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The Science and Practice of Pharmacy

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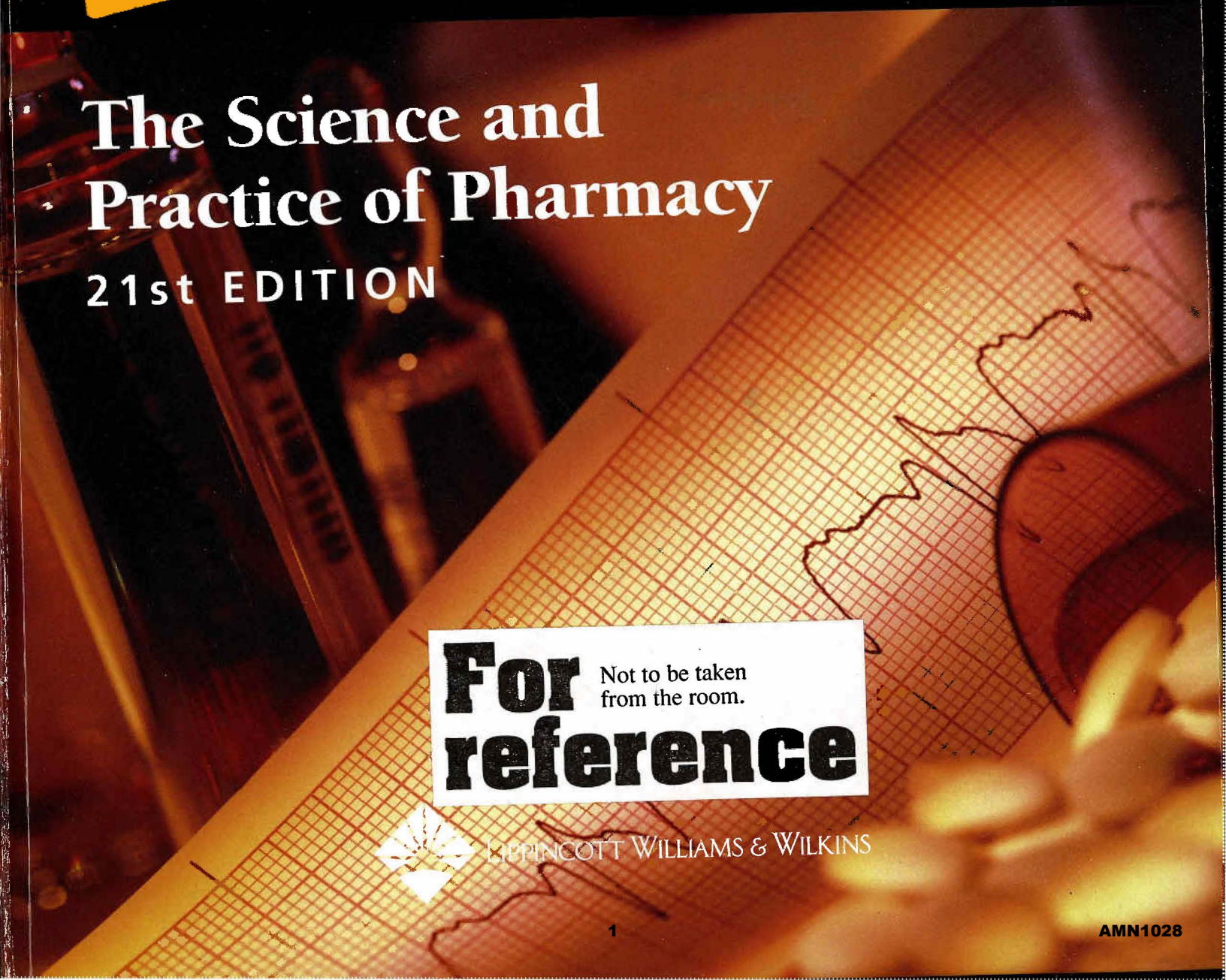

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The Science and Practice of Pharmacy

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CHAPTER 44

Medicated Topicals

Lawrence H Block, PhD

The application of medicinal substances to the skin or various body orifices is a concept as old as humanity. The papyrus records of ancient Egypt describe a variety of these medications for external use. Galen described the use in Roman times of a forerunner to today's vanishing creams.

Medications are applied in a variety of forms reflecting the ingenuity and scientific imagination of pharmacists through the centuries. New modes of drug delivery have been developed to remedy the shortcomings of earlier vehicles or, more recently, to optimize drug delivery. Conversely, some external medications have fallen into disuse because of changes in the practice of medicine.

Medications are applied to the skin or inserted into body orifices in liquid, semisolid, or solid form. Ophthalmics and topical aerosol products will not be discussed in this chapter. Ophthalmic use imposes particle size, viscosity, and sterility specifications that require separate, detailed discussion (see Chapter 43). The complexity of pharmaceutical aerosol systems necessitates their inclusion elsewhere (see Chapter 50).

BIOPHARMACEUTIC ASPECTS OF THE ROUTES OF ADMINISTRATION

EPIDERMAL AND TRANSDERMAL DRUG DELIVERY

The Skin

The skin often has been referred to as the largest of the body organs: an average adult's skin has a surface area of about 2 m^2. It is probably the heaviest organ of the body. Its accessibility and the opportunity it affords to maintain applied preparations intact for a prolonged time have resulted in its increasing use as a route of drug administration, whether for local, regional, or systemic effects.

Anatomically, human skin may be described as a stratified organ with three distinct tissue layers: the epidermis, the dermis, and the subcutaneous fat layer (Fig 44-1).

Epidermis, the outermost skin layer, comprises stratified squamous epithelial cells. Keratinized, flattened remnants of these actively dividing epidermal cells accumulate at the skin surface as a relatively thin region (about 10 μm thick) termed the *stratum corneum*, or *horny layer*. The horny layer is itself lamellar with the keratinized cells overlapping one another, linked by intercellular bridges and compressed into about 15 layers. The lipid-rich intercellular space in the stratum corneum comprises lamellar matrices with alternating hydrophilic layers and lipophilic bilayers formed during the process of keratinization. The region behaves as a tough but flexible coherent membrane.

The stratum corneum also is markedly hygroscopic—far more so than other keratinous materials such as hair or nails. Immersed in water the isolated stratum corneum swells to about three times its original thickness, absorbing about four to five times its weight in water in the process. The stratum corneum functions as a protective physical and chemical barrier and is only slightly permeable to water. It retards water loss from underlying tissues, minimizes ultraviolet light penetration, and limits the entrance of microorganisms, medications, and toxic substances from without. The stratum corneum is abraded continuously. Thus, it tends to be thicker in regions more subject to abrasion or the bearing of weight. Its regeneration is provided by rapid cell division in the basal cell layer of the epidermis. Migration or displacement of dividing cells toward the skin surface is accompanied by differentiation of the epidermal cells into layers of flat, laminated plates, as noted above. An acidic film (pH ranging between 4 and 6.5, depending on the area tested) made up of emulsified lipids covers the surface of the stratum corneum.

The dermis apparently is a gel structure involving a fibrous protein matrix embedded in an amorphous, colloidal, ground substance. Protein, including collagen and elastin fibers, is oriented approximately parallel to the epidermis. The dermis supports and interacts with the epidermis, facilitating its conformation to underlying muscles and bones. Blood vessels, lymphatics, and nerves are found within the dermis, though only nerve fibers reach beyond the dermal ridges or papillae into the germinative region of the epidermis. Sweat glands and hair follicles extending from the dermis through the epidermis provide discontinuities in an otherwise uniform integument.

The subcutaneous fat layer serves as a cushion for the dermis and epidermis. Collagenous fibers from the dermis thread between the accumulations of fat cells, providing a connection between the superficial skin layers and the subcutaneous layer.

HAIR FOLLICLES AND SWEAT GLANDS—Human skin is sprinkled liberally with surface openings extending well into the dermis. Hair follicles, together with the sebaceous glands that empty into the follicles, make up the pilosebaceous unit. Apocrine and eccrine sweat glands add to the total.

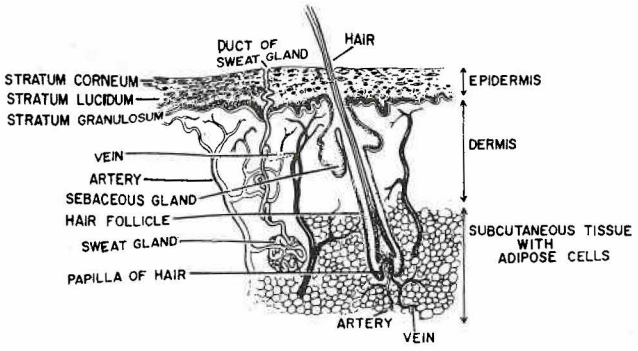

Figure 44-1. Vertical section of human skin.

PILOSEBACEOUS UNITS—Human hair consists of compacted keratinized cells formed by follicles. Sebaceous glands empty into the follicle sites to form the pilosebaceous unit. The hair follicles are surrounded by sensory nerves; thus, an important function of human hair is sensory. Human hair varies enormously within the same individual, even within the same specific body area. Follicular density varies considerably as well, from values of about 250 follicles per cm^2 for the scalp to 50 per cm^2, or less, for the thigh and other relatively nonhirsute areas. Follicular density is determined genetically, ie, no new follicles are formed after birth. One characteristic human trait is that although most of the body hairs never develop beyond the rudimentary vellus state, the only hairless areas are confined, primarily, to the palmar and plantar surfaces. Individual hairs can vary in microscopic appearance, diameter, cuticle appearance, and even presence or absence of medulla.

Sebaceous glands are similar anatomically and functionally but vary in size and activity according to location. Population in the scalp, face, and anogenital areas may vary from 400 to 900/cm^2. Fewer than 100/cm^2 are found in other areas. Sebaceous glands are richly supplied with blood vessels.

Sebaceous cells synthesize and accumulate lipid droplets. This accumulation results in enlarged cells that fragment to form sebum. Sebum is made up of a mixture of lipids, approximately as shown in Table 44-1.

The sebaceous gland, containing sebum, cell debris, and microorganisms such as *Propionibacterium acnes,* is connected to the pilosebaceous canal by a duct of squamous epithelium. When access to the surface is blocked and bacteria multiply, the result is the comedo of acne.

SWEAT GLANDS—Sweat glands are classified as apocrine and eccrine. Apocrine glands are secretory but are not necessarily responsive to thermal stimulation. Such glands do not produce sweat in the normal sense of the word. Apocrine glands, however, often are associated with eccrine sweat glands, particularly in the axilla.

Eccrine sweat glands are coiled secretory glands, equipped with a blood supply, extending from the dermis to the epidermal surface. Eccrine sweat glands function to regulate heat exchange in man. As such, they are indispensable to survival.

About 3 million eccrine glands are thought to be distributed over the human body. Distribution varies from less than 100 to more than 300/cm^2. Gland counts after thermal stimulation do not always agree with anatomical counts.

Table 44-1. Composition of Sebum

CONSTITUENTS	% W/W	CONSTITUENTS	% W/W
Triglycerides	57.5	Cholesterol esters	3.0
Wax esters	26.0	Cholesterol	1.5
Squalene	12.0		

Drug Effects and the Extent of Percutaneous Drug Delivery

Drugs are applied to the skin to elicit one or more of four general effects: an effect on the skin surface, an effect within the stratum corneum, a more deep-seated effect requiring penetration into the epidermis and dermis, or a systemic effect resulting from delivery of sufficient drug through the epidermis and the dermis to the vasculature to produce therapeutic systemic concentrations.

SURFACE EFFECTS—An activity on the skin surface may be in the form of a film, an action against surface microorganisms, or a cleansing effect. Film formation on the skin surface may be protective (eg, a zinc oxide cream or a sunscreen). Films may be somewhat occlusive and provide a moisturizing effect by diminishing loss of moisture from the skin surface. In such instances, the film or film formation *per se* fulfills the objective of product design. The action of antimicrobials against surface flora requires more than simple delivery to the site. The vehicle must facilitate contact between the surface organisms and the active ingredient. Skin cleansers employ soaps or surfactants to facilitate the removal of superficial soil.

STRATUM CORNEUM EFFECTS—Drug effects within the stratum corneum are seen with certain sunscreens; *p*-aminobenzoic acid is an example of a sunscreening agent that both penetrates and is substantive to stratum corneum cells. Skin moisturization takes place within the stratum corneum. Whether it involves the hydration of dry outer cells by surface films or the intercalation of water in the lipid-rich intercellular laminae, the increased moisture results in an apparent softening of the skin. Keratolytic agents, such as salicylic acid, act within the stratum corneum to cause a breakup or sloughing of stratum corneum cell aggregates. This is particularly important in conditions of abnormal stratum corneum such as psoriasis, a disease characterized by thickened scaly plaques.

The stratum corneum also may serve as a *reservoir phase* or depot wherein topically applied drug accumulates due to partitioning into or binding with skin components. This interaction can limit the subsequent migration of the penetrant unless the interaction capacity of the stratum corneum is surpassed by providing excess drug. Examples of drugs that exhibit significant skin interaction include benzocaine, estrogens, scopolamine, and corticosteroids.

EPIDERMAL, DERMAL, LOCAL, AND SYSTEMIC EFFECTS—The penetration of a drug into the viable epidermis and dermis may be difficult to achieve, as noted above. But, once transepidermal permeation has occurred, the continued diffusion of drug into the dermis is likely to result in drug transfer into the microcirculation of the dermis and then into general circulation. Nonetheless, it is possible to formulate drug delivery systems that provide substantial localized delivery without achieving correspondingly high systemic concentrations. Limited studies in man of topical triethanolamine salicylate, minoxidil, and retinoids demonstrate the potential of this approach.

Unwanted systemic effects stemming from the inadvertent transdermal penetration of drugs have been reported for a wide variety of compounds (eg, hexachlorophene, lindane, corticosteroids, or *N,N*-diethyl-*m*-toluamide) over the years. With the commercial introduction of transdermal drug delivery systems for scopolamine, nitroglycerin, clonidine, 17β-estradiol, fentanyl, nicotine, testosterone, lidocaine, and oxybutynin, transdermal penetration is being regarded increasingly as an opportunity rather than a nuisance.

