demanding conditions are met, transdermal therapy offers an excellent means of sustaining the action of a drug. Transdermal delivery also skirts frequently encountered oral delivery problems, such as first-pass metabolic inactivation and gastrointestinal upset. Transdermal therapy is actually an old medical strategy, as compresses and poultices have been used for centuries, although never with certainty of effect. The current, effective use of small adhesive patches to treat systemic disease or its symptoms has revolutionized the practice.

A. Therapeutic Stratification of the Skin

How does a person best organize his or her thinking relative to these different rationales? One can start by asking what the topical drug is supposed to do. Is it to be applied to suppress inflammation?—eradicate infectious microorganisms?—provide protection from the sun?—stop glandular secretions?—provide extended relief from visceral pain? Regardless of which feat the drug is to perform, the answer to the question directs us to where and sometimes how the drug must act to be effective or to a *target* for the drug. Once knowing the locus of action, one can then consider its accessibility. Clearly, if the drug cannot adequately access its target, little or no therapeutic benefit will be realized.

Sundry drug targets exist on, within, or beneath the skin. These include (a) the skin surface itself (external target), (b) the stratum corneum, (c) any one of several levels of the live epidermis, (d) the avascular, upper dermis, (e) any one of several deeper regions of the dermis, (f) one or another of the anatomically distinct domains of the pilosebaceous glands, (g) eccrine glands, (h) apocrine glands, (i) the local vasculature, and, following systemic absorption, (j) any of numerous internal tissues. As these targets become increasingly remote, delivery to them becomes sparser as the result distributional dilution and, consequently, adequacy of delivery becomes less certain. Moreover, the specific properties of these targets and their negotiability are very much determined by the state of health of the skin. Disease and damage alter the barrier characteristics of the skin and, therefore, target accessibility itself.

Causes of skin damage or eruptions are diverse and may alternatively be traced to mechanical damage, irritant or allergic reactions, an underlying pathophysiological condition, or an infection. Depending on the problem, the entire skin, or only a small part of it, may be involved. Moreover, disease may be manifest in one part of a tissue as a consequence of a biochemical abnormality in another. For instance, the cardinal expression of psoriasis is its thickened, silvery, malformed stratum corneum (psoriatic scale), but the disease actually results from maverick proliferation of keratinocytes in the germinal layer of the epidermis. Mankind suffers many skin problems, such as this, each unique in expression to the well-trained eye. The names of some common afflictions are listed in Table 6, with indication of the tissue source of the problems. Table 7 adds to the lexicon pathophysiological terms used to describe the expressions of disease. Irrespective of their fundamental tissue origins, most diseases fan out and involve other tissue components. Inflammation and skin eruption are common sequelae. The nature and developing pattern of a skin eruption become the determinants of its diagnosis. There are subtleties, and it often takes a dermatologist to make a proper differential diagnosis.

The pharmacist will, from time to time, be called on to examine an eruption or condition and make recommendation for treatment. If, and only if, the condition is unmistakable in origin, delimited in area, and of modest intensity, should the pharmacist recommend an over-the-counter (OTC) remedy for its symptomatic relief. Physicians neither need nor want to see inconsequential cuts, abrasions, or mosquito bites, nor unremarkable cases of chapped skin, sunburn, or poison ivy eruption, and so on. However, if infection is present and at all deep-seated, or if expansive areas of the body are involved, otherwise minor problems can pose a

Table 6 Common Afflictions: Brief Outline of Common Dermatological Disorders and Other Common Skin Problems

Skin problems	Examples
I. General involvements	
A. Physical damage	
1. Blunt instrument	Contusion, bruise
2. Sharp instrument	Cut, nick, animal bite
3. Scraping, rubbing	Abrasion, blister
4. Heat	Burns (1°, 2°, 3°), blister
5. Ultraviolet radiation	Sunburn
6. Insects	Mosquito bite, bee sting, ticks, mites (chiggers), lice, crab lice
B. Chemical damage	
1. Contact dermatitis	Poison ivy, poison oak
2. Contact allergy	Cosmetic dermatitis
3. Solvent extraction	"Dishpan hands"
II. Abnormalities of the epidermis	
A. Stratum corneum	
1. Tardigrade sloughing and thickening	Ichthyosis
2. Hyperdryness	Chapping, windburn
3. Hyperproliferative thickening, abnormal structural organization	Psoriasis
B. Viable epidermis	
1. Cell damage and inflammation	Eczema, general dermatitis
2. Fluid collection	Blister
3. Abnormal cell growth (not division)	Keratosis
4. Thickening of granular layer	Lichen planus
5. Hyperproliferation, incomplete keratinization	Psoriasis
6. Malignancy	Epithelioma
III. Abnormalities of the dermis and dermal–epidermal interface	
A. Melanocyte abnormalities	
1. Hyperfunction	Tanning, chloasma, freckles
2. Hypofunction	Vitiligo
3. Abnormal growth	Mole
4. Malignancy	Melanoma
B. Dermal–epidermal interface	
1. Lifting of the epidermis	Dermatitis hypetiformis
2. Overgrowth of papillary layer	Warts
C. Dermis	
1. Vascular reactions	Urticaria, hives
2. Abnormal growth of fibrinocyte	Scar, keloid
3. Abnormal polymerization	Scleroderma, lupus erythematosus
IV. Abnormalities of the glands (appendages)	
A. Hair follicle	
1. Hyperactivity	Hirsutism
2. Hypoactivity	Alopecia, baldness
B. Sebaceous glands	
1. Hyperactivity	Seborrhea
2. Occlusion	Acne, pimples
C. Eccrine sweat gland	
1. Hyperactivity	Hyperhidrosis
2. Occlusion, inflammation	Miliaria (pricky heat, heat rash)
V. Infectious diseases	
A. Bacterial	Carbuncles (boils)
B. Fungal	Athlete's foot, ringworm
C. Viral	Chickenpox, herpes simplex (cold sores)
D. Protozoal	Topical amebiasis

Source: Refs. 16 and 19.

Table 7 Pathophysiological Terms: Brief Definitions of Select Pathophysiological Terms

Term	Definition
Acne	Inflammatory disease of the sebaceous glands characterized by papules, comedones, pustules, or a combination thereof
Alopecia	Deficiency of hair
Bulla	Large blister or vesicle filled with serous fluid
Chloasma	Cutaneous discoloration occurring in yellow-brown patches and spots
Comedo (pl. comedones)	Plug of dried sebum in the sebaceous duct; blackhead
Dermatitis	Inflammation of the skin
Dermatitis herpetiformis	Dermatitis marked by grouped erythematous, papular, vesicular, pustular, or bullous lesions occurring in varied combinations
Eczema	An inflammatory skin disease with vesiculation, infiltration, watery discharge, and the development of scales and crusts
Hirsutism	Abnormal, heavy hairiness
Ichthyosis	A disease characterized by dryness, roughness, and scaliness of the skin caused by hypertrophy of the stratum corneum
Infiltration	An accumulation in a tissue of a foreign substance
Keloid	Growth of the skin consisting of whitish ridges, nodules, and plates of dense tissue
Keratosis	Any horny growth
Lichen planus	Inflammatory skin disease with wide, flat papules occurring in circumscribed patches
Lupus erythematosus	A superficial inflammation of the skin marked by disklike patches: with raised reddish edges and depressed centers, covered with scales or crusts
Miliaria	An acute inflammation of the sweat glands, characterized by patches of small red papules and vesicles, brought on by excessive sweating
Nodule	Small node that is solid to the touch
Papilla	Small, nipple-shaped elevation
Psoriasis	A skin disease characterized by the formation of scaly red patches, particularly on the extensor surfaces of the body (elbows, knees)
Pustule	Small elevation of the skin filled with pus
Scleroderma	A disease of the skin in which thickened, hard, rigid, and pigmented patches occur with thickening of the dermal connective tissue layer
Seborrhea	A disease of the sebaceous glands marked by excessive discharge
Urticaria	Condition characterized by the appearance of smooth, slightly elevated patches, whiter than the surrounding skin
Vesicle	Small sac containing fluid; a small blister
Vitiligo	A skin disease characterized by the formation of light-colored (pigment-free) patches

serious threat, and physician referral is mandatory. Patients should also be directed to counsel with a physician whenever the origins of a skin problem are in question.

B. Surface Effects

Of the many possible aforementioned dermatological targets, the skin surface is clearly the easiest to access. Surface treatment begins at the fringe of cosmetic practice. Special cosmetics are available to hide unsightly blemishes and birthmarks. These lessen self-consciousness and are psychologically uplifting. Applying a protective layer over the skin is sometimes desirable. For example, zinc oxide pastes are used to create a barrier between an infant and its diaper which adsorbs irritants found in urine, ameliorating diaper rash. These same pastes literally block out the sun and, at the same time, hold in moisture, protecting the ski enthusiast from facial sun and wind burns on the high slopes. Transparent films containing ultraviolet light-absorbing chemicals are also used as sunscreens. Lip balms and like products lay down occlusive (water-impermeable) films over the skin, preventing dehydration of the underlying stratum corneum and, thereby, allaying dry skin and chapping. The actions of calamine lotion and other products of the kind are limited to the skin's surface. The suspended matter in these purportedly binds urushiol, the hapten (allergen) found in poison ivy and oak. However, these may best benefit the patient by drying up secretions, relieving itchiness. In all these instances for which the film itself is therapeutic, bioavailability has little meaning.

Bioavailability does matter with topical antiseptics and antibiotics, even though these also act mainly at the skin's surface. These anti-infectives are meant to stifle the growth of surface microflora; thus, formulations that penetrate into the cracks and fissures of the skin where the microorganisms reside are desirable. The extent to which the surface is sanitized then depends on uptake of the anti-infective by the microbes themselves. Slipshod formulation can result in a drug being entrapped in its film and inactivated. For instance, little to no activity is to be expected when a drug is placed in a vehicle in which it is highly insoluble. Ointment bases that contain salts of neomycin, polymyxin, and bacitracin are suspect here, in that hydrocarbon vehicles are extremely poor solvents for such drugs. Inunction (rubbing in) may release such drugs, but the pharmacist should seek evidence that such formulations are effective before recommending them.

Deodorants are also targeted to the skin surface to keep microbial growth in check. Here they slow or prevent rancidification of the secretions of apocrine glands found in and around the axillae (armpits) and the anogenital regions. Medicated soaps also belong in this family.

C. Stratum Corneum Effects

The stratum corneum is the most easily accessed part of the skin itself, and there are two actions targeted to this tissue: namely, emolliency, the *softening of the horny tissue*, which comes about through remoisturizing it; and keratolysis, the chemical digestion and removal of thickened or scaly horny tissue. Tissue needing such removal is found in calluses, corns, and psoriasis, and as dandruff. Common agents such as salicylic acid and, to a lesser extent, sulfur, cause lysis of the sulfhydral linkages holding the keratin of the horny structure together, leading to its disintegration and sloughing.

It has been mentioned that elasticity of the stratum corneum depends on its formation and on the presence of adequate natural lipids, hygroscopic substances, and moisture [19,20]. Remoisturization (emolliency) can be induced by simply occluding the surface and blocking insensible perspiration. However, it is best accomplished by lotions, creams, or waxy formulations, or combinations thereof (e.g., lip balms) that replenish lost lipid constituents of the stratum corneum. The fatty acids and fatty acid esters these contain partly fill the microscopic

cracks and crevices in the horny layer, sealing it off, stabilizing its bilayer structures, and allowing it to retain moisture. Many emollient products also contain hygroscopic glycols and polyols to replenish and augment natural moisturizing factors of this kind, also assisting the stratum corneum in retaining moisture.

The introduction of moisturizing substances into the stratum corneum is ordinarily a straightforward process. Deposition of keratolytics, on the other hand, is not as easily achieved, as these agents must penetrate into the horny mass itself. Some salicylic acid-containing corn removers, therefore, are made up as concentrated nonaqueous solutions in volatile solvents. As these volatile solvents evaporate, drug is concentrated in the remaining vehicle and, thereby, thermodynamically driven into the tissue. These many examples illustrate that when the therapeutic target is at the skin's surface or is the stratum corneum, the therapeutic rationale behind the treatment usually involves enhancing or repairing or otherwise-modulating barrier functions (see Table 5).

D. Drug Actions on the Skin's Glands

A few products moderate operation of the skin's appendages. These include antiperspirants (as opposed to deodorants), which use the astringency of chemicals such as aluminum chloride to reversibly irritate and close the orifice of eccrine glands [21], impeding the flow of sweat. Astringents also decimate the population of surface microbes, explaining their presence in deodorants. The distinction between antiperspirants and deodorants is legally significant, as antiperspirants alter a body function and are regulated as drugs, whereas deodorants are classified as cosmetics. Thus, measurably reduced sweating has to be scientifically proved before it can be claimed for a product. Nevertheless, given the similarities in the compositions of deodorants and antiperspirants, they are likely functionally equivalent. Since eccrine glands are mediated by cholinergic nerves, sweating also can be shut off by anticholinergic drugs administered systematically [22] or topically. However, such drugs are too toxic for routine use as antiperspirants even when administered topically.

Acne is a common glandular problem arising from hyperproliferative closure of individual glands in the unique set of pilosebaceous glands located in and around the face and across the upper back. Irritation of cells lining the ducts of such glands initiates the formation of a lesions. Sheets of sloughed, sebum-soaked, keratinized cells that grow out from the walls surrounding the sebaceous duct are what clog the duct. Still-forming sebum is then trapped behind the obstruction, oftentimes bulging out the skin and giving rise to an observable lesion (papule). This may become infected and fill with a purulent exudate (pustule) or, after infection has set in, it may internally rupture and thereby begin the processes that lead to ulceration and scarring. Alternatively, the buildup of concentric sheets of sloughed cells may widen the glandular opening, with melanin in the widening plug darkening to the point of being black (blackhead).

Soap and water is considered a therapeutic treatment in acne when it is used to unblock the pores. Sebum is emulsified, and it and other debris is removed. Alcoholic solvents, often packaged as moistened pledgets, are used for the same purpose. With either treatment care must be exercised not to dry out and further irritate the skin. Both local and systemic antibiotics and antiseptics suppress the formation of lesions. It is believed these attenuate the population of anerobic microorganisms that are deep-seated in the gland, the metabolic by-products of which irritate the lining of the gland, setting off lesion formation. Mild cases of acne improve and clear under the influence of astringents, possibly for the same reason. Retinoids, oral and topical, reset the processes of epidermal proliferation and differentiation. Through such dramatic influences on cell growth patterns, they actually prevent the formation of lesions. How-

ever, because of concerns over toxicity, they tend to be used only in the most severe cases of acne and thus are prescribed for those patients whose acne lesions progress to cysts.

