between the protective substance and the tissue. In other words, ideal protectives are biologically inactive.

Many materials serving the purpose of protectives are also efficient adsorbents useful for adsorbing moisture from the surface of the skin. Since removing moisture tends to lessen mechanical friction and irritation, adsorbent action is an important property of protectives. Protective and adsorbent action is maximized with decreasing particle size. Small particles offer a larger surface area, allowing them to adhere to each other, adhere better to the surface of the skin, and adsorb moisture more efficiently. A fine state of subdivision of the particles also offers a smooth substance which is soothing to apply and aids in preventing irritation due to rubbing or friction.

Protectives are generally applied as dusting powders, suspensions containing the insoluble protective substance, or ointments. It should be remembered that protective and adsorbent substances are available for use internally for gastrointestinal irritations (see Chapter 8). Although the reason for using these is the same, the compounds and preparations are not. Topical protectives and adsorbents are usually applied to areas of the skin which are subject to constant irritation due to moisture and/or friction, or areas which have already become irritated or inflamed due to friction, allergy, and the like. If the area to which the protective is to be applied is abraded and exuding fluid, adsorbent-type protectives should not be used. These substances will mix with the exudate and dry to a crust which adheres to the open tissue. It is also possible that systemic absorption may be enhanced. The properties and uses of inorganic protective compounds and preparations are discussed in the following section.

Protective Products

Talc, U.S.P. XVIII ($3MgO \cdot 4SiO_2 \cdot H_2O$)

Talc U.S.P. is a native, hydrous magnesium silicate, sometimes containing a small proportion of aluminum silicate. The U.S.P. describes it as a very fine, white or grayish white, crystalline powder. It is unctuous, adheres readily to the skin, and is free from grittiness.

Talc is a layered silicate and is the softest mineral known. It has a smooth, greasy feeling to the touch, and in its lump form (steatite) it is known as soapstone. The form most desirable for cosmetic and pharmaceutical purposes is known as foliated talc and has a plate-like structure.

Chemically, talc may be considered to be a hydrated magnesium silicate having the elements illustrated by the formula represented above. This grouping of elements may be rearranged to provide a representation of talc as the magnesium salt of dimetasilicic acid, having the formula $Mg_3H_2(Si_2O_6)_2$. The actual composition of talc is somewhat variable, containing from 28.1 to 31.2% MgO, 57 to 61.7% SiO_2, and 3 to 7% H_2O. As a magnesium polysilicate, it is unreactive to acids and bases, and inert to most other reagents.

Talc is odorless, tasteless, and insoluble in water, dilute acids, and dilute bases. It has very low adsorptive properties, which is an important consideration for its use as a filtering aid, allowing filtration without danger of removing important constituents, e.g., alkaloids, dyes, etc.

Uses. In spite of its low adsorptive properties, the inert, unctuous nature of talc makes it a useful lubricating, protective dusting powder. It can be used to prevent irritation due to friction, and to protect areas from further irritation. It has been known for a number of years, however, that when used on broken skin—wounds and surgical incisions—talc can produce sterile abscesses or granulomas (a nodule of inflamed tissue in which granulation is occurring).[1] This problem precludes the use of talc-containing dusting powder on surgical gloves; absorbable dusting powders are now recommended for this purpose (cf. U.S.P. XVIII, p. 839). No problems are associated with the use of talc on the intact skin. Talc is used in preparations which may be perfumed for cosmetic purposes, or medicated with antimicrobial agents, such as boric acid.

The insoluble and chemically inert nature of talc, including its nonadsorptive properties, renders the material useful as a filtering aid. The best particle size for this purpose is 80/100 mesh, i.e., the powder that will pass through a No. 80 sieve but not a No. 100 sieve. Particles finer than this will not be retained by the usual filter papers, and filtered preparations will appear cloudy. Some of the pharmaceutical preparations that employ talc as a filtering or distributing agent are aromatic waters, Magnesium Citrate Solution, aromatic elixir, and Orange Syrup.

Insoluble Zinc Compounds

Zinc Oxide, U.S.P. XVIII (ZnO; Mol. Wt. 81.37)

Zinc Oxide U.S.P. is a very fine, odorless, amorphous, white or yellowish white powder, free from gritty particles. It gradually absorbs carbon dioxide from the air. When freshly ignited, it should contain not less than 99.0% and not more than 100.5% of ZnO. When heated to 400° or 500° C, the oxide develops a yellow color that disappears on cooling. *Zinc Oxide* is insoluble in water and alcohol, and will gradually absorb carbon dioxide from the air to form a basic zinc carbonate [$Zn_2(OH)_2CO_3$].