Percutaneous Absorption

Percutaneous absorption involves the transfer of drug from the skin surface into the stratum corneum, under the aegis of a concentration gradient, and its subsequent diffusion through the stratum corneum and underlying epidermis, through the der-

mis, and into the microcirculation. The skin behaves as a passive barrier to diffusing molecules. Evidence for this includes the fact that the impermeability of the skin persists long after the skin has been excised. Furthermore, Fick's Law is obeyed in the vast majority of instances.

Molecular penetration through the various regions of the skin is limited by the diffusional resistances encountered. The total diffusional resistance (R_{skin}) to permeation through the skin has been described by Chien as

$$R_{skin} = R_{sc} + R_e + R_{pd}$$

where R is the diffusional resistance, and the subscripts *sc, e,* and *pd* refer to the stratum corneum, epidermis, and papillary layer of the dermis, respectively. In addition, resistance to transfer into the microvasculature limits the systemic delivery of drug.

By and large, the greatest resistance to penetration is met in the stratum corneum (ie, diffusion through the stratum corneum tends to be the rate-limiting step in percutaneous absorption).

The role of hair follicles and sweat glands must be considered; however, as a general rule their effect is minimized by the relatively small fractional areas occupied by these appendages. On the other hand, liposomal vehicles and microbead (3 to 10 μm diameter) suspensions appear to accumulate selectively in pilosebaceous and perifollicular areas. In the very early stages of absorption, transit through the appendages may be comparatively large, particularly for lipid-soluble molecules and those whose permeation through the stratum corneum is relatively low. Surfactants and volatile organic solvents such as ethanol have been found to enhance drug uptake via the transfollicular route.

Rather than characterizing drug transfer into and through the skin in terms of the diffusional resistances encountered, one could define permeation in terms of the *pathways* followed by the diffusing species. Drug permeation through the intact skin of humans involves either an intercellular or transcellular path in the stratum corneum, for the most part, rather than the so-called shunt pathways (transglandular or transfollicular routes).

The conventional wisdom is that for the most part, lipophilic compounds transfer preferentially into the lipoidal intercellular phase of the stratum corneum, while relatively more hydrophilic compounds transfer into the intracellular domain of the stratum corneum. One should keep in mind that the often-postulated biphasic character of the horny layer—with hydrophilic cells in a lipophilic matrix—is overly simplistic: the hydrophilic cells themselves are enclosed within lipid bilayer membranes, while the lipophilic matrix comprises intercellular lipids that are, in fact, present in lamellar structures that *sandwich in* hydrophilic layers. As Boddé et al[1] have suggested, the intercellular pathway is *bicontinuous,* consisting of a nonpolar and a polar diffusion pathway between the corneocytes. The implications for dermatopharmacokinetic modeling are clear.

The stratum corneum can be regarded as a passive diffusion membrane but not an inert system; it often has an affinity for the applied substance. The adsorption isotherm is frequently linear in dilute concentration ranges. The correlation between external and surface concentrations is given in terms of the solvent membrane distribution coefficient K_m. The integrated form of Fick's Law is given as

$$J_s = \frac{K_m D C_s}{\delta}$$

and

$$K_p = \frac{K_m D}{\delta}$$

where K_p is the permeability coefficient, J_s is the steady state flux of solute, C_s is the concentration difference of solute across membrane, δ is the membrane thickness,

$$K_m \text{ is the } \frac{\text{solute sorbed per cm}^3 \text{ of tissue}}{\text{solute in solution per cm}^3 \text{ of solvent}} = \frac{C_m}{C_s},$$

and D is the average membrane diffusion coefficient for solute.

Permeability experiments have shown that the hydrated stratum corneum has an affinity for both lipophilic and hydrophilic compounds. The bifunctional solubility arises from the *hydrophilic* corneocytes and the lipid-rich lamellar structures in the intercellular space. Thus, attempts to predict permeability constants from oil:water or solvent:water partition coefficients have had limited success.

The effect of regional variation on skin permeability can be marked. It has been suggested that one ought to differentiate between two species of horny layer: the palms and soles (up to 600 μm thick), adapted for weight-bearing and friction; and the body horny layer (~10 μm thick), adapted for flexibility, impermeability, and sensory discrimination.

Overall, data suggest the following order for diffusion of simple molecules through the skin: plantar < palmar < arms, legs, trunk, dorsum of hand < scrotal and postauricular < axillary < scalp. Electrolytes in solution penetrate the skin poorly. Ionization of a weak electrolyte substantially reduces its permeability (eg, sodium salicylate permeates poorly compared with salicylic acid). The development of iontophoretic devices in recent years may minimize this problem with ionic penetrants. For any specific molecule, the predictability of regional variations in skin permeability continues to elude investigators. This will continue to be true as long as dermatopharmacokinetic models do not adequately reflect the anisotropicity of the skin's composition and structure, its interactions with the drug and the vehicle, and the physiological parameters that affect transfer.

In Vitro and *In Vivo* Studies

Classically, percutaneous absorption has been studied *in vivo* using radioactively labeled compounds or by *in vitro* techniques using excised human or animal skin. *In vivo* studies in recent years have made use of the skin-stripping method, which permits the estimation of the concentration or amount of the penetrating species as a function of depth of the stratum corneum. Layers of the stratum corneum can be removed or stripped successively away by the repeated application and removal of cellulose adhesive tape strips. Skin penetration of a drug and the effect of additives may be studied and evaluated through analysis of individual skin strips, which provide a profile of skin penetration. Rougier et al[2] have championed the use of the skin-stripping method, in conjunction with short-term exposure to the topically applied penetrant, as a predictor of skin permeation.

Clearly, the evaluation of new chemical entities (NCEs) of indeterminate toxicity mandates *in vitro* testing. A diffusion cell frequently used for *in vitro* experiments is shown in Figure

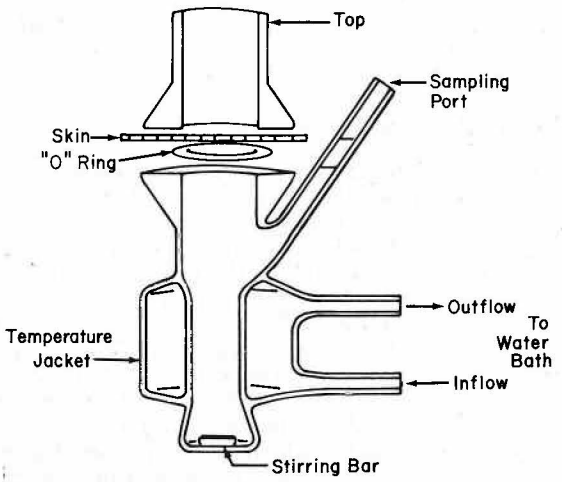

Figure 44-2. Schematic representation of diffusion cell. Top is open to ambient laboratory environment. (From Franz TJ. *J Invest Dermatol* 1975;64:191.)

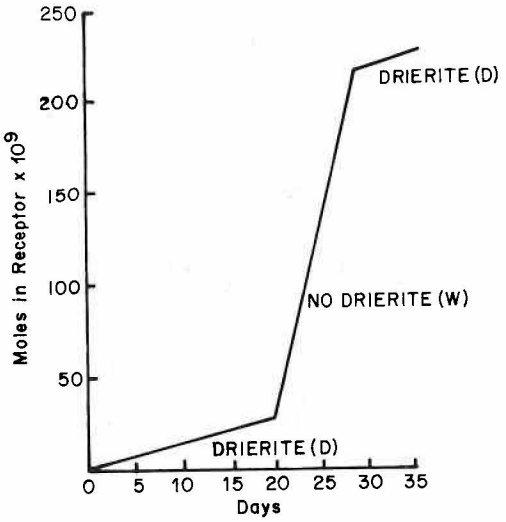

Figure 44-3. Change in cortisone penetration by alternately drying (D) and humidifying (W) the stratum corneum. (From Scheuplein RJ, Ross LW. *J Invest Dermatol* 1974;63:353.)

44-2.[3] In this system, the intact skin or the epidermis is treated as a semipermeable membrane separating two fluid media. The transport rate of a particular drug is evaluated by introducing the drug in solution on the stratum corneum side of the *membrane,* then measuring penetration by periodic sampling and analysis of the fluid across the skin membrane.

Investigators have recognized that transport across an immersed, fully hydrated stratum corneum may not represent the absorption system or rate observed in *in vivo* studies. Percutaneous absorption across a fully hydrated stratum corneum may be an exaggeration. It may be more representative of enhanced absorption that is seen after *in vivo* skin is hydrated by occlusive wrapping.

Using separated epidermal skin mounted in diffusion cells, Scheuplein and Ross[4] varied the atmosphere above the skin strip by use of Drierite to simulate dry conditions and wetted paper strips to simulate the effect of occlusion and observed marked reduction in penetration of cortisone under dry conditions but greatly enhanced penetration on humidifying the stratum corneum (Fig 44-3).[4]

The studies of Scheuplein and Ross,[4] and of Franz,[3] demonstrate that *in vitro* studies of percutaneous absorption under controlled conditions are relevant to *in vivo* drug penetration. As stated by Franz, "whenever a question is asked requiring only a qualitative or directional answer, the *in vitro* technique appears perfectly adequate."

Relevance of Animal Studies

PERCUTANEOUS ABSORPTION—Any evaluation of a study of percutaneous absorption in animals must take cognizance of species variation. Just as percutaneous absorption in man will vary considerably with skin site, so will absorption in various animal species. Bartek et al[5] investigated percutaneous absorption and found a decreasing order of permeability, thus, rabbit > rat > swine > man. They studied the *in vivo* absorption of radioactively labeled haloprogin, *N*-acetylcysteine, testosterone, caffeine, and butter yellow; their results with testosterone, shown in Figure 44-4,[6] illustrate the penetration differences observed with different animal skins.

Subsequently, using a similar *in vivo* technique, Wester and Maibach[7] investigated the percutaneous absorption of benzoic acid, hydrocortisone, and testosterone in the rhesus monkey. Radioactively tagged compounds were applied to the ventral surface of the forearm, and absorption was quantified on the basis of radioactivity excreted in the urine for 5 days following application. The investigators concluded that the percutaneous penetration of these compounds in the rhesus monkey is similar to that in man and regarded the data as encouraging because of the similarity.

The consensus is that rhesus monkeys and miniature pigs are good *in vivo* models for human percutaneous absorption, while smaller laboratory animals (eg, mouse, rat, rabbit) are not.

It should be stressed again that percutaneous absorption studies in animals, either *in vivo* or *in vitro,* only can be useful approximations of activity in man. The effect of species variation, site variability (about which little is known in animals), skin condition, experimental variables, and, of major importance, the vehicle, must be kept in mind.

As Bronaugh[8] notes, although human skin is preferable for *in vitro* permeation studies, its availability is limited. Additional constraints apply if one is only willing to use freshly obtained viable human skin from surgical specimens or biopsies, as opposed to skin harvested from cadavers.

Concern has been voiced over the notorious variability in barrier properties of excised skin, whether animal or human. Factors responsible for the variability include the source and characteristics of the donor skin (eg, elapsed time from death to harvesting of the skin, age and gender of the donor, health of the skin prior to the donor's death), exposure of the skin to chemicals or mechanical treatment (eg, shaving or clipping prior to harvesting of the skin), etc. The availability of a *living skin equivalent*—comprising a bilayered system of human dermal fibroblasts in a collagenous matrix upon which human corneocytes have formed a stratified epidermis—offers an alternative, less variable, model for evaluating human skin permeation and biotransformation.

Skin-flap methods represent *in vivo* and *in vitro* techniques for evaluating percutaneous absorption in animals or animal models: the general approach entails the surgical isolation of a skin section of an animal such that the blood supply is singular; this ensures that drug can be collected and assayed in the vascular perfusate as it undergoes absorption from the skin surface. The perfused skin flap can be maintained in the intact animal or mounted in an *in vitro* perfusion system, all the while maintaining its viability.

Animals also have been used to detect contact sensitization, measure antimitotic drug activity, measure phototoxicity, and evaluate the comedogenic and comedolytic potential of sub-

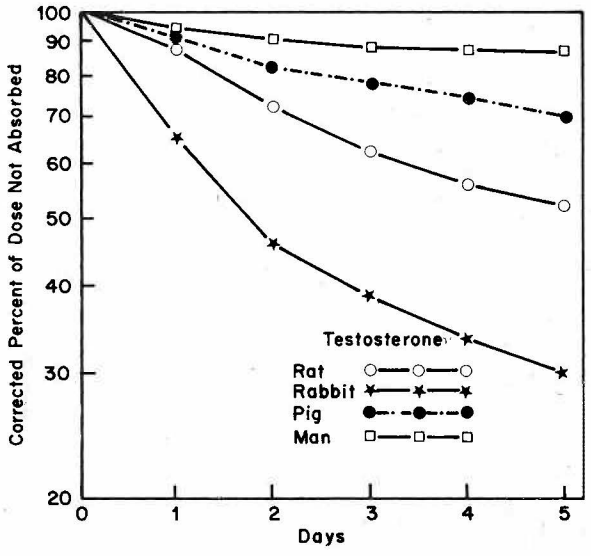

Figure 44-4. Percutaneous absorption of testosterone in rats, rabbits, swine and man for 5 days after application. (From Maibach HI, ed. *Animal Models in Dermatology.* Edinburgh: Churchill Livingstone, 1975.)

stances. In each of these test procedures, be it a safety test or assay model, the animal is considered a substitute for man. It is, therefore, important to realize that the animal is not man, even though man is the ultimate test animal. Animal-testing presents the investigator with unique advantages; lack of appreciation of the variables involved can destroy these advantages.

Mershon and Callahan[9] recorded and illustrated the considerations involved in selecting an animal test model. They interpreted the rabbit irritancy data of several investigators and impressively visualized different possible interpretations of the differing response between rabbit and man.