Hair is a product of the pilosebaceous apparatus and in this sense is glandular. It often grows out visibly in places where such display is unwanted. It may be shaved, but chemical hair removers (depilatories) along with other products are also used to remove it. In the main, the use of depilatories is cosmetic, rather than therapeutic. However, depilatories may be prescribed in hirsutism, when the existence of coarse, dark facial hair is psychologically distressing to the female patient for whom shaving is an anathema. Hair, like the stratum corneum is composed of layers of dead, keratinized cells. However, its keratin is more susceptible to the action of keratolytics because it is structured in ways that make it more chemically pervious. Thioglycolate-containing, highly alkaline creams generally dissolve hair in short order, without doing great harm to surrounding tissues. Facial skin is delicate, however, and depilatories must be used carefully here.

E. Effects in Deep Tissues

Local, Regional, and Systemic Delivery

When the target of therapy lies beneath the stratum corneum, topical drug delivery is more difficult and becomes more uncertain. Therefore, many potentially useful drugs find no place in topical therapy owing to their inability to adequately penetrate the skin. Nevertheless, a number of pathophysiological states can be controlled through local administration and subsequent percutaneous absorption. For example, most skin conditions are accompanied by inflammation of the skin; topical corticosteroids and nonsteroidal anti-inflammatory drugs alike are used to provide symptomatic relief in such instances. Corticosteroids are also used in psoriasis for which, in addition to suppressing inflammation, they somehow act on the basal epidermal layer to slow proliferation and restore the skin's normal turnover rhythm [23]. Pain originating in the skin can be arrested with locally applied anesthetics. Over-the-counter benzocaine and related prescription drugs are used for this purpose. Hydroquinone is applied to the skin to lighten excessively pigmented skin by oxidizing melanin deep within the surface. Another treatment that involves percutaneous absorption is the application of fluorouracil (5-FU) for the selective eradication of premalignant and basal cell carcinomas of the skin [22]. In all of these examples, the key to success is the ability we have to get therapeutic amounts of the drugs through the stratum corneum and into the viable tissues.

Systemic actions of some drugs can also be achieved by local application, in which case, their delivery is known as transdermal delivery. The application of warmed, soft masses of medicated bread meals and clays over wounds or aching parts of the body dates to antiquity. However, few such plasters and poultices (cataplasms) have survived into modern medicine. When analytical developments just past the middle of the twentieth century made it possible to measure the exceedingly low circulating levels of drugs that build up in the body during the course of therapy, research was begun on ways drugs might be delivered to lower their risks and extend their durations of action. Novel delivery systems involving nontraditional routes of administration were subsequently conceived, constructed, and put to test. Transdermal delivery with adhesive patches evolved as one of the innovations.

The possibilities for transdermal delivery might have been seen long ago in the systemic toxicities of certain topically contacted chemicals. As long as a century ago it was known that munitions workers who handle nitroglycerine suffered severe headaches and ringing in the ears (tinnitus). These same effects are experienced to a degree by those taking nitroglycerin to alleviate angina. The association between therapy and the inadvertent percutaneous absorption of nitroglycerin was finally made in the 1970s and a nitroglycerin ointment was introduced,

producing peak blood levels comparable with those attained on sublingual administration of traditional tablet triturates, but levels that were also sustained. Since the permeability of human skin is highly variable and patient needs themselves vary, patients using nitroglycerin ointments were (and are) instructed to gradually lengthen the ribbon of ointment expressed from the tube and rubbed into the skin until tinnitus and headache are experienced, and then back off on the dosage. The lastingness of the effects of nitroglycerin administered in this fashion freed patients from a fear of wakening in the middle of the night with a heart attack (angina). Consequently, nitroglycerin ointments became the first commercially successful, therapeutically proved transdermal delivery systems. But ointments are greasy and, as with all semisolids, suffer variability in their dosing, even with dose titration, given that different patients apply semisolids more or less thinly and, therefore, over more or less area.

Since about 1980, sophisticated adhesive patches for transdermal delivery of scopolamine (motion sickness), nitroglycerin (anginal symptoms), clonidine (regulation of blood pressure), β-estradiol (menopausal symptoms), and fentanyl (cancer pain) have been introduced into medicine [24–26]. These patches are affixed to an appropriate body location and deliver drug continuously for periods ranging from a day (nitroglycerin) to a week (clonidine). To achieve such long periods of delivery, the patches contain reservoirs of their respective drugs. In one early type of system, nitroglycerin was formulated into a liquid-filled sponge held in direct contact with the skin by an adhesive band around the periphery of the patch. In more recent patch designs a membrane is placed over the delivery surface of the patch. Adhesive covering this membrane anchors the patch to the skin over the entire contact area of the patch. This interfacing membrane can be turned into a *rate-controlling membrane* to regulate delivery and prevent dose dumping, should the patch be inadvertently placed over a site of inordinately high permeability. Actually, this rate-controlling concept was used in the design of the first patch, the scopolamine transdermal system. The development of transdermal patches for yet other drugs is an active research area.

It is obvious from the foregoing that the skin is a formidable barrier, irrespective of whether therapy is to be local, regional, or systemic, and the first concern in topical delivery is sufficiency of delivery. With local therapy, the aim is to get enough drug into the living epidermis or its surroundings to effect a pharmacological action there without producing a systemically significant load of the drug. The latter is actually a rare occurrence, except when massive areas of application are involved. Regional therapy involves effects in musculature and joints deep beneath the site of application. To be successful, this requires a greater delivery rate, because an enormous fraction of the drug that passes through the epidermis is routed systemically by the local vasculature. Indeed, the levels of drug reached in deep local tissues have proved to be only a few multiples higher than those obtained after systemic administration of the drug [27]. Even more drug has to be delivered per unit area to transdermally effectuate a systemic action.

Factors Affecting Functioning of the Skin Barrier

A matter of considerable consequence in topical delivery is variability in skin permeability between patients, which may be as much as tenfold. The underlying sources of this high degree of variability are thought to be many and diverse. Humans differ in age, gender, race, and health, all of which are alleged to influence barrier function. Yet, insofar as can be told, a full-term baby is born with a barrier-competent skin and, barring damage or disease, the skin remains so through life. There is little convincing evidence that senile skin, which tends to be dry, irritable, and poorly vascularized, is actually barrier-compromised [28]. However, premature neonates have inordinately permeable skins. The incubators used to sustain such infants provide a humidified environment—which abates insensible perspiration—and a warm one,

conditions that not only make the baby comfortable, but that also forestall potentially lethal dehydration and hypothermia [29].

Gender, too, affects the appearance of human skin. Nevertheless, there is little evidence that the skins of male and female differ much in permeability. However, there are established differences in the barrier properties of skin across the races of man. Although the horny layers of whites and blacks are of equal thickness, the latter has more cell layers and is measurably denser [30]. As a consequence, black skin tends to be severalfold less permeable [30,31].

Humidity and temperature also affect permeability. It has long been known that skin hydration—however brought about—increases skin permeability. Occlusive wrappings, therefore, are placed over applications on occasion to seal off water loss, hydrate the horny layer, and increase drug penetration. In the absence of such intervention, the state of dryness of the stratum corneum is determined by the prevailing humidity, explaining why the condition "dry skin" is exacerbated in the winter months in northern climates.

Temperature influences skin permeability in both physical and physiological ways. For instance, activation energies for diffusion of small nonelectrolytes across the stratum corneum lie between 8 and 15 kcal/mol [4,32]. Thus thermal activation alone can double the rate of skin permeability when there is 10° change in the surface temperature of the skin [33]. Additionally, blood perfusion through the skin, in terms of amount and closeness of approach to the skin's surface, is regulated by its temperature and also by an individual's need to maintain the body's 37°C isothermal state. Since clearance of percutaneously absorbed drug to the systemic circulation is sensitive to blood flow, a fluctuation in blood flow might be expected to alter the uptake of chemicals. No clear-cut evidence exists that this is so, however, which seems to teach us that even the reduced blood flow of chilled skin is adequate to efficiently clear compounds from the underside of the epidermis.

Above all else, the health of the skin establishes its physical and physiological condition, and, thus, its permeability. Consequences attributable to an unhealthy condition of skin can be subtle or exaggerated. Broken skin represents a high-permeability state, and polar solutes are several log orders more permeable when administered over abrasions and cuts. Irritation and mild trauma tend to increase the skin's permeability, even when the skin is not broken, but such augmentation is far less substantial. Sunburn can be used to illustrate many of the barrier-altering events that occur in traumatized skin. Vasodilation of the papillary vasculature, with marked reddening of the skin, is among the first signs that a solar exposure has been overdone. In its inflamed state, the skin becomes warm to the touch. After 1 or 2 days, epidermal repair begins in earnest, and the tissue is hyperproliferatively rebuilt in its entirety. It doubles in thickness, and a new stratum corneum is quickly laid down [34]. Because the newly formed stratum corneum's anchorage to existing tissues is faulty, the preexisting horny layer often eventually peels. Of more importance, hyperplastic repair leads to a poorly formed horny structure of increased permeability to water (as measured by transepidermal water loss) and presumably other substances. Given these events surrounding irritation, since many chemicals found in the workplace and home are mildly irritating—including the soaps we use to bathe and the detergents we use to clean house and clothes—is it really a wonder that the permeability of human skin is so demonstrably variable?

Some chemicals have prompt, destructive effects on the skin barrier. Saturated aqueous phenol, corrosive acids, and strong alkali instantly denature the stratum corneum and destroy its functionality, even as their corrosive actions stifle the living cells beneath. Although the stratum corneum may appear normal following such damage, the skin may be only marginally less permeable than denuded tissue [35]. Furthermore, permeability remains high during the full duration of wound repair and until a competent stratum corneum is laid down over the injured surface. Other chemicals are deliberately added to formulations to raise the permeability

of skin and improve drug delivery. For obvious reasons, these are referred to as skin penetration enhancers. More will be said of these later.

Thermal burning produces comparably high states of permeability immediately following burning, providing that the surface temperature of the skin is raised above 80°C, a temperature on the lower side of temperatures able to denature keratin [36]. However, burning temperatures below 75°C, although fully capable of deep tissue destruction in seconds, leave the structure of the stratum corneum itself relatively unscathed. Burn wounds of this kind remain impermeable until tissue repair and restructuring processes get under way and the necrotic tissue with its horny capping is sloughed. The differences in permeability state of burned skin immediately following the trauma can be highly consequential in terms of drug delivery. In the instance of deep burns obtained at lower than keratin-denaturing temperatures, topical delivery of antibiotics and antiseptics into a wound, as may be necessary to control wound sepsis, remains difficult for as long as the stratum corneum over the wound stays in place, and aggressive use of antiseptics is warranted. In the other extreme, there is risk of toxic systemic accumulation of the antiseptics and antibiotics, particularly in major burns covering 20% or more of the body surface area. Conservative treatment is warranted. Since burns are rarely well characterized relative to their permeability dimension, attending physicians and pharmacists need to monitor antiseptic usages carefully to control wound sepsis without poisoning the patient. Finally, if not surgically debrided, the necrotic tissue is eventually walled off, enzymatically digested, loosened, and sloughed, producing a denuded, open, granulating surface. Small full-thickness wounds are closed and sealed off quickly by reconstruction of the epidermis from the edges of the wound. Large full-thickness injuries take too long to heal by this process and require grafting. All such wounds remain highly permeable until covered over again with a healthy, fully differentiated epidermis.

As with burns, physical disruption of the stratum corneum opens the skin in proportion to the extent of damage. Cuts and abrasions are associated with high permeability at and around such injuries. Eruption of the skin in disease has a similar effect, at least to the extent that the stratum corneum's integrity is lost. The skin over eczematous lesions should be considered highly permeable. Not all skin diseases raise permeability, however. The states of permeability of ichthyosiform, psoriatic, and lichenified skin have not been well characterized, but in all likelihood are low for most drugs. It has proved difficult to get potent corticosteroids through psoriatic plaque, for instance, and occlusive wrapping is often called for.

Percutaneous Absorption: The Process

The process of percutaneous absorption can be described as follows. When a drug system is applied topically, the drug diffuses passively out of its carrier or vehicle and, depending on where the molecules are placed down, it partitions into either the stratum corneum or the sebum-filled ducts of the pilosebaceous glands. Inward diffusive movement continues from these locations to the viable epidermal and dermal points of entry. In this way, a concentration gradient is established across the skin up to the outer reaches of the skin's microcirculation, where the drug is swept away by the capillary flow and rapidly distributed throughout the body. The volume of the epidermis and dermis beneath a 100-cm^2 area of application, roughly the size of the back of the hand, is approximately 2 cm^3. The total aqueous volume of a 75-kg (≈165-lb) person is about 50,000 cm^3, yielding a systemic-to-local dilution factor well in excess of 10,000. Consequently, systemic drug levels are usually low and inconsequential. Thus, selectively high epidermal concentrations of some drugs can be obtained. However, if massive areas of the body (≥20% of the body surface) are covered with a topical therapeutic, systemic accumulation can be appreciable. For instance, corticosteroids have produced serious systemic toxicities on occasion when they have been applied over large areas of the body [37].

Moreover, as has already been pointed out, if the stratum corneum is not intact, many chemicals can gain systemic entrance at alarming rates. Together these factors may place a patient at grave risk and should always be taken into account when topical drugs are put in use. The pharmacist, therefore, should carefully measure how topicals are to be applied and be on alert for untoward systemic responses when body coverages are unavoidably extensive.