Chemically, zinc oxide reacts with dilute acids and aqueous solutions of ammonium compounds to form water soluble products. When treated with dilute hydrochloric acid, the oxide forms the Lewis acid, zinc chloride [rx (i)].

$$ZnO + 2HCl \rightarrow ZnCl_2 + H_2O \qquad \text{(i)}$$

Ammonia water and ammonium carbonate T.S. (test solution) form water soluble basic ammonia complexes with zinc oxide [rxs (ii) and (iii)].

$$ZnO + 4NH_4OH \rightarrow Zn(NH_3)_4(OH)_2 + 3H_2O \qquad \text{(ii)}$$

$$ZnO + 2(NH_4)_2CO_3 \rightarrow Zn(NH_3)_4(OH)_2 + 2CO_2\uparrow + H_2O \qquad \text{(iii)}$$

Acidic solutions of zinc oxide exhibit the properties of zinc ion.

USES. *Zinc Oxide* is a mild astringent and a weak antimicrobial compound. The U.S.P. classifies it as an astringent and topical protective. The antimicrobial-astringent action is due to the release of a small amount of zinc ion from hydrolysis in the acidic moisture on the skin [see rx (i)]. It is used as a protective in ointments (*Zinc Oxide Ointment*, U.S.P. XVIII), pastes (*Zinc Oxide Paste*, U.S.P. XVIII), and dusting powders in the treatment of skin ulcerations and other dermatological problems. As a dusting powder, it is frequently found in combination with other protectives or antimicrobial agents, e.g., talc and boric acid. *Zinc Oxide* is the primary ingredient in *Calamine*, U.S.P. XVIII (see below). *Zinc Gelatin*, U.S.P. XVIII is a protective jelly containing 10% ZnO. The pharmacological and biochemical actions of zinc are discussed in Chapter 6.

Calamine, U.S.P. XVIII, ($ZnO \cdot xFe_2O_3$).

Calamine U.S.P. is zinc oxide with a small proportion of ferric oxide. After ignition, it contains not less than 98.0% and not more than 100.5% of ZnO. The presence of the ferric oxide [Fe_2O_3; iron(III) oxide] gives the substance a pink color which varies according to the method of preparation and the amount of ferric oxide present. The material is a fine powder, odorless, and practically tasteless. It is insoluble in water, but almost completely soluble in mineral acids.

The term *calamine*, besides being applied to the official product, is also used to describe the impure, naturally occurring zinc carbonate. The official *Calamine* is obtained by calcination (powdered by heating) of the natural ore. The calcined product is then passed through a 100-mesh sieve to obtain the finely powdered material necessary for good cohesive and adhesive (adhering to skin) properties.

USES. *Calamine* is classified by the U.S.P. as a topical protective. It is used in dusting powders, ointments, and lotions (*Calamine Lotion*, U.S.P.) where it is applied to the skin for its soothing, adsorbent, protective properties. The only real difference between zinc oxide and calamine is the avoided. The primary use is as a prophylactic

Antimicrobials and Astringents

Antimicrobial Terminology. There are several terms employed i describing antimicrobial activity. Since some of these terms refer t specific aspects of this activity, it is necessary to become acquainted wit their definitions and general usage.

Antiseptic. This term is generally applied to any agent which either kill or inhibits the growth of microorganisms, i.e., bacteria, fungi, protozoans etc. The term is reserved, however, for those agents used against microorganisms growing on man specifically or living tissue in general.

Germicide. The term germicide refers to a more specific action in tha it describes agents which kill microorganisms. The *-cide* ending on th word arises from the Latin word *caedere*, which means "to kill." Hence this ending can be applied to the names of various classes of microorganism to provide terms for more specific agents, e.g., bactericide, fungicide amebicide, etc.

Those agents which do not kill microorganisms, but function primarily by inhibiting their growth, can be described by terms using the suffix *-stat* (from the Greek word *stasis*, meaning "standing still"). Therefore, the terms, bacteriostat, fungistat, etc., are employed with compounds having this aspect of activity against the indicated microorganisms.

Disinfectant. This term refers to the same type of activity as the term germicide, above. Its usage differs in that it is applied to those agents most appropriately used on inanimate objects, e.g., instruments, equipment, rooms, etc.

Sterilization. This refers to the use of a disinfectant or other procedure to render an object completely free of microorganisms. This frequently involves the use of chemicals or mechanical processes (e.g., heat) which are much too stringent for use on animal or human tissue.

The terms antiseptic and germicide may be further modified according to their area and type of use. For example, agents may be classified with respect to whether they are used topically or internally. Internal agents may be further subdivided into those that are absorbed (systemic), and those that are not absorbed (nonsystemic). The former compounds are distributed through the circulation and used to treat infections in various organs and tissues, while the latter agents remain and function in the area where they are applied, e.g., the gastrointestinal tract.

Mechanisms of Action. The mechanisms of action of inorganic antimicrobial agents can be divided into three general categories: oxidation, halogenation, and protein precipitation. These represent the primary chemical interactions or reactions that occur between the agent and microbial protein and result in the death of the microbe or inhibition of its growth. It is important to note that in contrast to certain organic compounds known as antibiotics, the sites of action of inorganic antimicrobial compounds are, for the most part, nonspecific. These agents will interact in a similar fashion with all protein, and in high enough concentrations will affect host protein as well as microbial protein.