While the ultimate system for establishing therapeutic efficacy is man, there are specific animal test models that are recognized to be valuable as prehuman-use screens predictive of drug activity in humans. For example, the rat-ear assay and the granuloma-pouch procedure in rats are recognized procedures for the estimation of steroid anti-inflammatory activity.

Lorenzetti[10] tabulated the potency of various topical steroids, comparing the rat-ear-edema assay with potency measured in humans by use of the vasoconstrictor procedure of Stoughton and McKenzie; the results are given in Table 44-2.[11] Animal assay models of this kind, particularly the steroid anti-inflammatory assays, are most useful as preliminary activity screens. The simplicity, safety, and reproducibility of the vasoconstrictor assay in humans recommend it over any corresponding animal procedure. However, a number of concerns have been raised over the years that need to be addressed, particularly if this bioassay is to be used to assess the bioequivalence of topical corticosteroid formulations. These concerns include the linearity of the vasoconstrictor response–drug concentration relationship and the visual assessment of the blanching or vasoconstrictor response.

As the *in vivo* vasoconstrictor response generally approaches a maximum, one must know whether the microcirculation of the skin has exceeded its capacity to respond linearly to the corticosteroid concentration attained in the skin. It may be that only relatively minimal responses will be elicited by relatively high concentrations. At the other end of the response-dose relationship, what is the minimum dose that will produce a reliable, replicable response? Rather than relying on the somewhat subjective visual evaluation of the response, investigators ought to make use of chromometers to provide objective, quantifiable data.

PILOSEBACEOUS UPTAKE—The study of the targeted delivery of drugs to follicles and/or sebaceous glands has become necessary in view of the selective uptake or deposition of antiacne drugs such as tretinoin in pilosebaceous units. Fortunately, the anatomical and physiological correspondence of hamster ear pilosebaceous units to those in humans has facilitated studies of the cutaneous and pilosebaceous disposition of drugs following topical application.[12]

Table 44-2. Relative Potency of Anti-Inflammatory Agents

COMPOUND	RAT-EAR EDEMA ASSAY	TOPICAL ANTI-INFLAMMATORY POTENCY HUMAN ASSAY VASOCONSTRICTOR
Dexamethasone	73.2 (49.4–110)	10–20
Dexamethasone 21-acetate	117.3 (85.9–106)	10–20
Prednisolone	2.44 (1.54–7.76)	1–2
Prednisolone 21-acetate	5.43 (4.05–7.70)	3
Betamethasone	97.3 (16.7–141)	3–5
Betamethasone 21-acetate	1072.0 (876–1179)	18–33
Fluorometholone	138.3 (57.9–333)	30–40
Fluorometholone acetate	219.5 (9.15–536)	
Fluprednisolone	31.8 (13.3–76.1)	4–6
Fluprednisolone acetate	61.3 (25.6–147)	
Hydrocortisone	1	1

( ) = 95% confidence limits.
From Maibach HI. In Maibach HI, ed. *Animal Models in Dermatology.* Edinburgh: Churchill Livingstone, 1975, p 221.

Other Factors Affecting Drug Absorption from the Skin

Percutaneous absorption of a drug can be enhanced by the use of occlusive techniques or by the use of so-called penetration enhancers.

SKIN HYDRATION AND TEMPERATURE—Occluding the skin with wraps of impermeable plastic film such as Saran Wrap prevents the loss of surface water from the skin. Since water is absorbed readily by the protein components of the skin, the occlusive wrap causes greatly increased levels of hydration in the stratum corneum. The concomitant swelling of the horny layer ostensibly decreases protein network density and the diffusional path length. Occlusion of the skin surface also increases skin temperature (~2 to 3°C), resulting in increased molecular motion and skin permeation.

Hydrocarbon bases that occlude the skin to a degree will bring about an increase in drug penetration. However, this effect is trivial compared with the effects seen with a true occlusive skin wrap. Occlusive techniques are useful in some clinical situations requiring anti-inflammatory activity, and occlusive wrappings are used most commonly with steroids. Since steroid activity can be enhanced so enormously by skin occlusion, it is possible to depress adrenal function unknowingly. Early in the 1960s, McKenzie demonstrated that penetration of steroid could be increased 100-fold by use of occlusion.

Transdermal delivery systems, with their occlusive backing, can effect increased percutaneous absorption as a result of increased skin temperature and hydration.

In experiments with healthy volunteers wearing transdermal nitroglycerin delivery systems, investigators[13] showed that exposure of the surrounding skin area to localized heating or cooling could cause extensive changes in nitroglycerin bioavailability, presumably due to changes in regional cutaneous blood flow and subsequent systemic uptake *(see below)*.

One consequence of occlusion of the skin surface, whether by a transdermal delivery system or a hydrocarbon film, is that an aqueous film may form at the formulation-skin interface. This aqueous film or interphase could result in decreased transfer efficiency, and, in the case of a transdermal delivery system, a loss of adhesion. Accordingly, the suppression of perspiration could enhance vehicle-skin partitioning efficiency and drug permeation.

PENETRATION ENHANCERS—This term has been used to describe substances that facilitate absorption through the skin. While most materials have a direct effect on the permeability of the skin, other so-called enhancers (eg, polyols, such as glycerin and propylene glycol) appear to augment percutaneous absorption by increasing the thermodynamic activity of the penetrant, thereby increasing the effective escaping tendency and concentration gradient of the diffusing species. Penetration enhancers with a direct effect on skin permeability include solvents, surfactants, and miscellaneous chemicals such as urea and *N,N*-diethyl-*m*-toluamide (Table 44-3).[14,15] The mechanism of action of these enhancers is complex since these substances also may increase penetrant solubility. Nonetheless, the predominant effect of these enhancers on the stratum corneum is either to increase its degree of hydration or disrupt its lipoprotein matrix. In either case, the net result is a decrease in resistance to penetrant diffusion. (The formulator should note that the inclusion of a penetration enhancer in a topical formulation mandates additional testing and evaluation to ensure the absence of enhancer-related adverse effects.)

Foremost among the solvents that affect skin permeability is water. As noted above, water is a factor even for *anhydrous* transdermal delivery systems due to their occlusive nature. Due to its safety and efficacy, water has been described as the

Table 44-3. Penetration Enhancers

Solvents	Dimethyl formamide
Water	Tetrahydrofurfuryl alcohol
Alcohols	*Amphiphiles*
Methanol	L-α -Amino acids
Ethanol	Anionic surfactants
2-Propanol	Cationic surfactants
Alkyl methyl sulfoxides	Amphoteric surfactants
Dimethyl sulfoxide	Nonionic surfactants
Decylmethyl sulfoxide	Fatty acids and alcohols
Tetradecylmethyl sulfoxide	*Miscellaneous*
Pyrrolidones	Clofibric acid amides
2-Pyrrolidone	Hexamethylene lauramide
N-Methyl-2-pyrrolidone	Proteolytic enzymes
N-(2-Hydroxyethyl) pyrrolidone	Terpenes and sesquiterpenes
	α-Bisabolol
Laurocapram	*d*-Limonene
Miscellaneous solvents	Urea
Acetone	*N,N*-Diethyl-*m*-toluamide
Dimethyl acetamide	

Data from Walters KA. In Hadgraft J, Guy RH, eds. *Transdermal Drug Delivery.* New York: Dekker, 1989, p 197; Ghosh TK, Banga AK. *Pharm Technol* 1993; 17(4):62; 1993; 17(5):68.

ultimate penetration enhancer. Other solvents include the classic enhancer, dimethyl sulfoxide (DMSO), which is of limited utility because of its potential ocular and dermal toxicity, its objectionable taste and odor (a consequence of its absorption and subsequent biotransformation), and the need for concentrations in excess of 70% to promote absorption. Analogs of DMSO such as decylmethyl sulfoxide are used currently in some topical formulations. In contrast with other solvents, laurocapram (Azone) has been shown to function effectively at low concentrations (≤5%). Furthermore, laurocapram's effect on skin permeability persists long after a single application, due apparently to its prolonged retention within the stratum corneum.

Surfactants, long recognized for their ability to alter membrane structure and function, can have a substantial effect on skin permeability.[16] However, given the irritation potential of surfactants applied chronically, their utility as penetration enhancers is limited. Their effect on permeability may be complicated further by surfactant/monomer aggregation to form micelles and the concomitant solubilization of the permeant. As the impact of surfactants on skin permeability of a penetrant is problematic, the effect of their inclusion in a formulation should be evaluated using appropriate *in vitro* and *in vivo* studies.

STRATUM CORNEUM BARRIER EFFICACY AND DERMAL CLEARANCE—Even though *in vitro* studies of percutaneous transport may reflect the resistance of the skin to drug diffusion, there is no way such studies can characterize adequately the transfer of diffusing drug into the microvasculature of the dermis and its subsequent transfer into general circulation.

Christophers and Kligman[17] evaluated the dermal *clearance* of ^{22}Na from the midback skin of volunteers following the intradermal injection of ^{22}Na as normal saline solution. The dermal *clearances,* expressed in terms of the half-life for disappearance of radioactivity, are plotted in Figure 44-5.[17] Similar results were obtained with disappearance of skin fluorescence after intradermal injection of sodium fluorescein. The data are indicative of markedly delayed dermal clearance in the aged. This may reflect, in part, a decrease in older subjects in dermal capillary loop density, a decrease in the rate and/or extent of dermal blood perfusion, or an increase in resistance to transfer into the capillaries.

The importance of blood-flow-limited percutaneous absorption was shown by Benowitz et al[18] who documented the effect of the intravenous administration of nicotine, a known cutaneous vasoconstrictor, on the systemic absorption of nicotine administered concurrently in the form of a transdermal delivery system. Plasma nicotine concentrations rose less rapidly and reached a lower peak at a later time than when nicotine was applied transdermally in the absence of the intravenous nicotine infusion. This raises concerns about the potential cutaneous interactions between vasoconstrictors *or* vasodilators *and* topically applied drugs intended for a systemic effect: bioavailability could be increased or diminished as a result! The assessment of the potency of corticosteroids by corticosteroid-induced skin blanching (ie, vasoconstriction, lends credence to this issue).

On the other hand, Christophers and Kligman[17] demonstrated increased *in vitro* skin permeation by sodium fluorescein in the stratum corneum excised from young and old subjects (Fig 44-6[17]). Thus, the stratum corneum of older subjects may offer less resistance to the penetration of topically applied drugs.

Given the substantial intersubject variations that occur in diffusional resistance and in dermal clearance, it is not surprising that *in vivo* studies of percutaneous absorption often demonstrate marked differences in systemic availability of drugs. Furthermore, the tendency to employ normal, healthy, *young* adults in these studies may not provide data that is indicative of drug permeation through the skin of older subjects or patients.

Roskos, Maibach, and Guy[19] made quantitative measurements of the percutaneous absorption of a number of drugs *in vivo* from the urinary excretion profiles of ^{14}C-radiolabeled drugs in young (18 to 40 years) and old (>65 years) subjects: while permeation of hydrocortisone, benzoic acid, aspirin, and caffeine was significantly lower in older subjects, testosterone and estradiol absorption was comparable in the two groups. Additional comprehensive studies of percutaneous absorption *as a function of age* continue to be warranted.

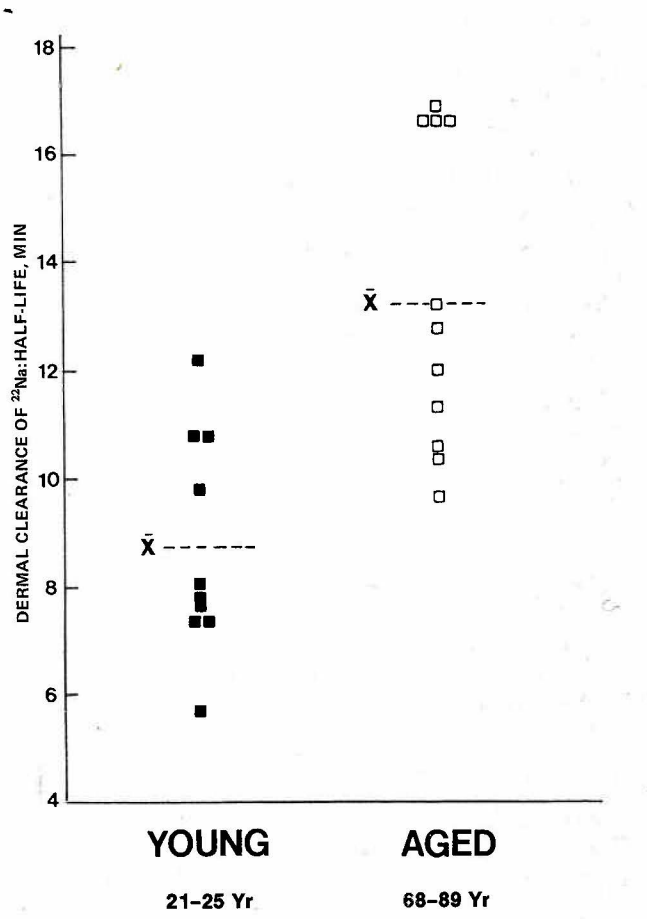

Figure 44-5. Dermal clearance of ^{22}Na in young and aged subjects after intradermal injection. (Data from Christophers E, Kligman AM. In Montagna W, ed. *Advances in the Biology of Skin,* vol 6. Oxford: Pergamon, 1965, p 163.)