The events governing percutaneous absorption following application of a drug in a thin, vehicle film are illustrated in Fig. 2. The important processes of dissolution and diffusion within the vehicle are cataloged. These will be discussed later. Two principal absorption routes are indicated in the sketch: (a) the transepidermal route, which involves diffusion directly across the stratum corneum; and (b) the transfollicular route, for which diffusion is through the follicular pore. Many words have been written concerning the relative importances of these two pathways. Claims that one or the other of the routes is the sole absorption pathway are ground-

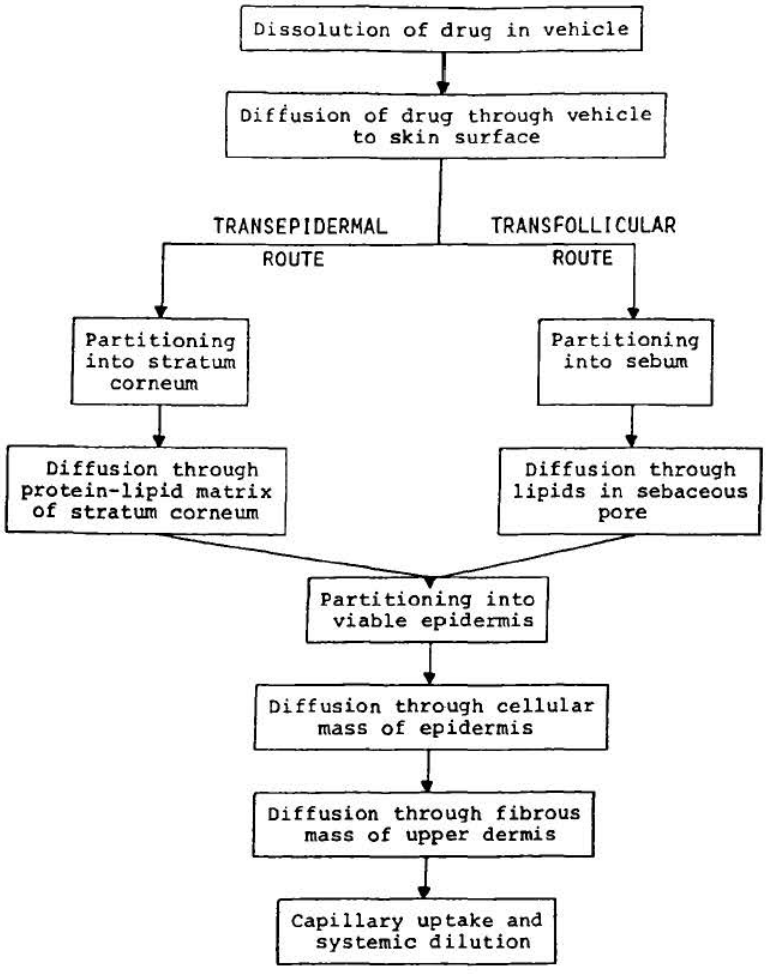

Fig. 2 Events governing percutaneous absorption.

less, since percutaneous absorption is a spontaneous, passive diffusional process that takes the path of least resistance. Therefore, depending on the drug in question and the condition of the skin, either or both routes can be important. There are also temporal dependencies to the relative importances of the routes. Corticosteroids breach the stratum corneum so slowly that clinical responses to them, which are prompt, are reasoned to be due to follicular diffusion [4].

One should not lose sight of the fact that the chemical barrier of the skin actually consists of all skin tissues between the surface and the systemic entry point. Although it is true that the stratum corneum is a source of high diffusional resistance to most compounds and, thus, the skin's foremost barrier layer, exceptional situations exist for which it is not the only or even the major resistance to be encountered. For example, extremely hydrophobic chemicals have as much or more trouble passing across the viable tissues lying immediately beneath the stratum corneum and above the circulatory bed, because such drugs have little capacity to partition into these tissues. Backing for the latter assertion comes from extensive clinical experience, as well as from physical modeling of percutaneous absorption. Consider that ointments can be used safely over open wounds, for their hydrocarbon constituents are not transported significantly across even denuded skin. Similarly, the skin is considerably more impermeable to octanol and higher alkanols than is the stratum corneum alone because of the presence of the viable tissue layer beneath.

Model of the Skin Barrier

The percutaneous absorption picture can be qualitatively clarified by considering Fig. 3, in which the schematic skin cross section is placed side by side with a simple model for percutaneous absorption patterned after an electrical circuit. In absorption across a membrane, the

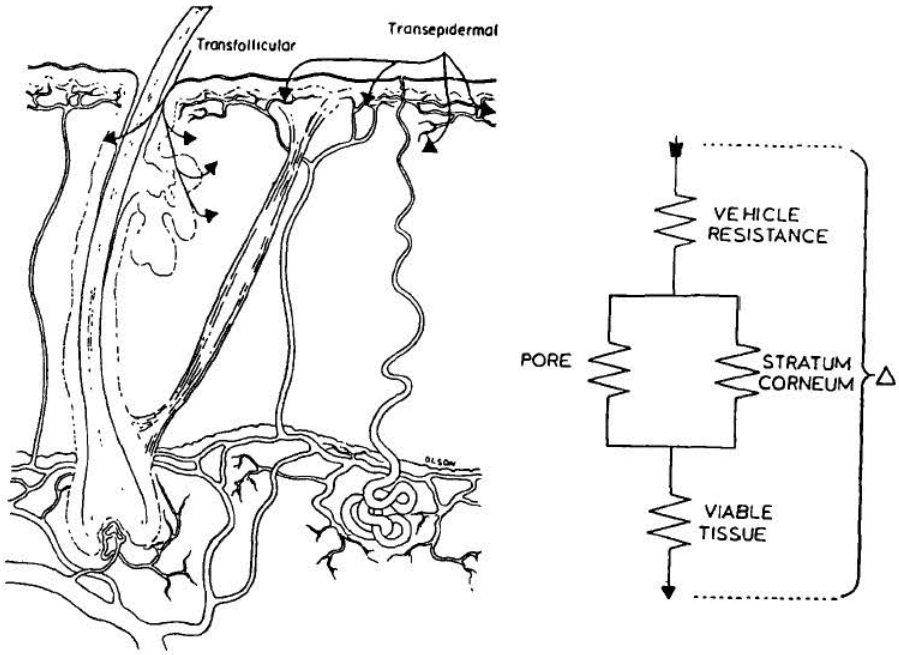

Fig. 3 Skin cross section beside a simple model.

current or flux is in terms of matter or molecules, rather than electrons, and the driving force is a concentration gradient (technically, a chemical potential gradient), rather than a voltage drop. Each layer of a membrane acts as a *diffusional resistor*. The resistance of a layer is proportional to its thickness (symbol = h); inversely proportional to the diffusive mobility of a substance within it, as reflected in a diffusion coefficient (D); inversely proportional to the capacity of the layer to solubilize the substance relative to all other layers, as expressed in a partition coefficient (K); and inversely proportional to the fractional area of the membrane occupied by the diffusion route (f) if there is more than one route in question [38]. In general, an individual resistance in a set may be represented by:

$$R_i = \frac{h_i}{f_i D_i K_i} = \frac{\text{[thickness]}}{\text{[fractional area][diffusion coefficient][partition coefficient]}} \quad (1)$$

The overall phenomenon of percutaneous absorption is describable after recognizing that the resistances of phases in series (phases encountered serially) are additive, and that diffusional currents (fluxes) through routes in parallel (differing routes through a given phase) are additive. Such considerations applied to skin allow one to explain, in semiquantitative terms, why percutaneous absorption through intact skin is slow for most chemicals and drugs, and why disruption of the horny covering of the skin profoundly increases the permeabilities of the ordinary run of solutes.

First, consider the transepidermal route. The fractional area of this route is virtually 1.0, meaning the route constitutes the bulk of the area available for transport. Molecules passing through this route encounter the stratum corneum and then the viable tissues located above the capillary bed. As a practical matter, the total stratum corneum is considered a singular diffusional resistance. Because the histologically definable layers of the viable tissues are also physicochemically indistinct, the set of strata represented by viable epidermis and dermis is handled comparably and treated as a second diffusional resistance in series. The estimated diffusion coefficients in the stratum corneum are up to 10,000 times smaller than found anywhere else in the skin, partly reflecting the considerable denseness of this tissue. Presuming diffusion to be through the intercellular lipid regime within the horny tissue, the estimates, which range from 1×10^{-9} cm^2/sec to a low of 1×10^{-13} cm^2/sec, have to be tempered with the knowledge that path tortuosity and excluded volume were not accounted for when estimating them. Regardless, small values such as this are associated with high resistance and low penetrability [4]. The breadth of the stratum corneum, fixed by nature, is an exceedingly thin 1×10^{-3} cm. The most variable parameter in the stratum corneum resistance equation is the partition coefficient, as this can take a value several log orders less than one when the permeant is a highly polar molecule, such as glucose, or a value several log orders greater than one when a hydrophobic molecule, such as β-estradiol, is involved. The wedge of living tissue between the stratum corneum and the capillaries is roughly 100 μm thick (1×10^{-2} cm). Permeation of this regime is facile and without great molecular selectivity, with diffusion coefficients being about one-tenth the magnitude of those found in a simple liquid such as water [39].

The follicular route can be analyzed similarly. The fractional area available for penetration by this route is on the order of 1/1000 [4], clearly a restricting factor. Here, partitioning is into sebum, and the distance that has to be traveled through the sebaceous medium filling the follicular duct can only be guessed at, but has to be greater than the thickness of the stratum corneum; 50 μm seems a reasonable estimate, the actual value almost certainly being within a factor of 2 of this. Diffusion coefficients in the quasiliquid sebum are from 100-fold to 1000-fold or more greater than in the stratum corneum [4,10]. Because sebum is lipoidal, partition

coefficients for entering this route must also range widely. A thickness of viable tissue, perhaps comparable with that found along the transepidermal route, must also be diffusionally negotiated before drug reaches the microcirculation.

The net chemical penetration of the skin is simply the sum of the accumulations by each of the mentioned routes and by other routes, for instance eccrine glands, where these contribute. The latter tiny glands are ubiquitously distributed over the body, but are generally discounted in importance owing to the limited fractional area they occupy and their unfavorable physiological states, either empty or profusely sweating.

All the salient features described here can be incorporated into a quantitative framework that takes into account stratification within the tissues and the parallel pathways [38]. It is instructive to consider even the simplest such model based on these descriptions and embodying only transepidermal and transfollicular routes. We can assume each distinct tissue acts as a homogeneous phase, a gross distortion of reality, but an assumption that, nevertheless, leads to a useful conceptual description. The resistance by the transepidermal route would be:

$$R_{\text{Transepidermal}} = R_{\text{stratum corneum}} + R_{\text{viable tissues transepidermally}}$$

or

$$R_{TE} = R_{sc} + R_{vt-TE} \tag{2}$$

Similarly, the transfollicular resistance would be

$$R_{TF} = R_{seb} + R_{vt-TF} \tag{3}$$

Since these routes are in parallel, the total resistance on combining them is:

$$R_{total} = \frac{1}{\left(\frac{1}{R_{sc} + R_{vt-TE}}\right) + \left(\frac{1}{R_{seb} + R_{vt-TF}}\right)} \tag{4}$$

The mass transfer coefficient (permeability coefficient; P) of a route is the reciprocal of the resistance of that route and, thus, we can amend Eq. (4) to read:

$$R_{total} = \frac{1}{P_{TE} + P_{TF}} \tag{5}$$

Similarly, the overall permeability coefficient; taking both routes into account, is the reciprocal of the total resistance and thus P_{total} is:

$$P_{total} = P_{TE} + P_{TF} \tag{6}$$

Before proceeding farther, we should add in the fact that water is invariably the medium used to obtain permeability coefficients and, accordingly, water is assumed to be the vehicle under consideration. This choice of vehicle effectively sets the partition coefficients between the aqueous tissues and the vehicle to unity. It is important to realize that the model becomes general, even when based on a water vehicle, when saturated aqueous solutions, which operate at the thermodynamic activity of the solid drug, are brought into the analysis. Substituting fractional areas, thickness, and diffusion coefficients for all the phases, but partition coefficients for only the stratum corneum and sebum, leads to the following expression for the overall permeability coefficient:

$$P_{total} = f_{TE}\left(\frac{D_{sc}K_{sc/w}D_{vt}}{D_{sc}K_{sc/w}h_{vt-TE} + D_{vt}h_{sc}}\right) + f_{TF}\left(\frac{D_{seb}K_{seb/w}D_{vt}}{D_{seb}K_{seb/w}h_{vt-TF} + D_{vt}h_{seb}}\right) \tag{7}$$

Finally, a general expression describing the steady state flux across a membrane, $\partial M/\partial t$, can be written as:

$$\frac{\partial M}{\partial t} = AP_{\text{total}}\,\Delta C \tag{8}$$

This equation teaches us that the total steady-state flux (total rate of permeation across a membrane in the steady state of permeation), $\partial M/\partial t$, is proportional to the involved area (A) and the concentration differential expressed across the membrane, ΔC. In an experiment, flux is the experimentally measured parameter, whereas A and ΔC are fixed in value before starting the experiment. The value of the permeability coefficient, P_{total}, is what is calculated at the end of the experiment using Eq. (8). The permeability coefficient, besides having the other attributes already ascribed to it, can be looked at as merely being the number that is needed to make an equality out of the combined area and concentration proportionalities of flux. It has units of distance/time (cm/hr) and is effectively the average velocity of the molecules penetrating a membrane, irrespective of the complexity of the membrane. Its magnitude depends on the properties of the vehicle, membrane, and permeant. Moreover, when the membrane consists of several phases, the permeability coefficient is also dependent on the juxtaposition of the phases. We can now write for the skin:

$$\frac{\partial M}{\partial t} = A\left\{f_{\text{TE}}\left(\frac{D_{\text{sc}}K_{\text{sc/w}}D_{\text{vt}}}{D_{\text{sc}}K_{\text{sc/w}}h_{\text{vt-TE}} + D_{\text{vt}}h_{\text{sc}}}\right) + f_{\text{TF}}\left(\frac{D_{\text{seb}}K_{\text{seb/w}}D_{\text{vt}}}{D_{\text{seb}}K_{\text{seb/w}}h_{\text{vt-TF}} + D_{\text{vt}}h_{\text{seb}}}\right)\right\}\Delta C \tag{9}$$

In Eq. (9), A is the involved area of the skin and the term ΔC is the permeant's concentration differential across the skin. In clinical situations ΔC is usually well approximated by the actual concentration in the topical vehicle because dilution by way of systemic absorption of the permeant is so great.

Equation (9) defines the steady state flux in terms of physically meaningful parameters. In other words, it is an anatomically based, mathematical representation (model) of the skin barrier. The first collection of terms in the greater parentheses defines the role of the transepidermal route, and the second, the role of the transfollicular pathway. Representative values for some of the parameters of Eq. (7) needed to probe the model are given in Table 8. The listed fractional areas, diffusivities, and strata thicknesses are based on the best information available. They are approximate at best, some being only guesses. Regardless, the impression generated when they are substituted in the conceptual model is consistent with what is known about percutaneous absorption. For instance, if the higher values of the diffusion coefficients found in Table 8, that is, 10^{-9} cm^2/sec for the stratum corneum, 10^{-7} cm^2/sec for sebum, and 10^{-6} cm^2/sec for the viable tissue, are converted to square centimeters per hour (cm^2/hr) and then substituted into Eq. (7) along with the ordinary thicknesses of the respective tissues (cm) and the respective fractional areas of the routes, and if the partition coefficients are set to unity, the resulting magnitudes arrived at for the bracketed transepidermal and transfollicular contributions suggest that the steady-state flux through the transepidermal route is roughly 30 times greater than the steady-state flux through the follicular pores. We learn from this that high sebum diffusivity, by itself, is not enough to offset the small fractional area of the follicular route. Partitioning tendencies favoring either stratum corneum or sebum accumulation could magnify or shrink this ratio. Unfortunately we do not have the kind of information needed to pass judgment on how these distribution coefficients generally relate to one another.