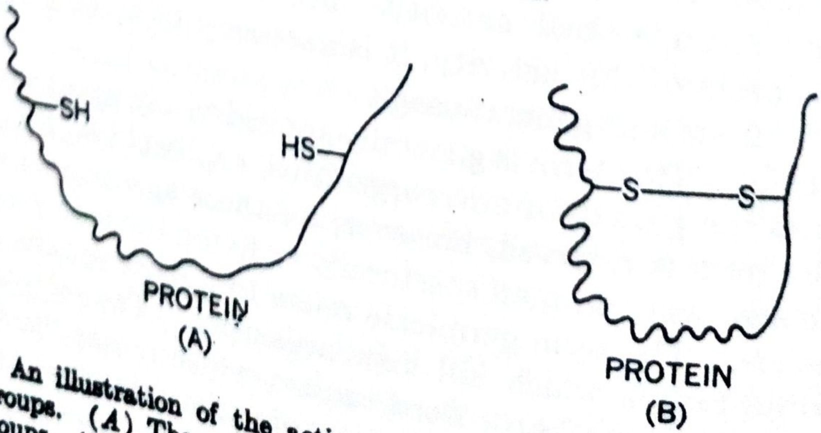

Fig. 9-1. An illustration of the action of oxidizing agents on protein-containing sulfhydryl groups. (*A*) The protein before oxidation showing the presence of free sulfhydryl groups. (*B*) The protein after oxidation showing the formation of a disulfide bridge between the two—SH groups.

Antimicrobial Astringent Products

Oxidative Antimicrobial Agents

Hydrogen Peroxide Solution, U.S.P. XVIII (H_2O_2; Mol. Wt. 34.02)

Hydrogen Peroxide Solution U.S.P. contains, in each 100 ml, not less than 2.5 g and not more than 3.5 g of H_2O_2. Suitable preservatives totaling not more than 0.05% may be added. It is a clear, colorless liquid which may be odorless or may have an odor resembling that of ozone. The solution will usually deteriorate upon standing or upon protracted agitation, and rapidly decomposes when in contact with many oxidizing or reducing substances. It is unstable on prolonged exposure to light, and may decompose suddenly when rapidly heated. The solution is acid to litmus and to the taste, and produces a froth in the mouth. It has a specific gravity of about 1.01.

Pure hydrogen peroxide, at room temperature, is a colorless, syrupy liquid with astringent properties. (Note: It is not used on the skin in this form.) It has a specific gravity of 1.463 at 0 ° C and, although unstable, it decomposes only very slowly in pure form. When heated to 100° C pure hydrogen peroxide decomposes explosively to form water and oxygen. It is miscible in all proportions with water, alcohol, or ether. It is more soluble in ether than in water, and ether will extract it from aqueous solutions.

Chemically, hydrogen peroxide may be considered to be stable in solutions of high purity; however, small amounts of contaminants, e.g., di- and polyvalent ions of chromium, iron, copper, mercury, etc., will catalyze the decomposition of unstabilized solutions. In the absence of impurities, exothermic decomposition to water and oxygen will occur very slowly. Aluminum does not act as a catalyst and, therefore, storage containers may be made of this metal.

Hydrogen peroxide solutions may be stabilized with acids, complexing agents, or adsorbents. Any inorganic or organic acid will stabilize the solution. The compound is a weak acid in aqueous solution, ionizing primarily to form the peroxide ion according to rx (v).

$$H_2O_2 \rightleftharpoons 2H^+ + O_2^{-2} \qquad pK_a = 11.62 \tag{v}$$

Its acidic strength is less than that of boric acid (see Chapter 4). The above equilibrium provides some indication of the mechanism of stabilization by acids. Any additional hydrogen ion will cause the equilibrium in rx (v) to shift toward hydrogen peroxide.

Alkaline solutions tend to be much less stable; however, the instability is due more to the impurities present in the standard grades of alkalies than to any direct alkaline catalysis.

Complexing or chelating agents are frequently used to stabilize hydrogen peroxide solutions. Some common agents employed for this purpose include acetanilid, quinine sulfate, and 8-hydroxyquinoline (oxinate, see Chapter 1) in concentrations ranging from 0.02 to 0.05%. These compounds will chelate trace amounts of polyvalent metals, thereby making them unavailable to catalyze the decomposition.

Many adsorbents (e.g., alumina and silica) will remove impurities from hydrogen peroxide solutions. Their stabilizing function is then somewhat comparable to the complexing agents. It should be noted, however, that the therapeutic uses of hydrogen peroxide are dependent upon its decomposition by the enzyme catalase (see below), and some of the compounds used to stabilize the solutions will also inactivate the enzyme at the site of action.

Depending upon the chemical environment, hydrogen peroxide will react as either an oxidizing or reducing agent. The oxidation state of oxygen in the peroxide ion, $(O{-}O)^{-2}$, is -1. When hydrogen peroxide functions as an oxidizing agent it forms two oxide ions, O^{-2}, requiring two electrons, and resulting in a change of the oxidation state of the oxygen to -2 [rx (vi)].