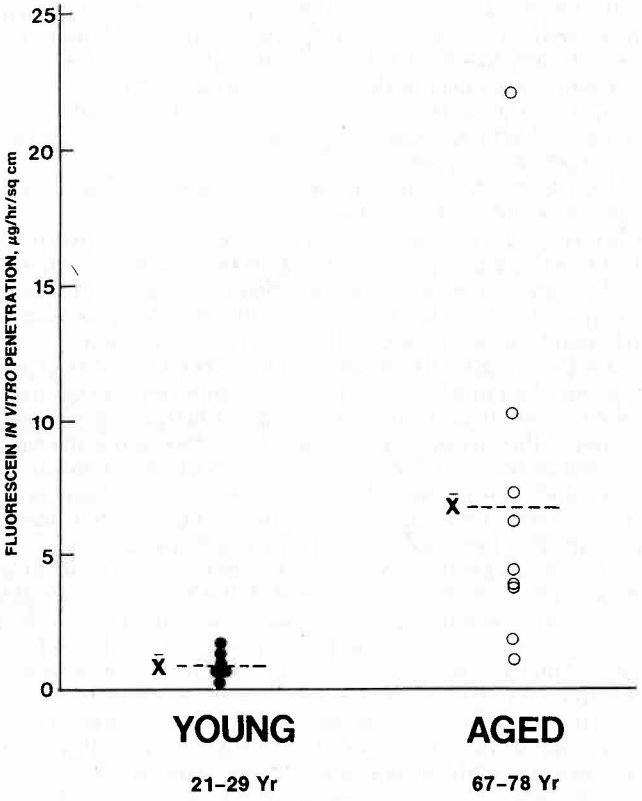

Figure 44-6. Flux of fluorescein through stratum corneum excised from young and aged subjects (Data from Christophers E, Kligman AM. In Montagna W, ed. *Advances in the Biology of Skin,* vol 6. Oxford: Pergamon, 1965, p 163.)

CUTANEOUS BIOTRANSFORMATION—Catabolic enzyme activity in the viable epidermis is substantial. In fact, the viable epidermis is metabolically more active than the dermis. If the topically applied drug is subject to biotransformation during skin permeation, local and systemic bioavailability can be affected markedly. Enzymatic activity in the skin, or for that matter in systemic fluids and tissues, can be taken advantage of to facilitate percutaneous absorption. Sloan and Bodor,[20] for example, synthesized 7-acyloxymethyl derivatives of theophylline that diffuse through the skin far more efficiently than theophylline itself (Fig 44-7[20]) but which are biotransformed rapidly to theophylline. Thus, theophylline delivery to systemic circulation can be enhanced substantially.

Further Considerations for Transdermal Drug Delivery

For a drug to qualify as a candidate for systemic delivery after topical application, it must satisfy requirements in addition to exhibiting good skin permeation. Successful candidates for transdermal drug delivery should be nonirritating and nonsensitizing to the skin. Since relatively little drug may reach systemic circulation over a relatively long time, drug candidates should be relatively potent drugs. In addition, the limitation to relatively potent drugs can ease problems of formulation, since the amount of drug that can be incorporated in the formulation may be limited by physicochemical considerations such as solubility.

In Silico Methods

In recent years, *in silico* or *in numero* modeling or computer simulation of percutaneous absorption has been advocated as a link between *in vitro* and *in vivo* studies. A number of relatively simplistic dermatopharmacokinetic models have been developed that do provide the formulator with some insight into transdermal drug delivery, in spite of the biological and physicochemical complexity of drug transport into and through the skin. By and large, these models are analogous to the classical pharmacokinetic models that have been employed to assess *in vivo* drug uptake and disposition. Some of the dermatopharmacokinetic models proposed differ from more classically oriented models in that drug transport in the vehicle and in the epidermis, particularly the stratum corneum, is modeled in accordance with Fickian diffusion. Thus, the formulator can anticipate the effect of variables such as the thickness of the applied (vehicle) phase, alterations in drug partitioning between the vehicle and the stratum corneum, and the frequency of reapplication on the overall appearance of drug systemically as a function of time following topical application.

RECTAL ABSORPTION

The bioavailability of rectally administered drugs is a relatively recent concern despite the antiquity of this dosage form; little was known about drug absorption or drug activity via suppository administration until recent years. Rectally instilled preparations, whether suppositories, foams, or solutions (enemas), tend to be confined to the rectum and sigmoid colon if the volume is less than about 50 mL. Foams tend to dissipate or spread to a lesser extent than solutions, particularly large-volume solutions (~100 to 200 mL). Though large-volume fluid formulations—solutions or enemas—may allow drug to reach the ascending colon, substantial intra- and intersubject variation is evident.[21] Literature information indicates that rectal drug absorption from suppositories can be erratic and may be substantially different from absorption following oral administration. With only a few recent exceptions, suppository studies are based on either *in vivo* or *in vitro* data, with few attempts to correlate *in vitro* results with *in vivo* studies.

Major factors affecting the absorption of drugs from suppositories administered rectally are the following: anorectal physiology, suppository vehicle, and the physicochemical properties of the drug.

ANORECTAL PHYSIOLOGY—The rectum is about 150 mm in length, terminating in the anal opening; its surface area is about 200 to 400 cm^2. In the absence of fecal matter the rec-

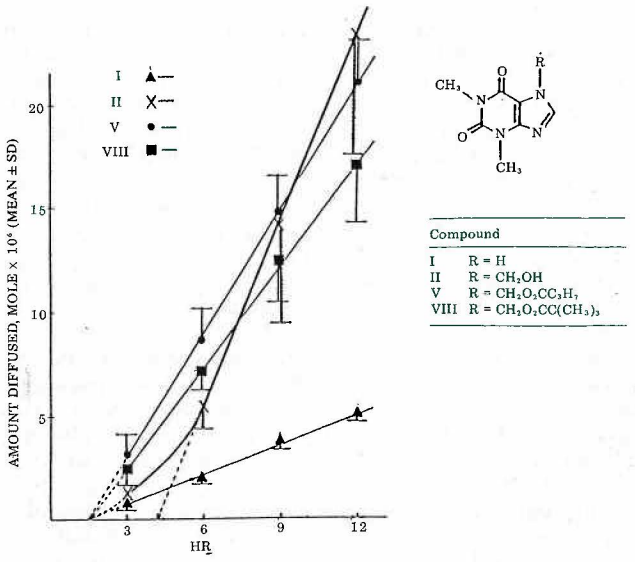

Figure 44-7. Diffusion of theophylline (I) and its derivatives through hairless mouse skin. (From Sloan KB, Bodor N. *Int J Pharm* 1982;12:299.)

tum contains a small amount of fluid (1 to 3 mL) of low buffering capacity. Fluid pH is said to be about 7.2; because of the low buffer capacity pH will vary with the pH of the drug product or drug dissolved in it. Bottger et al [22] studied the influence of pH on the rectal absorption of sodium benzoate in man by the technique of rectal lumen perfusion. This study demonstrates that strong buffers in rectal solutions induce a drastic effect on the pH of the boundary layer, an effect that is not seen if unbuffered solutions are used.

Most rectal suppositories today are torpedo-shaped, with the apex, or pointed end, tapering to the base, or blunt end, following the recommendation of HS Wellcome in 1893 that rectal suppositories should be inserted with the thicker end foremost so that when the anal sphincter contracts, expulsion is prevented. In the intervening 100 years or so, no study has correlated rectal suppository insertion with anorectal physiology until that of Abd-El-Maeboud et al,[23] who found that ease of insertion, retention, and lack of expulsion were enhanced when the suppository was inserted base or blunt end up. This was ascribed to reversed vermicular contractions of the external anal sphincter, which facilitate movement of the suppository upward into the rectum.

The rectal epithelium is lipoidal in character. The lower, middle, and upper hemorrhoidal veins surround the rectum. Only the upper vein conveys blood into the portal system; thus, drugs absorbed into the lower and middle hemorrhoidal veins will bypass the liver. Absorption and distribution of a drug therefore are modified by its position in the rectum, in the sense that at least a portion of the drug absorbed from the rectum may pass directly into the inferior vena cava, bypassing the liver.

Spreading characteristics of rectal formulations may be affected considerably by intraluminal rectal pressure—due, in part, to the weight of abdominal organs and to respiratory activity—and by periodic contractile activity of the rectal wall.[24]

Parrott[25] compared the absorption of salicylates after rectal and oral administration. Using urinary excretion data both aspirin and sodium salicylate were found to be equally bioavailable orally or rectally. Aspirin was released more rapidly from water-miscible suppositories than from the oily type. Conversely, sodium salicylate was released more rapidly from a cocoa butter vehicle.

Based on available data the bioavailability of a drug from a suppository dosage form depends on the physicochemical properties of the drug as well as the composition of the base. The drug-dissolution rate and, where appropriate, the partition coefficient between lipid and aqueous phase should be known.

For suppository formulation, the relative solubility of the drug in the vehicle is a convenient comparison measure. Lipid-soluble drugs present in low concentration in a cocoa butter base will have little tendency to partition and diffuse into rectal fluids. Drugs that are only slightly soluble in the lipid base will partition readily into the rectal fluid. The partition coefficient between suppository base and rectal fluid thus becomes a useful measure. In water-soluble bases, assuming rapid dissolution, the rate-limiting step in absorption would be transport of the drug through the rectal mucosa.

In the absence of evidence of any substantial carrier-mediated uptake mechanisms, the predominant mechanism of colorectal mucosal permeation appears to involve transcellular passage across cell membranes in accordance with the pH-partition hypothesis. Ease of access to the rectal mucosa has encouraged the evaluation of absorption enhancers. A wide variety of substances have been investigated for their ability to enhance rectal permeability to drugs. Agents such as EDTA have been used to chelate Ca^{2+} and Mg^{2+} in the vicinity of paracellular tight junctions and, thus, alter epithelial permeability. Other promoters of rectal absorption (eg, bile salts and nonsteroidal anti-inflammatory agents, including aspirin, salicylic acid and diclofenac) appear to exert their influence by affecting water influx and efflux rates across the rectal mucosa. Surfactants not only may modify membrane permeability but also enhance wetting or spreading of the base and dissolution of the drug. In any event, it should be evident that whatever the mechanism, enhancing the *rectal* absorption of drugs—especially those that undergo presystemic elimination—could result in substantially reduced dosage requirements and decreased risk of adverse reactions.

Clearly, the bioavailability of a drug administered rectally depends on the nature of the drug and the composition of the vehicle or base. The physical properties of the drug can be modified to a degree, as can the characteristics of the base selected as the delivery system. Preformulation evaluations of physicochemical properties then must be confirmed by *in vivo* studies in animals and ultimately in the primary primate, man.

***IN VIVO* RECTAL ABSORPTION STUDIES**—Dogs are probably the animal of choice in evaluating rectal drug availability. (The pig is a closer physiological match, but size and manageability argue in favor of the dog.) Blood and urine samples can be obtained from the dog, and rectal retention can be accomplished with facility. Smaller animals have been used; rabbits, rats, and even mice have been employed, but dosing and sampling become progressively more difficult.

Human subjects provide the ultimate measure of drug bioavailability. Subjects are selected on the basis of age, weight, and medical history. Subjects usually are required to fast overnight and evacuate the bowel prior to initiation of the study. Fluid volume and food intake usually are standardized in studies of this kind.

Given the difficulty of standardizing pharmacological endpoints, the usual measure of rectal drug bioavailability is the concentration of the drug in blood and/or urine as a function of time. A control group using oral drug administration provides a convenient means of comparing oral and rectal drug availability. Such a comparison is meaningful particularly in view of uncertainties and conflicts encountered in the literature. While there is general agreement about drug absorption from the rectum, there is less agreement on dosage adequacy and the relationship between oral and rectal dosage. This state of affairs argues in favor of adequate studies to establish proper dosage and verify bioavailability.

VAGINAL ABSORPTION

Passive drug absorption via the vaginal mucosa, as with other mucosal tissues, is influenced by absorption site physiology, absorption site pH, and the solubility and partitioning characteristics of the drug. The vaginal epithelial surface usually is covered with an aqueous film—emanating from cervical secretions—whose volume, pH, and composition vary with age, stage of the menstrual cycle, and location. Postmenarche, a vaginal pH gradient is evident, with the lowest values (pH ~4) near the anterior fornix and the highest (pH ~5) near the cervix.[26]

Following intravaginal administration, some drug absorption from the intact vaginal mucosa is likely, even when the drug is employed for a local effect. In fact, extensive drug absorption can occur from the vagina. For example, Patel et al[27] reported that plasma propranolol concentrations following vaginal dosing were significantly higher than those after per-oral administration of an equivalent dose; a reflection, in part, of decreased first-pass biotransformation following vaginal absorption. Nonetheless, the notion persists that the vaginal epithelium is relatively impermeable to drugs.

The widespread extemporaneous compounding of progesterone vaginal suppositories,[28,29] as well as the marketing of an intrauterine progesterone drug delivery system (Progestasert, *Alza*), has focused interest on systemic drug absorption following intravaginal administration. However, only limited reports of research on *in vitro* and *in vivo* aspects of vaginal absorption have appeared in the literature to date.

DOSAGE FORMS AND DRUG DELIVERY SYSTEMS FOR TOPICAL APPLICATION

The array of formulations and compositions employed for topical application confounds attempts at categorization. Nonetheless, if a distinction is made between drug *dosage forms* and drug *delivery systems*, some clarity emerges. **Dosage forms** contain the active drug ingredient in association with nondrug (usually inert) excipients that comprise the vehicle or formulation matrix. A conventional dosage form tends to be empirical in composition; its formulator's focus tends to emphasize stability and esthetics rather than efficacy. On the other hand, **delivery systems** involve a holistic approach to formulation that is optimized for the drug's relevant biopharmaceutic and pharmacokinetic characteristics in the patient population. Thus, a delivery system is formulated with functionality and efficacy in mind, not just stability and esthetics.

The Skin

In many (if not most) clinical situations, the rate-limiting step is penetration of the drug across the skin barrier (ie, percutaneous penetration through the skin alone). Diffusion of the drug from its vehicle should not be unknowingly the rate-limiting step in percutaneous absorption. Such a rate limitation or control may, of course, be an objective and the endpoint of specific drug optimization, but inappropriate formulation can reduce substantially the effectiveness of a topical drug substance.

In the formulation of a vehicle for topical drug application, many factors must be considered. Drug stability, intended product use, site of application, and product type must be combined in a dosage form or delivery system that will release the drug readily when placed in contact with the skin. Further, the release characteristics of the vehicle depend on the physical-chemical properties of the specific drug substance to be delivered to the skin: drug release from a vehicle is a function of the drug's concentration and solubility in the vehicle, and the drug's partition coefficient between the vehicle and the skin. A vehicle optimized for delivery of hydrocortisone may be quite inappropriate for delivery of a different steroid.