Arguably, the stratum corneum harbors a minor polar pathway, an assertion that is admittedly still being debated. There is evidence the horny tissue supports disproportionally high fluxes of polar solutes such as methanol, ethanol, propylene glycol, glycerol, and even glucose. Ions

Table 8 Representative Parameters to Probe Model

	Diffusion coefficient, D $(cm^2/sec)^a$[4,8]
Stratum corneum	$10^{-9}-10^{-13}$
Water	$\simeq 10^{-9}$
n-Alkanols (hydrated tissue)	$\simeq 10^{-9}$
n-Alkanols (dry tissue)	$\simeq 10^{-10}$
Small nonelectrolytes	$10^{-9}-10^{-10}$
Progesterone	$\simeq 10^{-11}$
Cortisone	$\simeq 10^{-12}$
Hydrocortisone	$\simeq 10^{-13}$
Follicular pore (sebum)	$10^{-7}-10^{-9}$
Viable tissue	$\simeq 10^{-6}$
	Tissue thickness, h (μm) [2,8,11]
Stratum corneum	
Dry (normal state)	~10
Hydrated (as by occlusion) state	20–30
Pore diffusional length	Approximately two to five times greater than the stratum corneum thickness
Viable tissue stratum	150–2000[b] (200)
	Fractional area of the routes, F [4,8]
Transepidermal	~1
Transfollicular	$\sim 10^{-3}$
Transeccrine	$<10^{-4}$[c]
	Tissue/vehicle partition coefficient, K
Stratum corneum	From <1 to >>1[d]
Sebum	From <<1 to >>1[d]
Viable tissue	
Aqueous vehicle	~1
Nonaqueous vehicle	From <<1 to >>1[d]

[a]These diffusivities are estimates obtained by in vitro experiment (stratum corneum) or by comparison with small tissues in which diffusivities have been measured (all others) They do not account for regional variations across the body surface, so on both counts must be considered highly approximate.

[b]Highly approximate and variable, depending on blood flow patterns.

[c]This is sufficiently small to discount transeccrine diffusion contributions in the general treatment.

[d]All depend on the physiocochemical nature of the drug and vehicle as well as the physicochemical nature of the respective tissues.

diffuse through it, too. Sebum, on the other hand, although actually not well characterized in terms of its prevailing physicochemical state, is seemingly a nonpolar composite, a condition that would make it unsuitable for solubilization of such compounds. On these meager grounds, the transepidermal route should dominate for small, nonpolar nonelectrolytes, and it appears that it does. Analysis definitively identifies the stratum corneum as the main diffusional resistor in such instances, explaining why it has become known as the *barrier layer* of the skin.

As compounds of increasing hydrophobicity are brought under consideration, distribution coefficients of the substances into both stratum corneum and sebum are commensurately increased, as each medium is a lipoidal matrix to good first approximation. A useful feature of homologous compounds formed by extending alkyl chain length is that oil/water partition coefficients of series members grow exponentially, affording probing of the partitioning dependencies mass transport. The slope of a log-linear plot of partition coefficient against alkyl chain length yields the sensitivity of partitioning to a methylene group, the so-called π-value. Based on *n*-alkanol data, the π-value of normal human stratum corneum appears to be about 0.3 [4]. It is 0.5 for octanol/water partitioning, and over 0.6 for hexane/water partitioning. These differing values have been interpreted to mean that the stratum corneum's lipoidal phase is considerably more polar (less sensitive to a $-CH_2-$group) than either of the example organic solvents. The view held of sebum suggests its π-value might be higher than the stratum corneum's as well, but this is purely speculative assertion [40,41]. This does not necessarily cause a shift in the relative importances of the two identified routes, as judged through modeling, however, for when $K_{seb/w}$ reaches 1, the transfollicular route is already approaching viable tissue control of permeation. Consequently, further increases in this partition coefficient would not be experienced as increases in permeation through the pathway. On the other hand, according to the model, $K_{sc/w}$ must approach 50 before the viable tissue becomes the rate-controlling part of the barrier. This is the published value for octanol, which actually does appear to be at the threshold of viable tissue control of its permeation.

The story becomes quite different when minimum values for diffusivities are incorporated in the steady-state model (10^{-13} cm^2/sec for the stratum corneum and 10^{-9} cm^2/sec for the follicular shunt route). Keeping everything else constant and inserting these values produces a substantial upgrading of the importance of the transfollicular contribution. However, given laboratory data with steroids, the transepidermal route seems to retain its dominant position in the steady state even here.

We can now use the model to illustrate what happens to permeability when the stratum corneum is damaged. One only needs to use zero for the value of h_{sc}, the stratum corneum thickness, to assess the effect of extreme damage. This choice functionally denudes the skin and the transepidermal contribution takes the simple form, D_{vt}/h_{vt-TE}. Consequent increases in permeability can be as much or more that 1000-fold for polar compounds. However, for highly nonpolar compounds, $K_{sc/w}$ is so large that only small increases in permeability are projected. The implication here is that the increase in permeability that accompanies damage depends on how lipophilic a compound is. This is true, for as $K_{sc/w}$ is increased, the stratum corneum resistance is reduced proportionally, whereas the resistance in the living tissue, which sets the upper limit on permeability, is not. Thus, the more nonpolar a compound is, the less its permeation is affected by stratum corneum damage.

So far only steady-state conditions for permeation have been considered. There is strong evidence that the nonstationary-state period, that is, the time it takes to build up the gradient in the tissues, plays an important role in some drug delivery situations [42]. This is because the shunt route can be breached in a far shorter period than the transepidermal route, as molecular mobilities (D) are larger here. The time it takes to build up gradients is characterized in terms of the diffusional lag time, as illustrated in Fig. 4. The lag time can be seen to be the

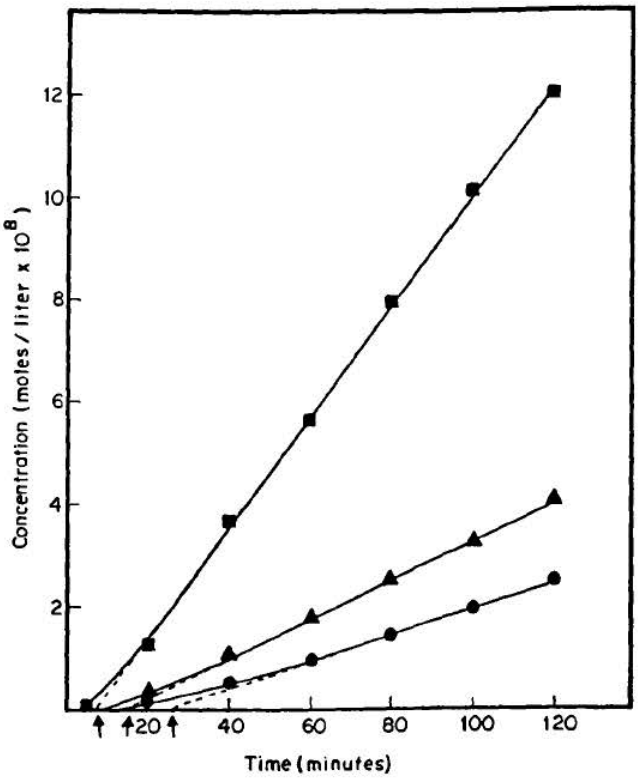

Fig. 4 Generalized permeation profile. From left to right the data are for n-butanol permeating hairless mouse skin at 20°, 25° and 30°C, respectively. Increasing temperature raises the flux (slope) and shortens the lag time.

intercept on the time axis found by extrapolating the steady-state line of a plot of cumulative amount of drug penetrated versus time. This lag time, t_L, is related to the diffusivity of a simple isotropic membrane by:

$$t_L = \frac{h^2}{6D} \tag{10}$$

where h is again used to signify the membrane's thickness and D is the diffusion coefficient. Lag times are different for parallel routes. Even though the diffusion coefficients we have for the skin are effective values embodying factors beyond molecular mobility, we can still estimate specific lag times for the two pathways under consideration through the skin using the diffusion coefficients tabulated in Table 8. Lag times for the transepidermal route would seem to range from minutes for small nonelectrolytes to multiple days for corticosteroids. On the other hand, transfollicular values seem to range from seconds to minutes. On this basis it appears likely that the first molecules to reach the viable epidermis come by the follicular path, although the amounts of drug reaching the lower epidermis early on may not be large owing to the limited

area of the path. Nevertheless, it is this kind of thinking that has led scientists to the idea that some clinical responses are due to diffusion through the follicular shunt. When the lag time through the stratum corneum pathway itself is short, transient diffusion through the shunt is far less likely to be clinically significant. Moreover, since it is the stratum corneum that is responsible for the long lag times by the transepidermal route, the foregoing nonstationary-state considerations do not apply when it is impaired.

Equations (8) and (9) do underscore the point that percutaneous absorption is proportional to area. Transdermal patches of nitroglycerin and other drugs are provided in different sizes to take advantage of this simple fact to adjust dosages. It cannot be stressed too strongly that a pharmacist must be cognizant of this area dependency for another, more compelling reason. Even if a drug if not readily percutaneously absorbed, its systemic effects are magnified in proportion to the area over which it is applied. No other factor is so frequently associated with the untoward actions of topically applied drugs. Consider that there have been unfortunate poisonings of infants following the liberal use of talcum powders containing borates as lubricants, perhaps but not necessarily, in conjunction a diminished skin barrier property resulting from diaper irritation. Borates are now outlawed for this purpose. Babies have been poisoned by bathing them with a hexachlorophene-containing liquid soap; bathing involves total body coverage. Hexachlorophene is no longer used in the manner. The inflammation associated with diaper rash is extensive, and topical corticosteroids have also been used too liberally on the bodies of infants and small children to treat this and other conditions, to the point of inducing serious toxicity. These kinds of problems are not limited to small children. Systemic toxicities have accompanied the treatment of psoriatic lesions with the keratolytic, salicylic acid, under circumstances when the lesions have been massive. And there are now documented cases of abuse of transdermal patches, including one in which a patient, confused about the manner of use, succumbed to fentanyl by wearing four patches simultaneously. Topically, area is dose.

Phenomenological Considerations in Percutaneous Delivery

The model that has been presented is useful for ferreting *patterns* of permeability as determined by chemical structure and by the physiological state of the skin. It would be inappropriate to use it to calculate actual permeability coefficients, however, because so many iffy approximations are made. Therefore, we must take a different tack to gain a sense of the absolute limits of drug delivery by way of cutaneous absorption. The lower limit of flux of compounds across the skin would be none at all; surprisingly, a situation that rarely appears to be seen. Even proteins penetrate the intact skin to a minuscule extent. However and obviously, it is more instructive to know the upper limit of achievable flux. Some idea of this can be gained from examining the rates of delivery of nitroglycerin and similarly facile penetrants of skin.

Nitroglycerin, a liquid at room temperature, is a relatively lipophilic nonelectrolyte compound of only 227 molecular weight, all properties that tend to make it an ideal skin penetrant. It is formulated in transdermal systems virtually as a neat liquid and, thus, near its upper attainable thermodynamic activity. It diffuses through the skin at between 0.02 and 0.04 mg cm^{-2} hr^{-1} from the transdermal reservoirs in which it is placed, rates that equate to the delivery of 0.5–1.0 mg cm^{-2} day^{-1} [24]. Consequently, 20 cm^2 patches are used to provide a daily delivery of between 10 and 20 mg of the drug [24]. Nicotine, another low molecular weight, somewhat hydrophobic, liquid compound at 25°C, permeates at comparably high rates from its patch delivery systems. Selegiline is another facile skin penetrant, having a similar battery of physical properties and the same limiting rate. Thus, by this analysis, 1 mg cm^{-2} day^{-1} looks to be about the upper achievable limit of delivery of drugs through the skin. This claim is made even in the face of the fact that water diffuses through the skin much faster than any

of these species. Water typically diffuses out of the skin into a dry atmosphere at a rate of 0.5 mg/cm^{-2} hr^{-1}, a flux over an order of magnitude greater than that seen with the compounds mentioned. Physiological water inside the skin has a thermodynamic activity equivalent to that of 0.9% NaCl, a highly dilute solution to say the least; thus, the driving force for water's escape from the body is not all that different than if cellular water were in a pure state. But water is a very unique molecule, both for its size and its interactions within the horny layer. Appearances are that its diffusion is not restricted to the intercellular domain of the stratum corneum, but rather, some water almost certainly works its way into and up through the keratin amassed in the intracellular space. It seems a major fraction of insensible perspiration exits the skin this way. Diffusion of nitroglycerin and the other drugs mentioned, on the other hand, is believed to be restricted to the lipoidal, intercellular domain of the stratum corneum.

If all nonpolar drugs were as skin-permeable as nitroglycerin, there would be many more topical and transdermal delivery systems. A good question is: Why are there so few? One reason is crystallinity for, in a general way, this limits the activity gradient that can be expressed across a membrane in a transport situation. We can superimpose a hypothetical crystallinity on nitroglycerin to illustrate the effect this might have on its activity and, thus, its delivery. By thermodynamic derivation the activity of the crystalline form of a compound relative to that of its liquid state (a *supercooled* liquid) is given by

$$\ln a_2 = -\frac{\Delta H_f(T_f - T)}{RT_fT} \tag{11}$$

where a_2 is the solid's activity, ΔH_f is its heat of fusion, T_f is its melting point (temperature of fusion), T is the experimental temperature (nominally 25°C), and R is the gas constant (1.987 in cal/mol per degree). By simple calculation, on assigning a melting point of 100°C and a plausible heat of fusion of 5000 cal/mol (about 20,000 J/mol) to our hypothetical crystalline form of nitroglycerin, its activity drops a little over fivefold. It would be possible to delivery only 200 $\mu g/cm^{-2}$ day^{-1}, or only about 4 mg from a 20 cm^2 patch if this were true. If nitroglycerin melted at 200°C, all else equal, it would have only 4% of the activity it has as a liquid, and the delivery rate would now be only 40 $\mu g/cm^{-2}$ day^{-1} (1 mg for a 20 cm^2 patch). Since most drugs are crystalline, some more so than in the illustration, delivery of 1 mg of drug per day from a 20 cm^2 area (roughly the area of a Ritz cracker) can be a true feat, to some extent making it clear why only very potent drugs are taken seriously for transdermal delivery. The underlying phenomenon here is that solubilities in all solvents are reduced by crystallinity over what they would otherwise be, including a drug's solubility in its delivery system matrix and, for that matter, in the skin's surface. Referring back to the model, the impact of this is directly on ΔC in Eq. (9), for the upper limit ΔC is the solubility of the compound. In other words, it is solubility that sets the upper limit on achievable delivery from the concentration gradient standpoint. These influences of crystallinity become particularly important when selecting compounds from the many that may be available to develop for topical or transdermal purposes. Everything else equal, low-melting compounds are far easier to deliver at therapeutically adequate rates.

Solubility in a particular solvent is also determined by the net interactions the solute has with the solvent in the solution phase. Generally, the activity of a dissolved solute is related to its concentration in solution through an activity coefficient; that is,

$$a_2 = X_2\gamma_2 \tag{12}$$

Here, X_2 is the mole fraction of the solute in the saturated solution, this manner of expressing concentration being made on theoretical grounds, and γ_2 is its activity coefficient. The activity

coefficient is nothing more nor less than the number needed to establish an equality between activity and concentration. Returning to the solubility expression we now have

$$\ln X_2 = \left[-\frac{\Delta H_f(T_t - T)}{RT_fT} \right] - \ln \gamma_2 \tag{13}$$

The right-hand side of Eq. 13 teaches us that solubility in a particular solvent depends on melting parameters, the same way activity does. However, the magnitude of the solubility also depends on the activity coefficient, as shown in the second right-hand term of Eq. (13). If the solute's solution phase interactions are strong (energetic), the activity coefficient is less than 1, and the solubility of the compound exceeds that of its ideal solution (where $\gamma_2 = 1.0$ and $a_2 = X_2$). Relatively weak interactions between the solute and solvent, on the other hand, are marked with activity coefficients greater than unity. Under such circumstance solubilities are lower than ideal. What one learns from all of this is that a high level of crystallinity is associated with low activity and vice versa, a factor set apart from the fact that compounds display as many solubilities as there are solvents to dissolve them in. The thermodynamic activity of a drug is the same in every one of its saturated solutions even though concentrations themselves are different from medium to medium owing to differing solute–solvent interactivity, the latter being couched in the activity coefficient term. One should not jump to the conclusion that drug delivery is the same from every saturated solution, however, as the solid to solution equilibria can rapidly kinetically break down on application of a dosage form, owing to drug dissolution in the vehicle not keeping up with partitioning of the drug into the skin. Additionally, when skin is the membrane, the enhancing attributes of different vehicles must also be considered.

The other two physical parameters of a drug that control its skin permeability are its size and its lipophilicity. It has only recently become clear that these, more than anything else, determine the magnitude of cutaneous permeability coefficients [43,44], as found in Eqs. (7) and (8). When extant human permeability coefficients (numbering over 90 compounds) were recently analyzed [44] by multiple linear regression within the following semiempirical equation:

$$\log_{10}(P) = \log_{10}\left(\frac{D^0}{h}\right) + \alpha \log_{10}(K_{oct/w}) - \beta(MW) \tag{14}$$

it was found that almost 70% of the variability in them is explicable by molecular size and partitioning attributes. For the record, D^0 in Eq. (14) is the hypothetical diffusivity of a molecule having zero molecular volume; h, as before, is the effective diffusion path length; α is a proportionality factor relating $K_{sc/w}$, as we have already defined it, to $K_{oct/w}$ or the respective octanol/water partition coefficient; β is a constant carried along from the dependency of diffusion coefficients on molecular size; and MW represents molecular weight (a surrogate for molecular volume). The computer-fit expression arising from a regression analysis involving all studied compounds is [43]

$$\log_{10}(P) = -6.3 + 0.71(K_{oct/w}) - 0.0061(MW) \tag{15}$$

Equation (15) provides its estimates of the permeability coefficients of compounds in units of centimeters per second (cm/sec). It can be used to make a "guesstimate" of the permeability coefficient of a compound through human skin from the compound's molecular weight and octanol/water partition coefficient alone. As with any parameter drawn out of statistically drawn relationships, such estimates must be used cautiously, for the absolute error of estimation for a single compound can be large.

V. UNIQUE PHYSICOCHEMICAL SYSTEMS USED TOPICALLY

As one scans the products at the drug counter, one finds an enormous variety of formulation types available for topical therapy or for cosmetic purposes. Solutions are commonly found. They come in packages that allow them to be rubbed on, sprayed on by aerosol and atomizers, painted on, rolled on, swabbed on by premoistened pledgets, and dabbed on from applicators. Assorted medicated soaps are available for a range of purposes. Emulsions for the skin are found in the form of shampoos and as medicated lotions. Powders to soothe and lubricate are placed in sprinkling cans, whereas others containing drugs are formulated into aerosols to be sprayed on the skin. There are numerous fluid suspensions to be used as makeup or for therapeutic purposes. Clear and opaque gels are also to be found in both cosmetic and therapeutic spheres, as are assorted semisolid creams, ointments, and pastes. The physical natures of these latter systems range from soft semisolids, intended to be squeezed out of tubes, to hardened systems, suitable for application in stick form. There are therapeutic and cosmetic oils for the bath. The list of products and formulation types is nearly endless.

Of all these formulations, it is the diverse semisolids that stand out as being uniquely topical. Semisolid systems fulfill a special topical need, as they cling to the surface of the skin to which they are applied, generally until being washed off or worn off. In contrast, fluid systems have poor substantivity and readily streak and run off the desired area. Similarly, powders have poor staying properties. Importantly, the fundamental physicochemical characteristics of solutions, liquid emulsions, and suspensions, and powders are independent of their route of application, and are discussed adequately elsewhere in this text and need not be reconsidered. This is not to say the compositions of such systems cannot be uniquely topical, for there are chemicals that can be safely applied to the skin, but that are unsafe to use systemically. There is need to elaborate the properties of semisolids.

A. General Behavior of Semisolids

The term *semisolid* infers a unique rheological character. Like solids, such systems retain their shape until acted on by an outside force, whereupon, unlike solids, they are easily deformed. Thus, a finger drawn through a semisolid mass leaves a track that does not fill up when the action is complete. Rather, the deformation made is, for all practical purposes, permanent, an outcome physically characterized by saying semisolids deform plastically. Their overall rheological properties allow them to be spread over the skin to form films that cling tenaciously.

To be semisolid, systems must have a three-dimensional structure that is sufficient to impart solidlike character to the undistributed system, but that is easily broken down and realigned under an applied force. The semisolid systems used pharmaceutically include ointments and solidified water-in-oil (w/o) emulsion variants thereof, pastes, oil-in-water (o/w) creams with solidified internal phases, o/w creams with fluid internal phases, gels, and rigid foams. The natures of the underlying structures differ remarkably across all these systems, but all share the property that their structures are easily broken down, rearranged, and re-formed. Only to the extent that one understands the structural sources of these systems does one understand them at all.

B. Ointments

Unless expressly stated otherwise, ointments are hydrocarbon-based semisolids containing dissolved or suspended drugs. They comprise fluid hydrocarbons, C_{16} to perhaps C_{30} straight-chain and branched, entrapped in a fine crystalline matrix of yet higher molecular weight hydrocarbons. The high molecular weight fraction precipitates out substantially above room temperature, forming interlocking crystallites [45]. The extent and specific nature of this structure determine

the stiffness of the ointment. It follows directly from this that hydrocarbon-based ointments liquify on heating, for the crystallites melt. Moreover, when cooled very slowly, they assume a fluidity much greater than when rapidly cooled, because slow cooling leads to fewer and larger crystallites and, therefore, less total structure. Ordinary white and yellow petrolatum are examples of such systems.

Several alternative means of forming hydrocarbon ointments illustrate their structural properties. Ointments can be made by incorporating high-melting waxes into fluid mineral oil (liquid petrolatum) at high temperature. On cooling, interlocking wax crystallites form, and the system sets up. Polyethylene, too, can gel mineral oil if dissolved into this vehicle at high temperature and the solution is then forced cooled [46]. A network of polyethylene crystallites provides the requisite solidifying matrix. This polyethylene-gelled system is more fluid on the molecular level than are the semisolid petroleum distillates, while at the same time, macroscopically behaving as an ointment. Consequently, diffusion of drugs through this vehicle is more facile, and drug release is somewhat greater than found with petrolatum-based systems [47]. Plastibase (Squibb) is the commercially available base of polyethylene-gelled mineral oil. It is useful for the extemporaneous preparation of ointments by cold incorporation of drugs. Pharmacists should not melt down this base to incorporate drugs, for its gelled state cannot be restored without special processing equipment.

If a material other than a hydrocarbon is used as the base material of an ointmentlike system, the ointment bears the name of its principal ingredient. There are silicone ointments that contain polydimethylsiloxane oil in large proportion. These reportedly act as excellent water barriers and superior emollients. Some are actually used to protect skin from undesirable influences of long immersion in water.

Ointments of the specific kinds just mentioned are taken to be good vehicles to apply to dry lesions, but not to moist ones. All the foregoing are also greasy and stain clothes. The principal ingredients forming the systems, hydrocarbons and silicone oils, are generally poor solvents for most drugs, seemingly setting a low limit on the drug delivery capabilities of the systems. This solubility disadvantage can be offset somewhat if hydrocarbon-miscible solvents are blended into the systems to raise solvency. Alternatively, they can be made over into emulsions to raise their abilities to dissolve drugs. Along these lines, absorption bases are conventional ointments that contain water-in-oil (w/o) emulsifiers in appreciable quantity. A water-in-oil emulsion is formed when an aqueous medium, perhaps containing the drug in solution, is worked into the base. Such emulsions are still ointments, as structurally defined, for it is the external phase of the formed emulsion that imparts the structure, and this retains its ointment-like character. The term *absorption base* refers to a water incorporation capacity and infers nothing about bioavailability. This is not to say that it is not better to have water-soluble drugs emulsified than to have them as undissolved solids in such systems from the bioavailability standpoint. For optimum results, the internal, presumably aqueous phase, should be close to saturated. Diverse additives are used to emulsify water into these systems, including cholesterol, lanolin (which contains cholesterol, cholesterol esters, and other emulsifiers), semisynthetic lanolin derivatives, and assorted ionic and nonionic surfactants, singularly or in combination.

Polyethylene glycol ointment is a water-soluble system that contains fluid, short-chain polyoxyethylene polymers (polyethylene glycols) in a crystalline network of high-melting, long-chain polyoxyethylene polymers (Carbowaxes, Union Carbide). The structure formed is totally analogous to that of the standard ointment. In one variation, this system functions well as a suppository base. Liquid polyethylene glycols are fully miscible with water, and many drugs that are insoluble in petroleum vehicles readily dissolve in the polar matrix of this base. In fact, with some drugs, delivery (bioavailability) can be compromised by an excessive capacity of the base to dissolve substances, resulting in poor vehicle-into-skin partitioning. Since

polyethylene glycols are highly water-soluble, bases formed from them literally dissolve off the skin when placed under a stream of running water.

C. Pastes

Pastes are basically ointments into which a high percentage of insoluble particulate solids have been added—as much or more than 50% by weight in some instances. This extraordinary amount of particulate matter stiffens the systems through direct interactions of the dispersed particulates and by adsorbing the liquid hydrocarbon fraction within the vehicle onto the particle surfaces. Insoluble ingredients, such as starch, zinc oxide, calcium carbonate, and talc, are used as the dispersed phase. Pastes make particularly good protective barriers when placed on the skin for, in addition to forming an unbroken film, the solids they contain can absorb, and thereby neutralize, certain noxious chemicals before they ever reach the skin. This explains why they are used to ameliorate diaper rash for, when spread over the baby's bottom, they absorb irritants (ammonia, others?) formed by bacterial action on urine. Like ointments, pastes form an unbroken, relatively water-impermeable film on the skin surface and, thus, are emollients; unlike ointments, the film is opaque and, therefore, an effective sun block. Accordingly, skiers apply pastes around the nose and lips to gain a dual protection. Pastes are actually less greasy than ointments because of the adsorption of the fluid hydrocarbon fraction to the particulates.

D. Creams

Creams are semisolid emulsion systems that have a creamy appearance as the result of reflection of light from their emulsified phases. This contrasts them with simple ointments, which are translucent. Little agreement exists among professionals concerning what constitutes a cream; therefore, the term has been applied both to absorption bases containing emulsified water (w/o emulsions) and to semisolid o/w systems, which are physicochemically totally different, strictly because of their similar creamy appearances. Logically, classification of these systems should be based on their physical natures, in which case, absorption bases would be ointments, and the term *cream* could be reserved exclusively for semisolid o/w systems, which in all instances derive their structures from their emulsifiers and internal phases.

The classic o/w cream is vanishing cream, which contains only 15% stearic acid or its equivalent as the internal phase. Vanishing cream and its variants are first prepared as ordinary liquid emulsions at high temperature; the structure that gives them their semisolid character forms as the emulsions cool. Both the aqueous and stearic acid phases are heated above the point at which the waxy components liquify and are then emulsified. Sufficient emulsifier is either formed in situ or added in to create a substantial micellar phase to exist in equilibrium with the liquified internal phase of the hot emulsion. In the instance of the classic vanishing cream, about 20% of the stearic acid it contains is neutralized with strong alkali to form the surfactant. Portions of the waxy alcohols or undissociated waxy acids are solubilized within such micelles. As these systems are then cooled, their emulsion droplets solidify and the micellar structures linking all together take on a liquid crystalline character [48]. The latter three-dimensional matrix has been referred to as *frozen micelles* and is what actually solidifies such creams. The compositions and amounts of both the internal phase and emulsifiers determine the extent and qualities of the structure. Creams such as this are more or less stiff depending on the level of micellar solubilization of and the melting properties of the internal waxy component [48]. Within the family of such creams, the internal phase ranges in composition from about 12 to 40% by weight.

Stiff o/w emulsions can also result from droplet interactions of the internal phase, but this requires emulsifying such a huge amount of internal phase that the droplets exceed close spherical packing. In this state, the emulsified particles are squashed together, losing their sphericities,

producing large interfacial areas of contact at the sites where the droplets meet. A fragile structure is obtained somewhere between that of a highly viscid liquid and a true semisolid. This cream type is far less common than systems built around frozen micellar structures.

A semisolid cream of the o/w type containing a solidified, liquid crystalline internal phase is an elegant topical system, preferred by many for general purposes. Such o/w systems are readily diluted with water and, thus, easily rinsed off the skin and are generally nonstaining. After application, volatile components of the cream, which may constitute as much as 80% of the total system, evaporate, and the thin application shrinks down into an even thinner layer. Stearic acid creams are particularly interesting in this regard. The small amount of internal phase they contain causes them to evaporate down to near nothingness. The dry, nontacky, translucent nature of the stearic acid crystals left on the skin contributes to the sense of their indetectability. Most hand lotions and creams and foundation creams used to make face powders adherent to the face are variants of the vanishing cream formula.