Higuchi (see *Bibliography*) discussed equations describing the rate of release of solid drugs suspended in ointment bases. Ostrenga et al[30] discussed the significance of vehicle composition on the percutaneous absorption of fluocinolone acetonide and fluocinolone acetonide 21-acetate (fluocinonide) (Fig 44-8). These investigators used propylene glycol/isopropyl myristate partition coefficients, *in vitro* (human) skin penetration, and finally *in vivo* vasoconstrictor studies to evaluate formulation variables. They concluded that

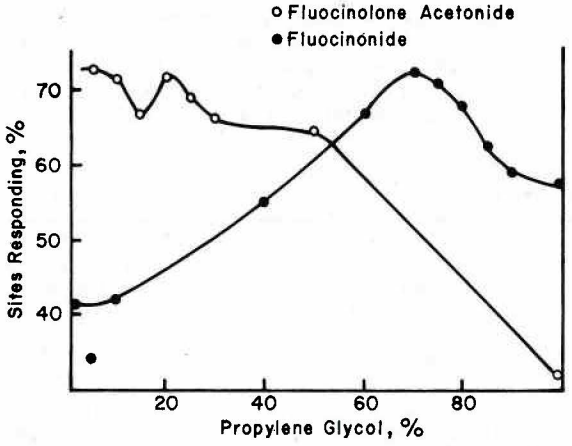

Figure 44-8. *In vivo* response as a function of vehicle composition (24-hour vasoconstriction). (From Ostrenga J, Steinmetz C, Poulsen B. *J Pharm Sci* 1971;60:1175.)

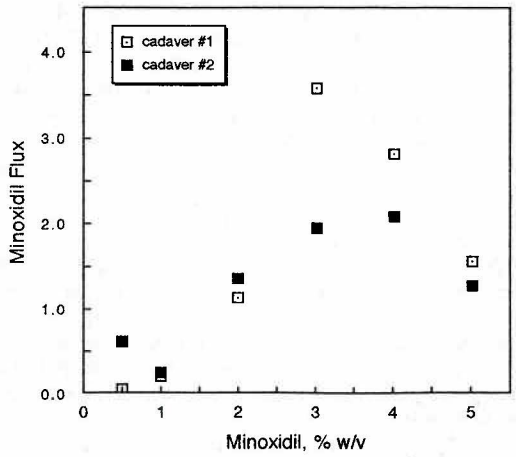

Figure 44-9. Minoxidil flux (x10^4 mg/cm^2/h) through human cadaver skin as a function of minoxidil concentration in the topically applied formulation. (Data from Flynn GL, Weiner ND, et al. *Int J Pharm* 1989;55:229.)

> "In general, an efficacious topical gel preparation is one in which (a) the concentration of diffusible drug in the vehicle for a given labeled strength is optimized by ensuring that all of the drug is in solution, (b) the minimum amount of solvent is used to dissolve the drug completely and yet maintain a favorable partition coefficient and (c) the vehicle components affect the permeability of the stratum corneum in a favorable manner."

The effect of propylene glycol concentration on *in vivo* vasoconstrictor activity is illustrated strikingly in Figure 44-8, taken from Ostrenga, Steinmetz, and Poulsen.[30]

Experimental work of the kind described by Ostrenga, Steinmetz, and Poulsen provides a means of optimizing drug release from a vehicle and penetration of the drug into the skin. This is a beginning. The formulator must proceed to develop a total composition in which the drug is stable and causes no irritation to sensitive skin areas. Safety, stability, and effective preservative efficacy must be combined with optimum drug delivery in the total formulation.

The work of Flynn, Weiner, and others[31] on the physicochemical stability of topical drug-delivery systems *postapplication* has facilitated the exploration of additional formulation factors that are crucial to the success of topical formulations. Flynn notes that the functionality of topical drug delivery systems stands in stark contrast to those of transdermal drug-delivery systems; while both delivery systems are open systems *kinetically* due to the formulation-skin interface, they differ to a considerable extent *thermodynamically* because most topical formulations are left open to the air postapplication, while transdermal delivery systems are self-contained closed systems.

One study focused on a topical delivery system for minoxidil. The vehicle was 60:20:20 ethanol:propylene glycol:water system, with just enough propylene glycol to maintain 2% minoxidil in solution, following the evaporation of the more volatile ethanol and water. Minoxidil fluxes across human cadaver skin, measured as a function of minoxidil concentration, increased as the initial concentration of drug increased, but only to about 3% (Fig 44-9). [31] At initial minoxidil concentrations greater than 3%, transport was disproportionately low, relative to initial concentration, due to early precipitation of the drug.

Evaporation and loss of volatile formulation components such as water or ethanol postapplication can be expected to affect topical drug-delivery system composition and performance. Flynn et al[31] have shown that so-called nonvolatile excipients (eg, propylene glycol) evaporate after topical application. Skin permeation by excipients also may occur after application lead-

ing to further compositional changes in the applied film on the skin surface. The impact of this evaporative and absorptive loss of adjuvants increases as the volume of the applied formulation is reduced. As Flynn et al[31] note, ". . . the momentary compositions, and thus delivery capabilities, of real vehicles are significantly influenced by the amounts applied."

TOPICAL DOSAGE FORMS

OINTMENTS—The USP defines ointments as semisolid preparations intended for external application to the skin or mucous membranes. They usually, but not always, contain medicinal substances. The types of ointment bases used as vehicles for drugs are selected or designed to facilitate drug transfer into the skin. Ointments also contribute emolliency or other quasi-medicinal benefits.

USP Classification and Properties of Ointment Bases

The USP recognizes four general classes of ointment bases: hydrocarbon bases (ie, oleaginous bases), absorption bases, water-removable bases, and water-soluble bases. These various bases are contrasted with one another in Table 44-4. The selection of the optimum vehicle based on the USP classification *per se* may require compromises. For example, stability or drug activity might be superior in a hydrocarbon base; however, patient acceptability is diminished because of the greasy nature of the base. The water solubility of the polyethylene glycol bases may be attractive, but the glycol(s) may be irritating to traumatized tissue. For some drugs, activity and percutaneous absorption may be superior when using a hydrocarbon base; however, it may be prudent to minimize percutaneous absorption by the use of a less occlusive base. In other instances, activity and percutaneous absorption may be enhanced by using a hydrophilic base. These problematic aspects of bioavailability of drugs in topical formulations are discussed above.

HYDROCARBON (OLEAGINOUS) BASES—Hydrocarbon bases are usually petrolatum *per se* or petrolatum modified by waxes or liquid petrolatum to change viscosity characteristics. Liquid petrolatum gelled by the addition of polyethylene also is considered a hydrocarbon ointment base, albeit one with unusual viscosity characteristics.

Hydrocarbon ointment bases are classified as oleaginous bases along with bases prepared from vegetable fixed oils or animal fats. Bases of this type include lard, benzoinated lard, olive oil, cottonseed oil, and other oils. These bases are emollient but generally require addition of antioxidants and other preservatives. They are now largely of historic interest.

Petrolatum USP is a tasteless, odorless, unctuous material with a melting range of 38°C to 60°C; its color ranges from amber to white (when decolorized). Petrolatum often is used externally, without modification or added medication, for its emollient qualities.

Petrolatum used as an ointment base has a high degree of compatibility with a variety of medicaments. Bases of this type are occlusive and nearly anhydrous and thus provide optimum stability for medicaments such as antibiotics. The wide melting range permits some latitude in vehicle selection, and the USP permits addition of waxy materials as an aid in minimizing temperature effects.

Hydrocarbon bases, being occlusive, increase skin hydration by reducing the rate of loss of surface water. Bases of this kind may be used solely for such a skin-moisturizing or emollient effect. Skin hydration on the other hand may increase drug activity as discussed earlier.

A gelled mineral oil vehicle (Plastibase) represents a unique member of this class of bases that comprises refined natural products: When approximately 5% of low-density polyethylene is added to liquid petrolatum and the mixture then heated and subsequently shock-cooled, a soft, unctuous, colorless material resembling white petrolatum is produced. The mass maintains unchanged consistency over a wide temperature range. It neither hardens at low temperatures nor melts at reasonably high temperatures. Its useful working range is between -15° and 60°C. Excessive heat, ie, above 90°C, will destroy the gel structure.

On the basis of *in vitro* studies, drugs may be released faster from a gelled mineral oil vehicle than from conventional petrolatum. This quicker release has been attributed to easier diffusion of drug through a vehicle with lower microscopic viscosity (ie, a vehicle that is essentially a liquid) than through petrolatum.

Despite the advantages hydrocarbon or oleaginous vehicles provide in terms of stability and emolliency, such bases have the considerable disadvantage of greasiness. The greasy or oily material may stain clothing and is difficult to remove. In terms of patient acceptance, hydrocarbon bases (ie, ointments) rank well below emulsion bases such as creams and lotions.

ABSORPTION BASES—Absorption bases are hydrophilic, anhydrous materials or hydrous bases that have the ability to absorb additional water. The former are anhydrous bases, which absorb water to become W/O emulsions; the latter are W/O emulsions, which have the ability to absorb additional water. The word absorption in this context refers only to the ability of the base to absorb water.

Hydrophilic Petrolatum USP is an anhydrous absorption base. Its W/O emulsifying property is conferred by the inclusion of cholesterol. This composition is a modification of the original formulation, which contained anhydrous lanolin. The lanolin was deleted because of reports of allergy; cholesterol was added. Inclusion of stearyl alcohol and wax adds to the physical characteristics, particularly firmness and heat stability.

Absorption bases, particularly the emulsion bases, impart excellent emolliency and a degree of occlusiveness on application. The anhydrous types can be used when the presence of water would cause stability problems with specific drug substances (eg, antibiotics). Absorption bases also are greasy when applied and are difficult to remove. Both of these properties are, however, less pronounced than with hydrocarbon bases.

Table 44-4. Classification and Properties of USP Ointment Bases

	HYDROCARBON BASE	ABSORPTION BASE	WATER-REMOVABLE BASE	WATER-SOLUBLE BASE
Example(s)	White Petrolatum, USP; White Ointment, USP	Hydrophilic Petrolatum, USP; Lanolin, USP	Hydrophilic Ointment, USP	Polyethylene Glycol Ointment, NF
Composition	Hydrocarbons	Anhydrous or W/O emulsion	O/W emulsion	Water-soluble constituents
Occlusiveness	High	Moderate to high	Low to moderate	Minimal
Principal Benefits or Uses	Maintains prolonged contact with application site; emollient effect	Allows incorporation of aqueous solutions; emollient effect	Water-washable; may be diluted with water; allows absorption of serous discharges	Water-washable; no water-insoluble residue

Commercially available absorption bases include Aquaphor *(Beiersdorf)* and Polysorb *(Fougera)*. Nivea Cream *(Beiersdorf)* is a hydrated emollient base. Absorption bases, either hydrous or anhydrous, are seldom used as vehicles for commercial drug products. The W/O emulsion system is more difficult to deal with than the more conventional O/W systems, and there is, of course, reduced patient acceptance because of greasiness.

WATER-REMOVABLE (WATER-WASHABLE) BASES— These bases are O/W emulsion bases, commonly referred to as creams, and represent the most commonly used type of ointment base. By far the majority of commercial dermatologic drug products are formulated in an emulsion (or cream) base. Emulsion bases are washable and removed easily from skin or clothing. Emulsion bases can be diluted with water, although such additions are uncommon.

As a result of advances in cosmetic chemistry the formulator of an emulsion base is faced with a bewildering array of potential ingredients. A glance at the cosmetic literature and such volumes as the Cosmetic, Toiletry and Fragrance Association's *International Cosmetic Ingredient Dictionary and Handbook* impresses one with the enormous number and variety of emulsion-base components, particularly surfactants and oil-phase components. Many of these substances impart subtle but distinct characteristics to cosmetic emulsion systems. While desirable, many of these characteristics are not really necessary in drug dosage forms or delivery systems. Furthermore, the likelihood of drug-excipient interactions, either physical or chemical, increases substantially (as does the cost) as the number of formulation components is increased. Thus the formulator of topical products should minimize the number of excipients in the formulation. Nonetheless, emulsion bases typically include antimicrobial preservatives, stabilizers (such as antioxidants, metal chelating agents, or buffers), and humectants (eg glycerin or propylene glycol), in addition to the emulsifiers, in order to ensure stability and efficacy.

Soaps and detergents (ie, emulsifiers) have, overall, a damaging effect on the skin. Both anionic and cationic surfactants can cause damage to the stratum corneum in direct proportion to concentration and duration of contact. Nonionic surfactants appear to have much less effect on the stratum corneum.

WATER-SOLUBLE BASES—Soluble ointment bases, as the name implies, are made up of soluble components or may include gelled aqueous solutions. The latter often are referred to as gels, and in recent years have been formulated specifically to maximize drug availability.

Major components, and in some instances the only components, of water-soluble bases are the polyethylene glycols (PEGs). Patch tests have shown that these compounds are innocuous, and long-term use has confirmed their lack of irritation. PEGs are relatively inert, non-volatile, water-soluble or water-miscible liquids or waxy solids identified by numbers that are an approximate indication of molecular weight. Polyethylene glycol 400 is a liquid superficially similar to propylene glycol, while polyethylene glycol 6000 is a waxy solid.

Polyethylene glycols of interest as vehicles include the 1500, 1600, 4000, and 6000 products, ranging from soft, waxy solids (polyethylene glycol 1500 is similar to petrolatum) to hard waxes. Polyethylene glycols, particularly 1500, can be used as a vehicle *per se;* however, better results often are obtained by using blends of high- and low-molecular-weight glycols, as in Polyethylene Glycol Ointment NF. The water-solubility of polyethylene glycol vehicles does not ensure availability of drugs contained in the vehicle. As hydrated stratum corneum is an important factor in drug penetration, the use of polyethylene glycol vehicles, which are anhydrous and nonocclusive, actually may hinder percutaneous absorption due to dehydration of the stratum corneum.