Through evaporation, the drug in a spread is concentrated in its forming film, a process that can be orchestrated to program drug delivery. If no thought is given to the consequences attending drying out of the formulation, however, the drug is just as likely to precipitate out, in which instance drug delivery comes to an abrupt stop. Therefore, one must ensure that the formed film has some capacity to dissolve its drug. To this end, low volatility, water-miscible solvents, such as propylene glycol, are added to many cream formulations. When ingredients such as water and alcohol evaporate, the film left after applying these creams becomes a rich concentrate of drug, its internal phase, and its less volatile external phase components. One strives to add just enough cosolvent to keep the drug solubilized in the equilibrium film, but also near saturation. It should be kept in mind that, unless the internal phase liquifies at body temperature, the waxy constituents cannot act as a solvent for the drug and, accordingly, do not lend the film much capacity for delivery.

The typical cream, a soft, emulsified mass of solidified particle in an aqueous, micelle-rich medium, does not form a water-impermeable (occlusive) film on the skin. Nevertheless, creams contain lipids and other moisturizers that replace substances lost from the skin in the course of everyday living. Creams thus make good emollients because, by replenishing lipids and in some instances also polar, hygroscopic substances, they restore the skin's ability to hold onto its own moisture.

The oleaginous phases of creams differ compositionally from hydrocarbon ointments. Many creams are patterned after vanishing cream and contain considerable stearic acid, but not all. In lieu of some or all of the stearic acid, creams sometime contain long-chain waxy alcohols (cetyl, C_{16}; stearyl, C_{18}), long-chain esters (myristates, C_{14}; palmitates, C_{16}; stearates, C_{18}), other long-chain acids (palmatic acid), vegetable and animal oils, and assorted other waxes of both animal and mineral origin.

Properly designed o/w creams are elegant drug delivery systems, pleasing in both appearance and feel post application. They are nongreasy and are rinsable. They are good for most topical purposes and are considered particularly suited for application to oozing wounds.

E. Gels (Jellies)

Gels are semisolid systems in which a liquid phase is trapped within an interlocking, three-dimensional polymeric matrix of a natural or synthetic gum. A high degree of physical or chemical cross-linking of the polymer is involved. It only takes from 0.5 to 2.0% of the most commonly used gelants to set up the systems. Some of these systems are as transparent as water itself, an aesthetically pleasing state. Others are turbid, as the polymer is present in colloidal aggregates that disperse light. Clarity of the latter ranges from slightly hazy to a whitish translucence not unlike that observed with petrolatum.

Agarose gels admirably illustrate the properties and, to an extent, the structural characteristics of most gels. Agarose solutions are water-thin when warm, but solidify near room temperature to form systems that are soft to rubbery, depending on the source and concentration of the agarose. A structure is set up as the result of the entwining of the ends of different polymer strands into double helices. Kinks in the polymer mark the terminal points of these windings. Because individual polymer strands branch to form multiple endings, a three-dimensional array of physically cross-linked polymer strands is formed. The process of physical cross-linking is actually a crystallization phenomenon tying polymeric endings together, fixing the strands in place, yielding a stable, yet deformable, structure [49]. Less extensive structure than that found in agar growth media results in a spreadable semisolid suitable for medical application.

The structure should persist to temperatures exceeding body temperature for the gelled systems to be the most useful. Importantly, gellation is never a result of mere physical entanglement of polymer strands, or otherwise, the systems would be only highly viscid. The polymers used to prepare pharmaceutical gels include natural gums, such as tragacanth, pectin, carrageen, agar, and alginic acid, and synthetic and semisynthetic materials, such as methylcellulose, hydroxyethylcellulose, carboxymethylcellulose, and carboxypolymethylene (carboxy vinal polymers sold under the name Carbopol, B. F. Goodrich).

Gels or jellies are used pharmaceutically as lubricants and also as carriers for spermacidal agents to be used intravaginally with diaphragms as an adjunctive means of contraception. Since the fluid phase of a gel does not have to be strictly water, but can contain appreciable amounts of water-miscible organic solvents, gels hold considerable potential for an even wider range of uses, for, by blending solvents, it is possible to form gelatinous films with varying evaporation rates, solvencies, and other release attributes. A good example of what can be accomplished is found in Topsyn Gel (Syntex), which contains the anti-inflammatory steroid fluocinonide in a propylene glycol matrix gelled with Carbopol [50]. This product is used to treat inflammatory reactions of the scalp in lieu of creams and ointments, as the latter have proved too greasy for the purpose.

F. Rigid Foams

Foams are systems in which air or some other gas is emulsified in a liquid phase to the point of stiffening. As spreadable topical systems go, medicated foams tend toward the fluid side, but, like some shaving creams, they can be stiffer and approximate a true semisolid. Like the second type of o/w emulsion that only borders on semisolidity, these derive structure from an internal phase—bubbles of an entrapped gas—so voluminous that it exceeds close spherical packing. Consequently, the bubbles interact with their neighbors over areas, rather than at points of contact. The interactions are often sufficient to provide a resistance to deformation and something approaching semisolid character. Whipped cream is a common example of this type of system. Here air is literally beaten into the fluid cream until it becomes stiff. Aerosol shaving creams and certain medicated quick-breaking antiseptic foams are examples of the foams currently found in cosmetic and therapeutic practice. These are supplied in pressurized cans which have special valves that emulsify gas into the extruded preparations.

G. Common Constituents of Dermatological Preparations

So many materials are used as pharmaceutical necessities and as vehicles in topical systems that they defy thorough analysis. Nevertheless, the pharmacist should make some effort to learn of the more common constituents and their principal functions. This can be done by reading labels and studying the compositions of formulations, including those presented in Table 9.

Table 9 Prototype Formulations

I. *Ointment* (white ointment, USP)

White petrolatum	95% (w/v)
White wax	5%

Melt the white wax and add the petrolatum; continue heating until a liquid melt is formed. Congeal with stirring. Heating should be gentle to avoid charring (steam is preferred), and air incorporation by too vigorous stirring is to be avoided.

II. *Absorption ointment* (hydrophilic petrolatum, USP)

White petrolatum	86% (w/w)
Stearyl alcohol	3%
White wax	8%
Cholesterol	3%

Melt the stearyl alcohol, white wax, and cholesterol (steam bath). Add the petrolatum and continue heating until a liquid melt is formed. Cool with stirring until congealed.

III. *Water-washable ointment* (hydrophilic ointment, USP)

White petrolatum	25% (w/w)
Stearyl alcohol	25%
Propylene glycol	12%
Sodium lauryl sulfate	1%
Methylparaben	0.025%
Propylparaben	0.015%
Purified water	37%

Melt the stearyl alcohol and white petrolatum (steam bath) and warm to about 75°C. Heat the water to 75°C and add the sodium lauryl sulfate, propylene glycol, methylparaben, and propylparaben. Add the aqueous phase and stir until congealed.

IV. *Water-soluble ointment* (polyethylene glycol ointment, USP 14)

Polyethylene glycol 4000 (Carbowax 4000)	50%
Polyethylene glycol 400	50%

Melt the PG 4000 and add the liquid PG 400. Cool with stirring until congealed.

V. *Cream base, w/o* (rose water ointment, NF 14)

Oleaginous phase	
Spermaceti	12.5%
White wax	12.0%
Almond oil	55.58%
Aqueous phase	
Sodium borate	0.5%
Stronger rose water, NF	2.5%
Purified water, USP	16.5%
Aromatic	
Rose oil, NF	0.02%

Melt the spermaceti and white wax on a steam bath. Add the almond oil and continue heating to 70°C. Dissolve the sodium borate in the purified water and stronger rose water, warmed to 75°C. Gradually add the aqueous phase to the oil phase with stirring. Cool to 45°C with stirring and incorporate the aromatic (rose oil).

Note: This is a typical cold cream formulation. The cooling effect comes from the slow evaporation of water from the applied films. The aromatic is added at as low a temperature as possible to prevent its loss by volatilization during manufacture.

Table 9 Continued

VI. *Cream base, o/w* (general prototype)

Oleagenous phase	
Stearyl alcohol	15%
Beeswax	8%
Sorbitan monooleate	1.25%
Aqueous phase	
Sorbitol solution, 70% USP	7.5%
Polysorbate 80	3.75%
Methylparaben	0.025%
Propylparaben	0.015%
Purified water, q.s. ad	100%

Heat the oil phase and water phase to 70°C. Add the oil phase slowly to the aqueous phase with stirring to form a crude emulsion. Cool to about 55°C and homogenize. Cool with agitation until congealed.

VII. *Cream base, o/w* (vanishing cream)

Oleagenous phase	
Stearic acid	13%
Stearyl alcohol	1%
Cetyl alcohol	1%
Aqueous phase	
Glycerin	10%
Methylparaben	0.1%
Propylparaben	0.05%
Potassium hydroxide	0.9%
Purified water, q.s. ad	100%

Heat the oil phase and water phase to about 65°C. Add the oil phase slowly to the aqueous phase with stirring to form a crude emulsion. Cool to about 50°C and homogenize. Cool with agitation until congealed.

Note: In this classic preparation, the stearic acid reacts with the alkaline borate to form the emulsifying stearate soap.

VIII. *Paste* (zinc oxide paste, USP)

Zinc oxide	25%
Starch	25%
Calamine	5%
White petrolatum, q.s. ad	100%

Titrate the calamine with the zinc oxide and starch and incorporate uniformly in the petrolatum by levigation in a mortar or on a glass slab with a spatula. Mineral oil should *not* be used as a levigating agent, since it would soften the product. A portion of the petrolatum can be melted and used as a levigating agent is so desired.

IX. *Gel* (lubricating jelly)

Methocel 90 H.C. 4000	0.8%
Carbopol 934	0.24%
Propylene glycol	16.7%
Methylparaben	0.015%
Sodium hydroxide, q.s. ad	pH 7
Purified water, q.s. ad	100%

Disperse the Methocel in 40 ml of hot (80°–90°C) water. Chill overnight in a refrigerator to effect solution. Disperse the Carbopol 934 in 20 ml of water. Adjust the pH of the dispersion to 7.0 by adding sufficient 1% sodium hydroxide solution (about 12 ml is required per 100 ml) and bring the volume to 40 ml with purified water. Dissolve the methylparaben in the propylene glycol. Mix the Methocel, Carbopol 934, and propylene glycol fractions using caution to avoid the incorporation of air.

Because of the many materials that are used in topical preparations and the diverseness of their physical properties, the formulation of topicals tends to be something of an art, perfected through experience. Only by making myriad recipes does one eventually gain insight about the materials and their use in the design of new formulations. Such insight allows the experienced formulator to manipulate the properties of existing formulations to gain a desired characteristic. Often one finds good recipes to use as starting points for formulations in the trade literature. Two factors have to be kept in mind when borrowing the compositions of such trade formulations: (a) trade recipes (recipes supplied with advertising material touting specific components) are often inadequately tested in terms of their long-term stability and (b) the dominant features used in judging the merits of trade-promoted formulas tend to be the initial appearance and overall elegance. Little to no attention can be paid to the drug delivery attributes of the prototypical systems when they are first prepared in the suppliers laboratories, because the drug delivery attributes are so compound-specific. Thus, it is left up to the pharmacist (industrial research pharmacist) to make adjustments in the formulas that are consistent with good delivery of specific drugs. Each drug requires unique adjustments, in accord with its singular set of physicochemical properties.

H. General Methods of Preparation of Topical Systems

Irrespective of whether the scale of preparation is large or small, ointments, pastes, and creams tend to be produced by one or the other of two general methods. Either they are made at high temperatures by blending the liquid and heat-liquefiable components together and then dispersing other solids (often including the drug) within the oily melt or, in the instance of emulsions, within the aqueous phase of the emulsion or the freshly formed emulsion itself (fusion methods); or the drug is incorporated in the already solidified base (cold incorporation). As earlier pointed out, the first of these methods is commonly used to make o/w creams of the vanishing cream type. The fusion method is also used to prepare many ointments. Cold incorporation comes into play in large-scale manufacture when the systems in preparation contain heat-labile drugs, in which instance the drug is first crudely worked into an existing ointment or cream base using a serial dilution technique and is then distributed uniformly with the aid of a roller mill. Cold incorporation is also mandated when the base itself is destroyed by heat, as happens with Plastibase (Squibb).

In the fusion method for ointments, mineral oil, petrolatum, waxes, and such other ingredients as belong in the formulation are heated together to somewhere between 60° and 80°C, depending on the components, and mixed to a uniform composition while in the fluidized state. Cooling is then effected using some short of a heat exchanger. To prevent decomposition, drugs and certain delicate adjuvants are added sometime during the cooling process. If insoluble solids need to be dispersed, the system is put through a milling process (colloid mill, homogenizer, ultrasonic mixer, or other) to disperse them fully. A hand homogenizer works well at the prescription counter for small-volume, extemporaneously prepared systems. Systems in preparation are always cooled with mild stirring until they are close to solidification. The rate of cooling is important, for rapid cooling, as mentioned, imparts a finer, more rigid structure. Stirring should be set to minimize vortexing and, thereby, prevent air incorporation into the solidifying system. Representative formulations with more system-specific, detailed directions are given in Table 9 for ointments and the other semisolid systems of note.

The fusion method for preparing creams is a bit more complex. In this instance the aqueous and oil phases are heated separately to somewhere between 60° and 80°C. As a general rule the oil phase is heated to 5°C above the melting point of the highest-melting waxy ingredient, and the water phase is heated to 5°C above the temperature of the oil phase, the latter to

prevent premature solidification during the emulsification process. Water-soluble ingredients are dissolved in the heated aqueous phase, and oil-soluble ingredients are dissolved in the oily melt, but only as long as they are heat-stable and not too volatile. If an o/w system is to be made, the emulsifiers are added to the aqueous phase and the emulsion is formed by slow addition of the oil phase. In the industry the crude emulsion is then passed through a high-shear mixer to form a finely divided emulsion state. Following this, the emulsion is cooled with gentle stirring until congealed, again taking care not to whip air into the formulation. Typically, the emulsions solidify between 40° and 50°C. If a w/o emulsion is to be made, the addition steps are usually reversed. Therefore and generally, the discontinuous phase is added to the continuous, external phase containing the emulsifier. However, methods vary here and, for a particular formula, the reverse order of addition may work best. Any means that reliably leads to a good emulsion is obviously acceptable.

A solid can be cold-incorporated directly into an already congealed system several ways. This is accomplished on a small scale by levigating the solid with a small portion of the total base it is to be suspended in to obtain a pastelike mass. The drug is worked into the base on a glass plate with the aid of a spatula, or is triturated in by using a mortar and pestle. After the initial mix is made smooth, a portion of the vehicle, roughly equal in bulk to that of the pasty mass, is added and blended in. This latter procedure is repeated several times more (geometric dilution) until the drug is uniformly dispersed throughout its total vehicle. In large-scale manufacture, solids are crudely dispersed into the base using a blender and then roller mills, in which a film of the formulation is passed from one roller to another and so on, in each passage with kneading and mixing, are used to obtain fine dispersion. As outlined when discussing absorption bases, the drug may also be dissolved in water to form a solution to be levigated into an ointment base or cream. Such addition softens creams even to the point of converting them to thick lotions. The chosen vehicle must have an inherent capacity to emulsify or otherwise take up the solution. Aromatic materials, such as essential oils, perfume oils, camphor, and methol, which volatilize if added when the base is hot, are incorporated into these semisolids while they are still being mixed, but near the temperature at which a particular system starts to congeal. Volatile materials are often introduced into the formulation as hydroalcoholic solutions.

The preparation of gels can also involve high-temperature processing. It is easier to disperse methylcellulose in hot than in cold water, for instance. The polymer then goes into solution and thickens or sets up as the temperature is lowered. Adding the hot methylcellulose dispersion to ice water gets one quickly to the final equilibrium state. Tragacanth gels, on the other hand, must be prepared at room temperature owing to the extreme heat lability of this natural gum. A little alcohol or propylene glycol can be mixed into this gum before adding water to it to facilate wetting and its dispersion. In contrast with these two materials, Carbopols are gelled by uniformly dispersing the polymer in an acidic medium and then neutralizing the medium with strong alkali. The alkali ionizes carboxyl groups on the polymer, instantaneously drawing the polymer into solution. Organic solvents can be gelled with Carbopol as well by selecting soluble amines for the neutralization.

Several prototype gel formulations are given in Table 9 to illustrate general compositional requirements and manufacturing methods. The design of specific systems tailored to meet predetermined, demanding performance criteria, particularly for bioavailability, generally requires modification of published formulations or a totally original approach.

VI. PERFORMANCE OF TOPICAL THERAPEUTIC SYSTEMS

Topical preparations, like all other dosage forms, must be formulated, manufactured, and packaged in a manner that assures that they meet general standards of bioavailability, physical

(physical system) stability, chemical (ingredient) stability, freedom from contamination, and elegance. Like all other pharmaceuticals, these factors must remain essentially invariant over the stated shelf life of the product, and they must be reproducible from batch to batch.

A. Bioavailability

Chemical Structure, Delivery, and Clinical Response

Much has already been said concerning the chemical structural dependencies of skin permeation. However, the goal of all treatment is successful therapy, not delivery per se, and consequently the intrinsic activities of the drugs must also be taken into account when selecting compounds for dermatological and transdermal development. The pharmacological response depends on delivering sufficient drug of a given activity to the target zone. Clearly, the more potent a compound is, the less of it that needs to be delivered. Since topical delivery is difficult at best, potency often dictates which compound from within a family of drugs should be developed, for the highly potent analog, reasonably formulated, offers the best chance of obtaining clinically sufficient delivery. Conversely, marginally potent analogs, even when expertly formulated, often fail because of inadequate delivery. An excellent example of this principle is found with the narcotic analgesics. Because of its extraordinary potency, fentanyl, with a daily palliative requirement of 1 mg, and not morphine, which requires between 60 and 120 mg to alleviate pain over the course of a day, is what has made its way into transdermal use. The fact that fentanyl is also physicochemically more suited to transdermal delivery than is morphine does not controvert the axiom concerning potency.

Unlike mass transport across membranes, which relates to chemical structure in predictable ways, the potencies of drugs as seen in pharmacological, pharmacodynamic, or other tests are highly structurally specific within a class of drugs and are without commonality across classes. A drug's activity involves a complex merging of these separate structural influences, with bioavailability always one of the concerns. Such concern is minimal when a truly superficial effect is involved. For example, the most potent antiseptic, as measured in the test tube, is also likely to have nearly the highest topical potency. The intrinsic activities of compounds may be poor indicators of relative topical potentials when deep skin penetration is required, however, because the structural features benefiting the biological response are often distinct from those that favor permeation. Thus, tissue permeability can be an important and sometimes a dominant factor in the clinical structure–activity profile.

We have seen that the determinants of skin permeation are the activity (concentration) of a drug in its vehicle, the drug's distribution coefficients between the vehicle and the skin and across all phases the skin, and the drug's diffusion coefficients within the skin strata. Congeners, if comparably sized, exhibit little variance in their diffusion coefficients. However, the structural differences seen within congeneric families profoundly affect the solubility, partitioning, and in-transit binding tendencies of the family members, in addition to determining their binding with receptors. Drug delivery and resulting clinical effectiveness are captive of the former phenomena [51]. For example, the 21-ester of hydrocortisone is more hydrophobic than its parent, its ether/water partition coefficient being about 18 times that of hydrocortisone [52]. Given the strong parallels in partitioning behaviors that exist across partitioning systems, it stands to reason that similar order-of-magnitude increases exist for the acetate's stratum corneum/water and sebum/water partition coefficients. At the same time, acetylating hydrocortisone at the 21-position increases the melting point 12°C. Consequently, not only does derivatization drop the aqueous solubility precipitously, but it depresses solubility in all other solvents as well [53]. Although the increase in partition coefficient raises the permeability coefficient relative to hydrocortisone, this effect is more than offset by reduced solubility, and

far less of the acetate derivative can be delivered through the skin from respective saturated solutions [54]. However, as the aklyl chain length of the ester is methodically extended (C_3, C_4, . . . , C_7), the growing bulkiness of alkyl group increasingly interferes with crystalline packing. Consequently, melting points fall incrementally from the 224°C peak of the acetate ester to 111°C when a chain length of 7, the heptanoate ester, is reached [53]. An especially sharp drop of 69°C is experienced between chain lengths 5 and 6. Because of declining crystallinity beyond the chain length of 2, solubilities of the esters in organic solvents rise markedly. Moreover, aqueous solubilities, although methodically depressed by increasing hydrophobicity, remain many times higher than they otherwise would be. The net effect of these concerted forces is that the hexanoate and heptanoate esters of hydrocortisone are well over an order of magnitude more skin permeable than hydrocortisone when they are administered as saturated solutions [53,54].

Armed with this insight, we can examine the pharmacological ramifications of esterifying hydrocortisone. In Fig. 5 the ability of hydrocortisone esters to suppress inflammation induced by tetrahydrofurfural alcohol, which acts simultaneously as irritant and vehicle, is shown as a function of the alkyl chain length of the esters [55]. An optimum chain in effect is seen at an alkyl chain length of 6 (hexanoate), with substantially longer and shorter esters being measurably less effective. The behavior is exactly what would be predicted from partitioning and solubility considerations. That this is not an isolated behavioral pattern with corticosteroids can be seen in Fig. 6 in which vasoconstriction data of McKenzie and Atkinson for three betamethasone ester families, 21-esters, 17,21 *ortho*-esters, and 17-esters, are shown as functions of the ether/water partition coefficients of the compounds [56]. Vasoconstriction, blanching of the skin under the site of steroid application, is a proved index of a steroid's combined potency and ability to permeate through skin. Maxima are apparent in the data for the first two of these series and the indications are that the 17-ester series is also peaking. Both maxima lie between ether/water partition coefficients of 1,000 and 10,000 [52] as, interestingly and probably significantly, does the optimum ether/water partition coefficient of the hydrocortisone esters. The differing shapes and heights of the curves are not readily quantitatively explained, but reflect differences in intrinsic vasomotor activities of each ester type. The coincidence of the maxima on the partitioning scale, on the other hand, seemingly relates to an optimum lipophilicity for delivery.

The decline in activity at the longer chain lengths (see Fig. 6) also has a plausible explanation. Two factors are reasoned to be operative here, declining solubilities, coupled with changes in the absorption mechanism associated with stratification of the barrier. Aqueous solubilities of homologs exponentially decline as alkyl chain length is extended [57,58]. Whereas melting points are negatively affected and depressed early in the series, the crystalline structure eventually accommodates the alkyl chain, and further increases in chain length reverse the trend, reducing all solubilities [58]. Through all of this, o/w partition coefficients, which are unaffected by crystallinity, increase exponentially, which has the effect of exponentially increasing the ability of the stratum corneum and sebum phases to transport steroids relative to that of the viable tissue layer. In other words, the resistance of the stratum corneum drops precipitously without a commensurate drop in the resistance of the viable tissue layer. As a result, the latter takes control of the permeation process [10,37,59]. Once this change in mechanism is manifest, the permeation of homologs from their saturated solutions mirrors the downward trend in aqueous solubilities, with further increases in chain length (hydrophobicity) marked with exponential declines in steady-state fluxes. The homologs quickly become inactive [59]. In effect, the homologs become so insoluble in water that they are thermodynamically restrained from partitioning into the viable tissues on breaching the stratum corneum (or pore liquids). These features are in total agreement with expectations drawn from the earlier presented skin permeability model.

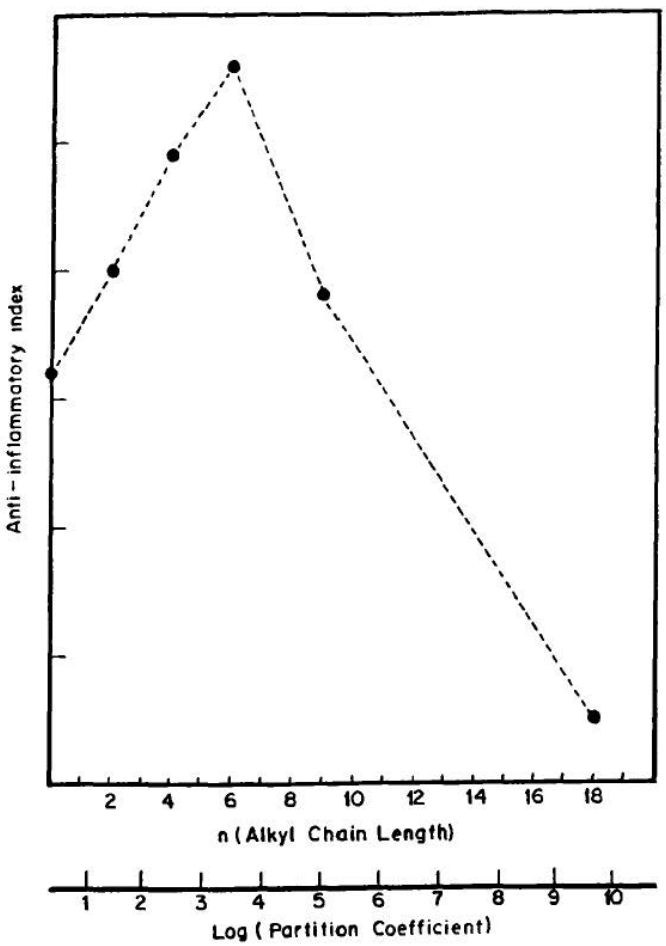

Fig. 5 Ability of hydrocortisone esters to suppress inflammation.

Clearly, the physicochemical properties of a drug are a decisive factor in its overall activity. When possible, molecular structures should be optimized to obtain the best clinical performance. Rarely does an oral drug have physicochemical features most suitable for topical or transdermal therapy, and it can take a great deal of systematic research to identify where the best balance of activity and permeability lies. Experience with the corticosteroids suggests that as much as 100-fold improvement in clinical activity may be attainable through molecular design, for today's most potent topical corticosteroids are more active than hydrocortisone by a factor at least this large.

Vehicle Properties and Percutaneous Absorption

The role solubility plays relative to maximal flux across membranes is clear from the preceding paragraphs. To kinetically reach the skin's surface, an appreciable fraction of a drug must also be in solution in the vehicle designed around it. Otherwise, diffusion of the drug through the

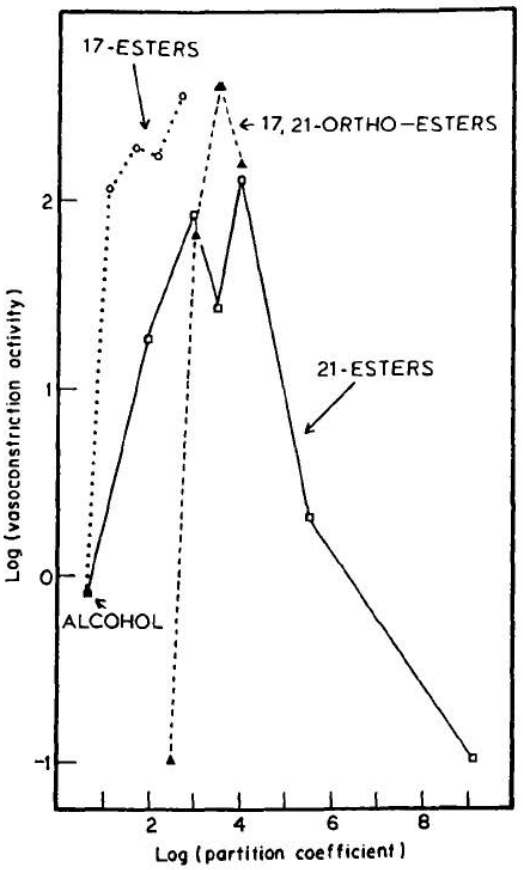

Fig. 6 Vasoconstriction data of betamethasone family.

vehicle to its interface with the skin may not completely compensate for drug lost through partitioning into the skin, kinetically dropping the drug's activity within this critical juncture of the formulation and the skin below saturation, lowering the drug's release into the surface tissues. Taken to an extreme, low vehicle solubility sets up a situation in which drug dissolution within, and diffusion through, the vehicle becomes delivery rate-controlling [60,61]. In instances for which a drug's pharmacological activity depends on getting all the drug that is possible into the tissues, this is a problem. The outcome is similar when the drug is formulated in a highly unsaturated state in the first place. Again, it will not partition into the skin to the fullest possible extent, resulting in less than maximal bioavailability. Assuming maximal delivery is the goal, the optimum between these extremes is achieved by adjusting the solvency of the vehicle so that all or most all the drug is in solution, but at the same time, the vehicle is saturated or close thereto. This has the effect of balancing the kinetic and thermodynamic factors. It is for this reason that solvents such as propylene glycol are added to topical formulations. Slowly evaporating propylene glycol provides a chemical environment in which

drugs dissolve or remain dissolved, facilitating delivery. Therefore, one frequently finds propylene glycol (from 5 to 15%) in topical corticosteroid creams and other formulations.

These principles, which have been clinically validated, establish the critical role the vehicle plays in a drug's activity. Although pharmacists do not have the wherewithal to actually test products at the dispensing counter, nevertheless, they should be aware of these principles to select and dispense products from manufacturers who can demonstrate that such formulation factors have been given due consideration. These delivery dependencies also stand to caution the pharmacist. Extemporaneous mixing of commercial products, for example, one containing a steroid and another an antibiotic, and the diluting of products with homemade vehicle are suspect practices, because the compositional changes associated with such blending are likely to adversely affect the delivery attributes of otherwise carefully designed systems [62].