Aqueous gel vehicles containing water, propylene, and/or polyethylene glycol and gelled with a carbomer or a cellulose derivative also are classed as water-soluble bases. Bases of this kind, sometimes referred to as gels, may be formulated to optimize delivery of a drug, particularly steroids. In such a preparation, propylene glycol is often used for its solvent properties as well as for its antimicrobial or preservative effects.

Gelling agents used in these preparations may be nonionic or anionic. Nonionics include cellulose derivatives, such as methylcellulose or hypromellose (hydroxypropyl methylcellulose). Sodium carboxymethylcellulose is an anionic cellulose derivative.

Carbomers are the USP designation for various polymeric acrylic acids, crosslinked with carbohydrates or polyalcohol derivatives, that are dispersible but insoluble in water. When the acid dispersion is neutralized with a base a clear, stable gel is formed. Carbomers for which monographs appear in the USP include carbomers 910, 934, 934P, 940, 941, and 1342, as well as the more complex carbomer copolymer and carbomer interpolymer.

Other gelling agents employed in topical formulations include sodium alginate and the propylene glycol ester of alginic acid (Kelcoloid). Sodium alginate is a hydrophilic colloid that functions satisfactorily between pH 4.5 and 10; addition of calcium ions will gel fluid solutions of sodium alginate.

Gels can also be formed or stabilized by the incorporation of finely divided solids such as colloidal magnesium aluminum silicate (Veegum) or colloidal (fumed) silicon dioxide (Aerosil, Cab-O-Sil). These inorganic particulates can function as emulsifiers and suspending agents, as well as gellants. Their compatibility with alcohols, acetone, and glycols makes them particularly useful in topical gel formulations.

PREPARATION

Ointment preparation or manufacture depends on the type of vehicle and the quantity to be prepared. The objective is the same (ie, to disperse the drug uniformly throughout the vehicle). Normally, the drug materials are either in finely powdered form or in solution before being dispersed in the vehicle.

Incorporation of Drug by Levigation

The incorporation of a drug powder in small quantities of an ointment (ie, 30-90 g) can be accomplished by using a spatula and an ointment tile (either porcelain or glass). The drug material is levigated thoroughly with a small quantity of the vehicle or a miscible liquid component of the formulation (eg, propylene glycol; light mineral oil) to form a concentrate. The concentrate then is diluted geometrically with the remainder of the base.

If the drug substance is water-soluble it can be dissolved in water and the resulting solution incorporated into the vehicle by use of a small quantity of lanolin if the base is oleaginous. Generally speaking, an amount of anhydrous lanolin equal in volume to the amount of water used will suffice.

On a larger scale, mechanical mixers (eg, Hobart mixers, pony mixers) are used. The drug substance in finely divided form usually is added slowly or sifted into the vehicle contained in the rotating mixer. When the ointment is uniform, the finished product may be processed through a roller mill to ensure complete dispersion and reduce any aggregates.

An alternative procedure involves preparing and milling a concentrate of the drug in a portion of the base. The concentrate then is dispersed in the balance of the vehicle, using a mixer of appropriate size. Occasionally, the base may be melted for easier handling and dispersing. In such cases the drug is dispersed and the base slowly cooled, using continuous agitation to maintain dispersion.

Emulsion Formulations

Emulsions are prepared generally by combining the "oil"-soluble ingredients (eg, petrolatum, waxes, fats) and heating the admixture to about 75°C (ie, a temperature at which the oil-phase ingredients are molten). The "water"-soluble ingredients

are combined separately and heated to slightly above 75°C. The aqueous phase then is added to the oil phase, slowly and with constant agitation. When the emulsion is formed, the mixture is allowed to cool, maintaining slow agitation.

At this stage in the process, the medicinal ingredients usually are added as a concentrated slurry, which usually has been milled to reduce any particle aggregates. Volatile or aromatic materials generally are added when the finished emulsion has cooled to about 35°C. At this point, additional water may be added to compensate for any evaporative losses occurring during exposure and transfer at the higher temperatures of emulsion formation.

While the product remains in the tank in bulk, quality-control procedures are performed (ie, for pH, active ingredients, etc). If control results are satisfactory the product is filled into the appropriate containers.

IRRITANCY TESTING OF TOPICAL PRODUCTS

Ointment bases may cause irritant or allergic reactions. Allergic reactions are usually due to a specific base component. Irritant reactions are more frequent and more important, hence a number of test procedures have been devised to test for irritancy levels, both in animals and in man. The consequences of species differences and specificity must be included in the evaluation of animal-test results.

In the past, the most common method for evaluating irritancy was the Draize dermal irritation test in rabbits. In this procedure the test material was applied repeatedly to the clipped skin on the rabbit's back. Endpoints were dermal erythema and/or edema. The assignment of numerical scores for erythema and edema enabled the mathematical and statistical analysis of results.

In the human, a variety of test procedures are used to measure irritancy, sensitization potential, and phototoxicity. Among the most common are the 21-day cumulative irritancy patch test, the Draize-Shelanski repeat-insult patch test, and the Kligman "maximization" test.

21-DAY CUMULATIVE IRRITANCY PATCH TEST—In this test the test compound is applied daily to the same site on the back or volar forearm. Test materials are applied under occlusive tape, and scores are read daily. The test application and scoring are repeated daily for 21 days or until irritation produces a predetermined maximum score. Typical erythema scores range from 0 (no visible reaction) to 4 (intense erythema with edema and vesicular erosion). Usually, 24 subjects are used in this test. Fewer subjects and a shorter application time in days are variants of the test.

DRAIZE-SHELANSKI REPEAT-INSULT PATCH TEST—This test is designed to measure the potential to cause sensitization. The test also provides a measure of irritancy potential. In the usual procedure the test material or a suitable dilution is applied under occlusion to the same site for 10 alternate-day 24-hr periods. Following a 7-day rest period, the test material is applied again to a fresh site for 24 hours. The challenge sites are read on removal of the patch and again 24 hours later. The 0–4 erythema scale is used. A test panel of 100 individuals is common.

KLIGMAN "MAXIMIZATION" TEST—This test is used to detect the contact sensitizing potential of a product or material. The test material is applied under occlusion to the same site for 48-hr periods. Prior to each exposure the site may be pretreated with a solution of sodium lauryl sulfate under occlusion. Following a 10-day interval the test material again is applied to a different site for 48 hours under occlusion. The challenge site may be treated briefly with a sodium lauryl sulfate solution.

The "maximization" test is of shorter duration and makes use of fewer test subjects than the Draize-Shelanski test. The use of sodium lauryl sulfate as a pretreatment increases the ability to detect weaker allergens.

These test methods are adequate to detect even weak irritants and weak contact sensitizers. Positive results, however, do not automatically disqualify the use of a substance as unsafe. The actual risk of use depends on concentration, period of use, and skin condition. Benzoyl peroxide in tests such as the Draize-Shelanski and Kligman "maximization" is a potent sensitizer, yet the incidence of sensitization among acne patients is low.

THE EVOLUTION OF TRANSDERMAL DRUG DELIVERY SYSTEMS

Conventional medicated topicals (eg, creams and ointments) seldom permit substantial systemic uptake of the drug or drugs incorporated therein. This is a consequence, in part, of the limited persistence or residence time of the topical formulation on the skin surface. In effect, a drug does not remain in contact with the absorbing surface long enough for sufficient drug to transfer into the skin and, ultimately, into systemic circulation. Furthermore, there is the concomitant problem of the gradual depletion of drug from the region of the topical formulation immediately adjacent to the skin surface and the corresponding reduction in the concentration gradient for drug transfer from the topical formulation to the skin.

The emergence of adhesive transdermal drug-delivery systems (TDDSs) in the early 1980s permitted skin residence times to increase from hours to days. The novel matrix- or reservoir-formulations employed in these TDDSs also provided for the maintenance of relatively uniform concentrations of diffusible drug in the formulation, thereby preventing the formation of drug-depleted regions within the topical formulation and helping to ensure relatively constant drug-release rates. As noted above, skin occlusion by the water-impermeable backing film of TDDSs further facilitates TDDS systemic efficacy by increasing skin hydration and temperature with a corresponding increase in the rate and extent of skin permeation. The inclusion of skin-penetration enhancers in medicated topicals serves to decrease diffusional resistance and increase transport.

Nonetheless, these—by now—*conventional* TDDSs have their limitations: the increased residence time of occlusive TDDSs on the skin surface leads to an increased incidence of skin maceration and adverse cutaneous reactions. In addition, effective skin permeation is limited to relatively small (<1 kD), lipophilic drug molecules. Thus, increasingly more attention is being placed on alternative TDDSs—eg, electrically modulated systems and mechanical systems—which circumvent the need for partitioning and diffusion of the drug out of the formulation matrix and into and through the skin:

Electrically modulated systems, or *electrotransport* systems, facilitate drug transport by an external electrical field. Electrotransport mechanisms include *iontophoresis, electroosmosis,* or *electroporation.*

Mechanically (physically) *modulated* systems are exemplified by systems employing *phonophoresis* or those using *microneedle arrays* to achieve transdermal drug delivery.

ELECTRICALLY MODULATED DRUG DELIVERY THROUGH THE SKIN[32,33]—For some poorly absorbed (ionic) compounds, parenteral administration appears to be the only viable option for regional or systemic delivery, as chemical penetration enhancers (Table 44-3) often do not function well for these compounds. Given the increased risk of adverse reactions associated with the use of such enhancers, the increased evaluation of iontophoretic devices for the enhancement of topical drug delivery has been of great interest. Iontophoretic drug delivery implies the delivery of ionic drugs into the body by means of an electric current. While the stratum corneum forms the principal barrier to electrical conductivity—due, in part, to its lower water content—the skin also acts as a capacitor. Thus, biological tissues such as the skin provide for a reactive electrical circuit. Ionic transport through the skin in the presence of a uniform electric field can be described, in part, in accordance

with the Nernst-Planck equation

$$J_i = -D\frac{dC}{dx} + \frac{DzeEC}{kT}$$

where J_i is the flux of ions across the membrane, C is the concentration of ions with valence z and electron charge e, dC/dx is the concentration gradient, E is the electric field, k is Boltzmann's constant, and T is the absolute temperature. Thus, the ionic flux is the sum of the fluxes that arise from the concentration gradient and the electric field. Given the complexity of the skin's composition, the thickness of the stratum corneum, and the occurrence of electroosmotic effects, the Nernst-Planck equation is only a first approximation of the overall transdermal flux of a solute. Faraday's Law

$$\frac{Q}{t} = \frac{t_j i}{|z|F}$$

further characterizes the iontophoretic flux Q/t in terms of the current i (in amperes) and its duration t (in seconds), the transference number parameter t_j, and the Faraday constant, F. Additional factors that influence the rate and extent of iontophoretic delivery through the skin include pH and ionic strength of the drug solution.

Although iontophoretic techniques have been shown to increase percutaneous absorption of ionizable or ionic drugs (including lidocaine, salicylates, and peptides and proteins such as insulin) markedly, the clinical safety and efficacy of drug-delivery systems employing iontophoretic technology have yet to be evaluated fully.

Problematic aspects of electrotransport include cutaneous irritation or erythema and the effect of the electrical field on the integrity and stability of the formulation. Electrically induced alterations in the formulation generally arise as a result of iontophoresis (due to the increased flux of ions) or electroosmosis (due to the electrically induced convective transport of water molecules and associated electrically neutral solutes).[34,35] The use of pulsed or intermittent current electrotransport systems has been suggested as an alternative to continuous current systems. *Electroporation*—the use of pulsed electrical current to provoke the transient formation of pores in biomembranes—also has been suggested as an alternative, or complement, to iontophoresis. In any event, the potential of electrically modulated drug-delivery systems for the effective transdermal delivery of large, polar or ionic molecules (eg, proteins, peptides, DNA) necessitates continued research in this field. One encouraging advance in this area is the development of flexible wafer-thin arrays of conductive layers or filaments for drug delivery systems that are less bulky and potentially more acceptable to patients.

MECHANICALLY MODULATED DRUG DELIVERY—*Phonophoresis,* or *sonophoresis,* is defined as the movement of drug molecules through the skin under the influence of ultrasound. In general, ultrasound frequencies of 1–3 MHz and intensities of 0.01–2 W/cm^2 have been used with varying degrees of effectiveness,[36] although high-frequency, low-intensity ultrasound has been observed to increase transdermal drug flux and decrease percutaneous diffusional lag times.[37] A more recent analysis of ultrasound-enhanced transdermal transport indicates that low-frequency sonophoresis is much more important than high-frequency sonophoresis in enhancing transport.[38] Various thermal and nonthermal changes have been implicated to explain phonophoretically induced increases in drug transport through the skin. Although the effect of temperature increases on molecular diffusivity and flux is clear, nonthermal effects of ultrasound (eg, cavitation) are less clear. Transient ultrasound-induced cavitation (ie, the generation and oscillation of gas bubbles) in the stratum corneum apparently perturbs barrier permeability and solute transport in the aqueous regions of the stratum corneum. Evidence for this is the lack of correlation between phonophoretic permeability and permeant lipophilicity.

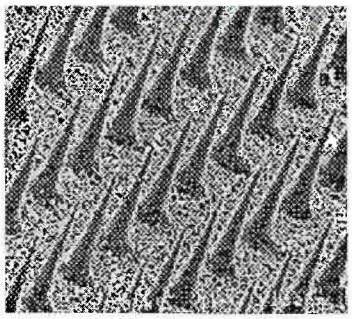

Figure 44-10. Electron micrograph of a microneedle array for transdermal drug delivery (courtesy, Georgia Institute of Technology; ©Georgia Tech Res Corp.).

Silicon microneedle arrays[39] have been proposed recently as painless adjuncts to transdermal delivery systems. The 150-μm long needles (Fig 44-10) can penetrate the stratum corneum, thereby facilitating drug access to the living epidermis and dermis and ultimately to systemic circulation. The needles—prepared by reactive ion etching microfabrication techniques originally developed for integrated circuits—leave holes about 1 μm in diameter when removed from the skin.

SUPPOSITORIES

Suppositories are solid dosage forms of various weights and shapes, usually medicated, for insertion into the rectum, vagina, or urethra. After insertion, suppositories soften, melt, disperse, or dissolve in the cavity fluids.

The use of suppositories dates from the distant past, this dosage form being referred to in writings of the early Egyptians, Greeks, and Romans. Suppositories are suited particularly for administration of drugs to the very young and the very old, a notion first recorded by Hippocrates.

Types

RECTAL SUPPOSITORIES—The USP describes rectal suppositories for adults as tapered at one or both ends and usually weighing about 2 g each. Infant rectal suppositories usually weigh about one-half that of adult suppositories. Drugs having systemic effects, such as sedatives, tranquilizers, and analgesics, are administered by rectal suppository; however, the largest single-use category is probably that of hemorrhoid remedies dispensed over the counter. The 2-g weight for adult rectal suppositories is based on use of cocoa butter as the base; when other bases are used the weights may be greater or less than 2 g.

VAGINAL SUPPOSITORIES—The USP describes vaginal suppositories, or pessaries, as usually globular or oviform and weighing about 5 g each. Vaginal medications are available in a variety of physical forms (eg, creams, gels, or liquids), which depart from the classical concept of suppositories. Vaginal tablets, or inserts prepared by encapsulation in soft gelatin, however, do meet the definition and represent convenience both of administration and manufacture.

URETHRAL SUPPOSITORIES—Urethral suppositories, or bougies, are not described specifically in the USP, either by weight or dimension. Traditional values, based on the use of cocoa butter as a base, are as follows for these cylindrical dosage forms: diameter: 5 mm; length: 50 mm female, 125 mm male; weight: 2 g female, 4 g male. An intraurethral insert containing the prostaglandin alprostadil is available for the treatment of erectile dysfunction. The commercial formulation, described as a sterile micropellet (1.4 mm in diameter and 6 mm long) consisting of the drug and polyethylene glycol 1450 is inserted 3 cm deep into the urethra by use of a hollow applicator.

SUPPOSITORY VEHICLE—The ideal suppository base should meet the following general specifications:

- The base is nontoxic and nonirritating to mucous membranes.
- The base is compatible with a variety of drugs.
- The base melts or dissolves in rectal fluids.
- The base should be stable on storage; it should not bind or otherwise interfere with release or absorption of drug substances.

Rectal suppository bases can be classified broadly into two types: fatty and water-soluble or water-miscible. The traditional cocoa butter vehicle is immiscible with aqueous tissue fluids but melts at body temperature. Water-soluble or water-miscible vehicles also have been used. In general, formulators have been reluctant to use glycerinated gelatin as a rectal suppository base because of its relatively slow dissolution. More typical of this class is the polyethylene glycol vehicle. Drug absorption from such dissimilar bases can differ substantially. Lowenthal and Borzelleca[40] investigated the absorption of salicylic acid and sodium salicylate administered to dogs. The drugs were formulated in a cocoa butter base and in a base composed of polyethylene glycol, synthetic glycerides, and a surfactant. Absorption of salicylic acid and sodium salicylate was about equal from the cocoa butter base; however, salicylic acid gave higher plasma levels than sodium salicylate when the glycol base was used.

SUPPOSITORY BASES

The USP lists the following as usual suppository bases: cocoa butter, cocoa butter substitutes (primarily, vegetable oils modified by esterification, hydrogenation, and/or fractionation), glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights, and fatty acid esters of polyethylene glycol.

COCOA BUTTER AND OTHER FATTY BASES—Theobroma oil, or cocoa butter, is a naturally occurring triglyceride. About 40% of the fatty acid content is unsaturated. As a natural material there is considerable batch-to-batch variability. A major characteristic of theobroma oil is its polymorphism (ie, its ability to exist in more than one crystal form). While cocoa butter melts quickly at body temperature, it is immiscible with body fluids; this may inhibit the diffusion of fat-soluble drugs to the affected sites. Oleaginous vehicles, such as cocoa butter, seldom are used in vaginal preparations for esthetic reasons: many women consider them messy and prone to leakage.

If, in the preparation of suppositories, the theobroma oil is overheated, ie, heated to about 60°C, molded, and chilled, the suppositories formed will melt below 30°C. The fusion treatment of theobroma oil requires maximum temperatures of 40 to 50°C to avoid a change in crystal form and melting point. Theobroma oil, heated to about 60°C and cooled rapidly, will crystallize in an alpha configuration characterized by a melting point below 30°C. The alpha form is metastable and will slowly revert to the beta form, with the characteristic melting point approaching 35°C. The transition from alpha to beta is slow, taking several days. The use of low heat and slow cooling allows direct crystallization of the more stable beta crystal form.

Certain drugs will depress the melting point of theobroma oil. This involves no polymorphic change, although the net effect is similar. Chloral hydrate is the most important of these substances because its rectal hypnotic dose of 0.5 to 1.0 g will cause a substantial melting-point depression. This effect can be countered by addition of a higher-melting wax, such as white wax or synthetic spermaceti. The amount to be added must be determined by temperature measurements. The effect of such additives on bioavailability also must be considered.

Various cocoa butter substitutes (hard fat, hydrogenated vegetable oil) are available commercially that offer a number of advantages over cocoa butter such as decreased potential for rancidity and phase transition (melting and solidification) behavior tailored to specific formulation, processing, and storage requirements. However, as with cocoa butter, these semisynthetic glyceride mixtures are also subject to polymorphic transformations. Batch-to-batch variations of the physical properties of all of these bases, whether cocoa butter or cocoa butter substitutes, can play havoc with the final products' characteristics. The formulator should ensure that the melting and congealing behavior of these bases and the formulations prepared from them is evaluated thoroughly.

WATER-SOLUBLE OR DISPERSIBLE SUPPOSITORY BASES—Water-miscible suppository bases are of comparatively recent origin. The majority are composed of polyethylene glycols or glycol-surfactant combinations. Water-miscible suppository bases have the substantial advantage of lack of dependence on a melting point approximating body temperature. Problems of handling, storage, and shipping are simplified considerably.

Polymers of ethylene glycol are available as polyethylene glycol polymers (Carbowax, polyglycols) of assorted molecular weights. Suppositories of varying melting points and solubility characteristics can be prepared by blending polyethylene glycols of 1000, 4000, or 6000 molecular weight.

Polyethylene glycol suppositories, while prepared rather easily by molding, cannot be prepared satisfactorily by hand-rolling. The drug-glycol mixture is prepared by melting and then is cooled to just above the melting point before pouring into dry unlubricated molds. Cooling to near the melting point prevents fissuring caused by crystallization and contraction. The USP advises that labels on polyethylene glycol suppositories should instruct patients to moisten the suppository before inserting it.

Water-miscible or water-dispersible suppositories also can be prepared using selected nonionic surfactant materials. Polyoxyl 40 stearate is a white, water-soluble solid melting slightly above body temperature. A polyoxyethylene derivative of sorbitan monostearate is water-insoluble but dispersible. In using surfactant materials, the possibility of drug-base interactions must be borne in mind. Interactions caused by macromolecular adsorption may have a significant effect on bioavailability.

PEG-based water-miscible suppository bases, devised by Collins, Hohmann, and Zopf,[41] are exemplified by a low-melting formulation employing 96% PEG 1000 and 4% PEG 4000 and a more heat-stable formulation with 75% PEG 1000 and 25% PEG 4000. Both may be prepared conveniently by molding techniques.

Water-dispersible bases may include polyoxyethylene sorbitan fatty acid esters. These are either soluble (Tween, Myrj) or water-dispersible (Arlacel), used alone or in combination with other wax or fatty materials. Surfactants in suppositories should be used only with recognition of reports that such materials may either increase or decrease drug absorption.

HYDROGELS—In recent years, hydrogels, defined as macromolecular networks that swell but do not dissolve in water, have been advocated as bases for rectal and vaginal drug delivery. The swelling of hydrogels (ie, the absorption of water) is a consequence of the presence of hydrophilic functional groups attached to the polymeric network. Cross-links between adjacent macromolecules result in the aqueous insolubility of these hydrogels.

The use of a hydrogel matrix for drug delivery involves the dispersal of the drug in the matrix, followed by drying of the system and concomitant immobilization of the drug. When the hydrogel delivery system is placed in an aqueous environment (eg, the rectum or the vagina), the hydrogel swells, enabling the drug to diffuse out of the macromolecular network. The rate and extent of drug release from these hydrogel matrices depend on the rate of water migration *into* the matrix and the rate of drug diffusion *out of* the swollen matrix.

Hydrogels employed for rectal or vaginal drug administration have been prepared from polymers such as polyvinyl alcohol, hydroxyethyl methacrylate, polyacrylic acid, or polyoxyethylene. Although hydrogel-based drug-delivery systems have yet to appear in suppository or insert form commercially,

research efforts in this direction are increasing, given their potential for controlled drug delivery, bioadhesion, retention at the site of administration, and biocompatibility.

GLYCERINATED GELATIN—Glycerinated gelatin usually is used as a vehicle for vaginal suppositories. For rectal use a firmer suppository can be obtained by increasing the gelatin content. Glycerinated gelatin suppositories are prepared by dissolving or dispersing the drug substance in enough water to equal 10% of the final suppository weight. Glycerin (70%) then is added and Pharmagel A or B (20%), depending on the drug compatibility requirements. Pharmagel A is acid in reaction, Pharmagel B is alkaline. Glycerinated gelatin suppositories must be formed by molding. The mass cannot be processed by hand-rolling. These suppositories, if not for immediate use, should contain a preservative such as methylparaben and propylparaben.

PREPARATION

Suppositories are prepared by rolling (hand-shaping), molding (fusion), and cold compression.

ROLLED (HAND-SHAPED) SUPPOSITORIES—Hand-shaping suppositories is the oldest and the simplest method of preparing this dosage form. The manipulation requires considerable skill, yet avoids the complications of heat and mold preparation.

The general process can be described as follows:

Take the prescribed quantity of the medicinal substances and a sufficient quantity of grated theobroma oil. In a mortar reduce the medicating ingredients to a fine powder or, if composed of extracts, soften with diluted alcohol and rub until a smooth paste is formed. The correct amount of grated theobroma oil then is added, and a mass resembling a pill mass is made by thoroughly incorporating the ingredients with a pestle, sometimes with the aid of a small amount of wool fat. When the mass has become plastic under the vigorous kneading of the pestle, it quickly is loosened from the mortar with a spatula, pressed into a roughly shaped mass in the center of the mortar, and then transferred with the spatula to a piece of filter paper that is kept between the mass and the hands during the kneading and rolling procedure. By quick, rotary movements of the hands, the mass is rolled to a ball, which immediately is placed on a pill tile. A suppository cylinder is formed by rolling the mass on the tile with a flat board, partially aided by the palm of the other hand, if weather conditions permit. The suppository *pipe* frequently will show a tendency to crack in the center, developing a hollow core. This occurs when the mass has not been kneaded and softened sufficiently, with the result that the pressure of the roller board is not carried uniformly throughout the mass but is exerted primarily on the surface. The length of the cylinder usually corresponds to about four spaces on the pill tile for each suppository, thus making the piece, when cut, practically a finished suppository except for the shaping of the point. When the cylinder has been cut into the proper number of pieces with a spatula, the conical shape is given it by rolling one end on the tile with a spatula, or in some cases even by shaping it with the fingers to produce a rounded point.

COMPRESSION-MOLDED (FUSED) SUPPOSITORIES—This method of suppository preparation also avoids heat. The suppository mass, such as a mixture of grated theobroma oil and drug, is forced into a mold under pressure, using a wheel-operated press. The mass is forced into mold openings, pressure is released, and the mold removed, opened, and replaced. On a large scale, cold-compression machines are hydraulically operated, water-jacketed for cooling, and screw-fed. Pressure is applied via a piston to compress the mass into mold openings.

FUSION OR MELT MOLDING—In this method the drug is dispersed or dissolved in the melted suppository base. The mixture then is poured into a suppository mold, allowed to cool, and the finished suppositories removed by opening the mold. Using this procedure, one to hundreds of suppositories can be made at one time.

Suppository molds are available for the preparation of various types and sizes of suppositories. Molds are made of aluminum alloy, brass, or plastic and are available with from six to several hundred cavities.

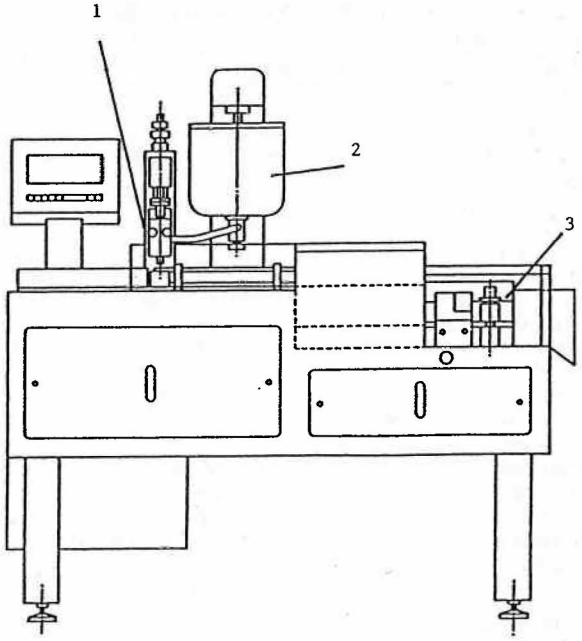

Figure 44-11. A cross-section of the Sarong SpA semiautomatic equipment for the production of suppositories in preformed plastic or foil shells. The fully jacketed piston-type *dosing pump* (1) meters the suppository melt in the jacketed tank (2) into preformed shells that pass directly beneath injection nozzles. The strips of filled preformed shells continue into a cooling chamber (3) prior to sealing and cartoning.

The method of choice for commercial suppository production (Fig 44-11) involves the automated filling of molds or preformed shells by a volumetric dosing pump that meters the melt from a jacketed kettle or mixing tank directly into the molds or shells. Strips of preformed shells pass beneath the dosing pump and are filled successively, passed through cooling chambers (to promote solidification), sealed, and then packaged. Quality control procedures (eg, weight, fill volume, leakage) are conducted readily *online*.

An alternative to the melt-and-pour processes described above is that of injection molding, which has been described by Snipes.[42] This process is distinctive in that it makes use of the injection-molding technique developed for the fabrication of plastics. Polyethylene glycols are the excipients of choice in this process, with polyethylene oxide, povidone, or silicon dioxide added to adjust viscosity or plasticity. Long-chain saturated carboxylic acids also have been added to reduce the hygroscopicity inherent with the use of the polyethylene glycols. Typically, the molten excipient admixture is extruded or injected under pressure into precision-machined multicavity molds, followed by the ejection of the molded units from the mold cavities. Advantages claimed for this method include the wide range of shapes and sizes that can be prepared at very high production rates with great precision.

Suppositories usually are formulated on a weight basis so that the medication replaces a portion of the vehicle as a function of specific gravity. If the medicinal substance has a density approximately the same as theobroma oil, it will replace an equal weight of oil. If the medication is heavier, it will replace a proportionally smaller amount of theobroma oil.

For instance, tannic acid has a density of 1.6 compared with cocoa butter (see Table 44-5).[43,44] If a suppository is to contain 0.1 g tannic acid, then 0.1 g ÷ 1.6, or 0.062 g, cocoa butter should be replaced by 0.1 g of drug. If the blank weight of the suppository is 2.0 g, then 2.0 - 0.062 g, or 1.938 g, cocoa butter is required per suppository. The suppository will actually weigh 1.938 g + 0.1 g, or 2.038 g. Table 44-5 indicates the density fac-

Table 44-5. Density Factors for Cocoa Butter Suppositories

MEDICATION	FACTOR	MEDICATION	FACTOR
Alum	1.7	Menthol	0.7
Aminophylline	1.1	Morphine HCl	1.6
Aminopyrine	1.3	Opium	1.4
Aspirin	1.3	Paraffin	1.0
Barbital	1.2	Peruvian balsam[a]	1.1
Belladonna extract	1.3	Phenobarbital	1.2
Benzoic acid	1.5	Phenol[a]	0.9
Bismuth carbonate	4.5	Potassium bromide	2.2
Bismuth salicylate	4.5	Potassium iodide	4.5
Bismuth subgallate	2.7	Procaine	1.2
Bismuth subnitrate	6.0	Quinine HCl	1.2
Boric acid	1.5	Resorcinol	1.4
Castor oil	1.0	Salicylic acid	1.3
Chloral hydrate	1.3	Sodium bromide	2.3
Cocaine HCl	1.3	Spermaceti	1.0
Digitalis leaf	1.6	Sulfathiazole	1.6
Gallic acid	2.0	Tannic acid	1.6
Glycerin	1.6	White wax	1.0
Ichthammol	1.1	Witch hazel fluidextract	1.1
Iodoform	4.0	Zinc oxide	4.0
		Zinc sulfate	2.8

[a] Density adjusted taking into account white wax in mass.
Data from Davis H. *Bentley's Text-Book of Pharmaceutics,* 7th ed. London: Bailliere, Tindall & Cox, 1961 and Buchi J. *Pharma Acta Helv* 1940;20:403.

tor, or the density compared with cocoa butter, of many substances used in suppositories.

It always is possible to determine the density of a medicinal substance relative to cocoa butter, if the density factor is not available, by mixing the amount of drug for one or more suppositories with a small quantity of cocoa butter, pouring the mixture into a suppository mold and carefully filling the mold with additional melted cocoa butter. The cooled suppositories are weighed, providing data from which a working formula can be calculated as well as the density factor itself.

When using suppository bases other than cocoa butter, such as a polyethylene glycol base, it is necessary to know either the density of the drug relative to the new base or the densities of both the drug and the new base relative to cocoa butter. The density factor for a base other than cocoa butter is simply the ratio of the blank weights of the base and cocoa butter.

For instance, if a suppository is to contain 0.1 g tannic acid in a polyethylene glycol base, then 0.1 g ÷ 1.6 x 1.25, or 0.078 g, polyethylene glycol base should be replaced by 0.1 g drug (the polyethylene glycol base is assumed to have a density factor of 1.25). If the blank weight is 1.75 g for the polyethylene glycol base, then 1.75 g - 0.078 g, or 1.672 g, of base is required per suppository. The final weight will be 1.672 g base + 0.1 g drug, or 1.772 g.

When the dosage and mold calibration are complete the drug-base mass should be prepared using minimum heat. A water bath or water jacket usually is used. The melted mass should be stirred constantly but slowly to avoid air entrapment. The mass should be poured into the mold openings slowly. Prelubrication of the mold will depend on the vehicle. Mineral oil is a good lubricant for cocoa butter suppositories. Molds should be dry for polyethylene glycol suppositories.

After pouring into tightly clamped molds the suppositories and mold are allowed to cool thoroughly using refrigeration on a small scale or refrigerated air on a larger scale. After thorough chilling any excess suppository mass should be removed from the mold by scraping, the mold opened, and the suppositories removed. It is important to allow cooling time adequate for suppository contraction. This aids in removal and minimizes splitting of the finished suppository.

PACKAGING AND STORAGE—Suppositories often are packaged in partitioned boxes that hold the suppositories upright. Glycerin and glycerinated gelatin suppositories often are packaged in tightly closed screwcapped glass containers. Though many commercial suppositories are wrapped individually in aluminum foil or PVC-polyethylene, strip-packaging is commonplace.

Alternatively, suppositories may be molded directly into their primary packaging. In this operation the form into which the suppository mass flows consists of a series of individual molds formed from plastic or foil. After the suppository is poured and cooled, the excess is trimmed off, and the units are sealed and cut into 3s or 6s as desired. Cooling and final cartoning then can be carried out.

Suppositories with low-melting ingredients are best stored in a cool place. Theobroma oil suppositories, in particular, should be refrigerated.

OTHER MEDICATED APPLICATIONS

Poultices (Cataplasms)

Poultices, or cataplasms, represent one of the most ancient classes of pharmaceutical preparations. A poultice is a soft, moist mass of meal, herbs, seed, etc, usually applied hot in cloth. The consistency is gruel-like, which is probably the origin of the word poultice.

Cataplasms were intended to localize infectious material in the body or to act as counterirritants. The materials tended to be absorptive, which together with heat accounts for their popular use. None is now official in the USP. The last official product was Kaolin Poultice NF IX.

Pastes

The USP defines pastes as semisolid dosage forms that contain one or more drug substances intended for topical application. Pastes are divided into fatty pastes (eg, Zinc Oxide Paste) and those made from a single-phase aqueous gel (eg, Carboxymethylcellulose Sodium Paste). Another official paste is Triamcinolone Acetonide Dental Paste.

The term *paste* is applied to ointments in which large amounts of solids have been incorporated (eg, Zinc Oxide Paste). In the past, pastes have been defined as concentrates of absorptive powders dispersed (usually) in petrolatum or hydrophilic petrolatum. These fatty pastes are stiff to the point of dryness and are reasonably absorptive considering they have a petrolatum base. Pastes often are used in the treatment of oozing lesions, where they act to absorb serous secretions. Pastes also are used to limit the area of treatment by acting both as an absorbent and a physical dam.

Pastes adhere reasonably well to the skin and are poorly occlusive. For this reason, they are suited for application on and around moist lesions. The heavy consistency of pastes imparts a degree of protection and may, in some instances, make the use of bandages unnecessary. Pastes are less macerating than ointments.

Because of their physical properties pastes may be removed from the skin by the use of mineral oil or a vegetable oil. This is particularly necessary when the underlying or surrounding skin is traumatized easily.

Powders

Powders for external use usually are described as dusting powders. Such powders should have a particle size of not more than 150 μm (ie, less than 100-mesh) to avoid any sensation of grittiness, which could irritate traumatized skin. Dusting powders usually contain starch, talc, and zinc stearate. Absorbable Dusting Powder USP is composed of starch treated with epichlorohydrin, with not more than 2.0% magnesium oxide added to maintain the modified starch in impalpable powder form; as it is intended for use as a lubricant for surgical gloves it should be sterilized (by autoclaving) and packaged in sealed paper packets.

The fineness of powders often is expressed in terms of mesh size, with impalpable powders generally in the range of 100- to 200-mesh (149 to 75 μm). Determination of size by mesh analysis becomes increasingly difficult as particle size decreases below 200-mesh.

Dressings

Dressings are external applications resembling ointments, usually used as a covering or protection. Petrolatum Gauze is a sterile dressing prepared by adding sterile, molten, white petrolatum to precut sterile gauze in a ratio of 60 g of petrolatum to 20 g of gauze. Topical antibacterials are available in the form of dressings.

Creams

Creams are viscous liquid or semisolid emulsions of either the O/W or W/O type. Pharmaceutical creams are classified as water-removable bases in the USP and are described under *Ointments*. In addition to ointment bases, creams include a variety of cosmetic-type preparations. Creams of the O/W type include shaving creams, hand creams, and foundation creams; W/O creams include cold creams and emollient creams.

Plasters

Plasters are substances intended for external application, made of such materials and of such consistency as to adhere to the skin and attach to a dressing. Plasters are intended to afford protection and support and/or to furnish an occlusive and macerating action and to bring medication into close contact with the skin. Medicated plasters, long used for local or regional drug delivery, are the prototypical transdermal delivery system.

Plasters usually adhere to the skin by means of an adhesive material. The adhesive must bond to the plastic backing and to the skin (or dressing) with proper balance of cohesive strengths. Such a proper balance provides for removal (ie, adhesive breakage at the surface of application) thus leaving a clean (skin) surface when the plaster is removed.

Contraceptives

In the context of this chapter, contraceptives are considered in the form of creams, jellies, or aerosol foams intended for vaginal use to protect against pregnancy. Contraceptive creams and jellies are designed to melt or spread, following insertion, over the vaginal surfaces. These agents act to immobilize spermatozoa.

Creams and jellies for contraceptive use may contain spermicidal agents such as nonoxynol 9, or they may function by a specific pH effect. A pH of 3.5 or less has an appreciable spermicidal effect. It is important to note that a final *in situ* pH of 3.5 or less is required; thus, the dilution effect and pH change brought about by vaginal fluids must be considered. To achieve the proper pH effect and control, buffer systems composed of acid and acid salts such as lactates, acetates, and citrates are used frequently.

Preservatives in Topical Formulations

Antimicrobial preservative substances are included in ointment formulations to maintain the potency and integrity of product forms and to protect the health and safety of the consumer. The USP addresses this subject in its monograph *Microbiological Attributes of Non-Sterile Pharmaceutical Products*. The significance of microorganisms in nonsterile products should be evaluated in terms of the use of the product, the nature of the product, and the potential hazard to the user. The USP suggests that products applied topically should be tested for the presence of *P aeruginosa* and *S aureus*. In addition, products intended for rectal, urethral, or vaginal administration should be tested for yeasts and molds.

The attributes of an ideal preservative system have been defined by various authors as

- Effective at relatively low concentrations against a broad spectrum or variety of microorganisms that could cause disease or product deterioration
- Soluble in the required concentration
- Nontoxic and nonsensitizing at in-use concentrations
- Compatible with ingredients of the formulation and package components
- Free from objectionable odors and colors
- Stable over a wide range of conditions
- Inexpensive

No preservative or preservative system meets these ideal criteria. In fact, preservative substances once considered most acceptable, if not ideal, now have been questioned. Methylparaben and propylparaben, second and third only to water in frequency of use in cosmetic formulations, have been associated with allergic reactions.

Use of parabens as preservatives in topical products began more than a half-century ago. Animal testing indicated that they virtually are nontoxic and the compounds, usually in combination, became nearly ubiquitous as preservatives in dermatologic and cosmetic products. In spite of concerns about contact sensitization, topical parabens do not appear to constitute a significant hazard to the public based on their low index of sensitization and low overall toxicity.

Alternative preservation substances available for use in topical formulations, together with comments on possible limitations, are given in Table 44-6.[45] It is probably sensible to

Table 44-6. Topical Preservatives: Benefits and Risks

PRESERVATIVES	LIMITATIONS RELATIVE TO USE IN COSMETIC/DERMATOLOGIC FORMULATIONS
Quaternary ammonium compounds	Inactivated by numerous ingredients including anionics, nonionics, and proteins
Organic mercurial compounds	Potentially toxic; many sensitize the skin Limited use in formulations used near or in the eye
Formaldehyde	Volatile compound with an objectionable odor Irritating to the skin High chemical reactivity
Halogenated phenols[a]	Objectionable odor Often inactivated by nonionics, anionics or proteins Limited gram-negative antibacterial activity
Sorbic acid, potassium sorbate	pH-dependent (can be used only in formulations below the pH of 6.5 to 7.0) Higher concentrations are oxidized by sunlight resulting in product discoloration Limited antibacterial activity
Benzoic acid, sodium benzoate	pH-dependent (limited to use in formulations with pH of 5.5 or less) Replaced by newer antimicrobials because of its limited antimicrobial activity

[a]eg, hexachlorophene, *p*-chloro-*m*-cresol (PCMC), *p*-chloro-*m*-xylenol (PCMX), dichloro-*m*-xylenol (DCMX).

note that with few exceptions, most of these compounds—in contrast to the parabens—do not have a half-century history of use nor have had extensive patch-testing experiments carried out.

Following selection of preservative candidates and preparation of product prototypes, the efficacy of the preservative system must be evaluated. A variety of methods to accomplish this have been proposed. The organism challenge procedure is currently the most acceptable. In this procedure, the test-product formulation is inoculated with specific levels and types of microorganisms. Preservative efficacy is evaluated on the basis of the number of organisms killed or whose growth is inhibited as determined during a specific sampling schedule. Critical to the organism challenge procedure are the selection of challenge microorganisms, the level of organisms in the inoculum, the sampling schedule, and data interpretation.

In addition to efficacy in terms of antimicrobial effects, the preservative system must be assessed in terms of chemical and physical stability as a function of time. This often is done using antimicrobial measurements in addition to chemical analysis.

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