There is another way vehicles can influence percutaneous absorption, which is by altering the physicochemical properties of the stratum corneum. In the main, modification of the barrier results in increased skin permeability, but a buttressing effect is also achievable with substances having the capacity to solidify the horny structure. To repeat a point, simply hydrating the stratum corneum promotes absorption. This may be accomplished by covering the skin with a water-impermeable bandage or other wrapping (an occlusive dressing). The blockage of evaporative water loss leads to hydration of the stratum corneum, softening it and increasing the diffusive mobilities of chemicals through it. The occlusive covering also prevents evaporation of volatile vehicle components, compositionally stabilizing a spread film, maintaining its solvency for the drug. It is estimated that occlusive hydration increases percutaneous absorption from five- to tenfold, enlargements that are often clinically significant [63]. The technique has been used with corticosteroids in refractory dermatoses, such as psoriasis.

The following interesting phenomena associated with the occlusion of corticosteroids are enlightening. When applied under an occlusive dressing corticosteroids induce vasoconstriction at lower concentrations than when applied in the open. When the dressing is removed, vasoconstriction subsides in a few hours. However, as many as several days later blanching can sometimes be restored simply by rewrapping the area of application [64]. This suggests that steroid molecules somehow bottled up in the stratum corneum are released when occlusion is reestablished. It appears that, as the stratum corneum dehydrates and returns to its normal state, substances such as the corticosteroids that may be present are entrapped within one of its physical domains, freezing them in place until either the stratum corneum is sloughed or until occlusive hydration is reinstated. The phenomenon is referred to as the skin's *reservoir effect.* The application of drugs dissolved in volatile solvents, such as actone and ethanol, also creates reservoirs in the stratum corneum, for as the solvents evaporate, the concentrating drug is driven into the skin's surface. Certain solvents also momentarily increase the solvency of the stratum corneum [65].

A few water-miscible organic solvents are taken up by the stratum corneum in amounts that soften its liquid crystalline, lipoidal domain [65], particularly when applied in concentrated form. If used very liberally (under laboratory conditions), these so-called skin penetration enhancers even elute interstitital lipids and denature keratin [66,67]. Under these admittedly artificial conditions, the increases in percutaneous absorption resulting from their actions can be dramatic. Dimethyl sulfoxide (DMSO), dimethylacetamide (DMA), and diethyltoluamide (DEET) are key examples. Dimethyl sulfoxide has long been touted as a skin penetration enhancer. Experimental studies indicate that it reversibly denatures keratin, opening up the protein matrix, facilitating permeation [66,67]. It also extracts lipids from the skin when applied liberally. Even when used sparingly, neat DMSO is imbibed to a degree by the stratum corneum, increasing the ability of the tissue to dissolve substances of all kinds [68]. This favors the absorption of drugs by allowing more drug to dissolve in the tissue, steepening diffusion

gradients that can be expressed across the tissue. Moreover, a crossflow of DMSO (inward) and water (outward) is set up when concentrated DMSO is placed over the skin, which delaminates the stratum corneum, apparently with a pooling of solvent between the separated layers. Of all the possible actions of DMSO, the latter two seem to be the most important because extraction of skin lipids and denaturation of keratin require far more DMSO than found in a topical application of ordinary thickness (20–30 μm). These collective factors, in the extreme, effectively chemically remove the stratum corneum as a contributing part of the skin barrier [33]. In reality, however, the limited amounts of enhancer actually applied limit enhancement. Moreover, much of the enhancement capacity is lost if the solvents are in any way diluted. Thus, the use of neat organic solvents as skin penetration enhancers is only a sometimes practice.

It has long been known that certain surfactants (e.g., sodium lauryl sulfate) are skin irritants, even when in relatively diluted states, in part because they impair the barrier function of the stratum corneum, facilitating their own absorption. Concern over irritation precludes serious consideration of agents such as these as enhancers. However, certain weaker amphiphilic substances (e.g., methyl oleate, glyceryl monolaurate, propylene glycol monolaurate), some of which have long been used as ingredients in cosmetics if not therapeutic systems, are showing they have an unrealized potential as enhancers. Of special importance, surface-active (amphiphilic) substances such as these are effective in the small amounts that can actually be applied to skin in spread films. Amphiphilic molecules penetrate into and blend with the stratum corneum's own lipids, which themselves are polar, amphiphilic substances. Thermoanalytical and spectroscopic evidence indicates that, in doing so, they relax the ordered structure of the stratum corneum's natural lipids, facilitating diffusion through existing channels and perhaps freeing up new channels [69–71]. Moreover, the reduction in liquid crystallinity invariably increases the capacity of the stratum corneum to dissolve substances, further magnifying the effect. It appears that relatively short alkyl chains (C_{10}, C_{12}) and relatively weak polar end groups favor enhancement.

These emerging structural requirements of enhancement have launched a quest for new, even more powerful enhancers. Several potent amphiphiles have surfaced from this pursuit which, at their worst, are only mildly tissue provocative, key examples being *N*-dodecylazacycloheptan-2-one (Azone) and methyl decyl sulfoxide. Each of these example compounds contains a short alkyl chain (Azone = C_{12}; decyl methyl sulfoxide = C_{10}) attached to a highly water-interactive but nonionic head group. Neither compound is at all water-soluble of itself, indicating that neither has the amphiphilic balance to form its own micelles. Of the two compounds, Azone has been the most scrutinized. It promotes the absorption of polar solutes at surprisingly low percentage concentrations. Its effects on animal skins have been especially profound; up to several hundred-fold improvements in the in vitro permeation rates of highly polar cyclic nucleosides through hairless mouse skin have been reported [72], for example. However, Azone does not appear to be comparably effective on human skin, but those actions it has are effected at low concentrations [73]. As with any agent of this kind, its actions are dependent on formulation and how this affects the thermodynamic activity of the enhancer in the delivery system. Concern over toxicity and the availability of alternative substances with established safety pedigrees have become impediments to the introduction of enhancers having new, totally unfamiliar chemical structures.

The effects of skin penetration enhancers on the stratum corneum may or may not be lasting, depending on the degree of chemical alteration of the stratum corneum that is experienced. Irreversibility is a perceived problem to the extent that the skin is left vulnerable to the absorption of other chemicals that come in contact with the conditioned area for as long as the area remains highly permeable. The fear is that such vulnerability will stay high until the

greater part of the stratum corneum is mitotically renewed, which minimally takes several whole days. Moreover, the enhancing solvents are themselves absorbed to some degree, another source of toxicological concern. DMSO is known to increase intraocular pressure; DMA has been associated with liver damage; Azone may irritate, but its real liability is that its chemical structure is totally novel and without toxicological precedent. Although worry over toxicity may be out of proportion to the actual degrees of exposure attending the ordinary circumstances of clinical use of dermatological products, nevertheless, concern is warranted, given the occasional use of products over expansive areas. Consequently, compounds of proved safety, and their structural kind, are factoring out as the enhancers of the 1990s.

Transdermal Delivery: Attributes of Transdermal Delivery Systems

We are learning more and more that the conditions of use of topical delivery systems has profound influence on their performance. Transdermal systems, specifically the adhesive patches that are used to treat systemic disease, and dermatologicals, are subject to very different operating environments and conditions. Transdermal delivery is aimed at achieving systematically active levels of a drug. A level of percutaneous absorption that leads to appreciable systemic drug accumulation is absolutely essential. Ideally, one would like to avoid any buildup of a drug within the local tissues, but, nevertheless, buildup is unavoidable, for the drug is driven through a relatively small diffusional area of the skin defined by the contact area (absorption *window*) of the application. Consequently, high accumulations of drug in the viable tissues underlying the patch are preordained by the nature of the delivery process. Irritation and sensitization can be associated with such high levels; therefore, careful testing is done to rule out these complications before a transdermal delivery system gets far along in development.

Table 10 outlines general expectations associated with transdermal delivery. The water-impermeable backing materials of present, and we can presume, most future, transdermal systems cause them to operate occlusively. There is good reason for this. Foremost is again that occlusion facilitates drug delivery. In laboratories where these systems are designed, it has been learned that occlusion is often essential to achieving adequate rates of delivery. Furthermore, transdermal drugs, such as nitroglycerin and nicotine, are themselves relatively volatile compounds. Although they can be packaged in a fashion that prevents drug loss, a backing material that is substantially impermeable is also needed to prevent these compounds from evaporating

Table 10 Listing of the Norms of Operation of Transdermal Patches

Occluded applications
Composition relatively invariant in use
System size (area) predetermined
Specific site prescribed for application
Application technique highly reproducible
Delivery is sustained
Generally operate at unit drug activity, at least operate at steady activity
Delivery is zero-order
Serum levels related to product efficacy
Bioequivalency based on pharmacokinetic (blood level) endpoint
Unavoidable local tissue levels consequential only to system toxicity
Individual dose interruptable
Whole system removed when spent
Delivery efficiency is low (only a fraction of drug content is delivered)

off into space after placing patches containing them on the skin. Impermeable polymer or foil backings also block the diffusive transport of body water to the atmosphere by way of the patch. Insensible perspiration at the site of the patch is thus held in check, but not without creating a substantially moist environment at the interface the patch has with the skin. Consequently, if given enough time, organisms already in the skin can colonize within this interface.

Other than for possibly the insensible perspiration they absorb, transdermal patches tend to operate as thermodynamically static systems, meaning as compositionally fixed systems, from the moment they are applied until their removal. Marketed ethanol-driven estradiol and fentanyl patches are exceptions here, as these meter out ethanol and drive it into the stratum corneum to propel the absorption process. Compositional steadfastness is still the rule, however, and it is this feature that bestows the zero-order delivery attribute on the ordinary transdermal patch. Drug is present within the patches in reservoir amounts, irrespective of whether or not the reservoir compartment is easily distinguished, for enough drug has to be present to sustain delivery over the full course of patch wear, no matter if 1 day, 3 or 4 days, or 7 days is the time objective.

In some prototypes (e.g., the nitroglycerin transdermal systems), huge excesses of drug are placed in the patch to assure that the drug's activity remains essentially level during the patch's wear. Only a small fraction of the drug, well under 50% of the patch's total content, is actually delivered during the prescribed time the patch is to be worn. In situations in which the drug is prohibitively expensive or prone to abuse (e.g., fentanyl), efficiencies have to be raised to the maximum that are physically achievable, and the fractional delivery of formulated drug has been made to approach or exceed 50%. Part of the inherent stability of the delivery environment of patches results because their main materials of construction are polymers, fabricating laminates, and adhesives, all of which tend to be chemically robust. Solubilizing solvents (e.g., ethanol) and skin penetration enhancers (e.g., propylene glycol monolaurate) may also be present, and their absorption into the skin may change compositions, but even here, the processes are carefully orchestrated to gain a stable, long-term delivery environment.

A transdermal patch is a self-contained system that is applied as it is packaged, with its only manipulation being removal of the release liner to expose and ready its adhesive surface. The size of a patch, meaning its area of contact with the skin, is determined even before it is made. All of this area, or only an inner portion of it, may actually be involved in drug delivery, but, either way, the area is fixed. Since absorption is proportional to area, to meet the differing drug requirements of individual patients, patches of different sizes are generally made available. The application site is also a constant of therapy in that a specific site or sites are recommended for use (not always for scientifically supportable reasons, e.g., nitroglycerin patches are worn over the heart). Users tend to follow such dictates. Beyond this, the manner of application is also highly reproducible. Thus, there is as tight a control over absorption area and application site variables here as can be found in all of therapy. The only variability not customarily controlled for is that associated with the skin's permeability itself, but even here some systems have been made to operate with high-delivery precision by incorporating a rate-controlling membrane into them. Altogether the manner of use of the systems is highly reproduced from one application to the next.

Measures of function of transdermal systems distinguish them among the systems we use topically. Since systemic actions are sought, blood levels of the drug in question must reach and remain within therapeutic bounds. More often than not the requisite blood level is known from a drug's use by other routes of administration. Thus, a clear systemic target level usually exists, and an absolute rate of delivery commensurate with reaching this is a built-in feature of the patch. The requisite delivery rate can be estimated in several ways, even before any attempt is made to design a transdermal system. For instance, once an upper size limit is set

for the patch, the total daily oral requirement of the drug can be used to calculate the minimal delivery rate in milligrams per square centimeter per hour. This is done after making an appropriate downward adjustment in the transdermal dose to account for oral drug losses attributable to first-pass metabolism. Alternatively, the rate can be estimated from an established blood level and a known rate of systemic clearance (as the product of these). Comparing performances of transdermal delivery systems is also a straightforward matter. Bioequivalency of different systems built around a specific drug are easily measured in terms of the blood levels they produce. And if therapy is not going well, one can bring delivery to a reasonably abrupt halt by simply removing a patch.

Topical Delivery: Attributes of Topical Delivery Systems

Topical delivery systems fill an important niche in therapy. Although not an efficient means of delivery in the sense that as little as 1% and usually no more that 15% of the drug in a dermatological application is systemically absorbed (systemically recoverable), nevertheless, topical delivery allows one to achieve total tissue levels of a drug far in excess of those achievable by the drug's systemic administration. At the same time, systemic toxicities of the drug are rarely encountered with topical administration, with the exceptions occurring when dermatological formulations are used liberally over extensive areas. Because only small amounts of a drug are ordinarily applied topically, in most instances the systemic levels achieved are so limited that one has trouble even measuring them. Thus, albeit imprecise, topical therapy actually represents a brute force form of drug targeting and has been discussed in this context. The principal drug delivery systems for this purpose are ointments, creams, and gels, with miscellaneous other powder, liquid, and semisolid vehicles sometimes being employed. The norms of topical delivery, which are in striking contrast with the norms of transdermal delivery, are outlined in Table 11.

We tend to think of them as being much the same, but the functioning of semisolid dermatologicals stands in stark contrast with that of transdermal delivery systems. To begin with, most topical applications are left open to the atmosphere. Amounts applied per unit area depend on the individual making the application. Of singular importance relative to system function, extraordinary physicochemical changes accompany the evaporative concentration of these formulations, possibly including the precipitation of the drug or other substances that were com-

Table 11 Listing of the Norms of Operation of Dermatological Formulations

Open application
Experience profound compositional shifts in use
May experience phases changes in use
Site is the disease's location
Operate at variable drug activity
Highly nonstationary state kinetics
Application technique and amount are highly individualized
Applications short-acting
Local tissue levels tied to efficacy
Used on diseased, damaged skin
No easy bioequivalency endpoint
Systemic absorption absolutely undesirable, but some unavoidable
Therapy interruptable by washing off application
System removal inadvertent—*wear and tear*
Delivery efficiency is low (only a small fraction of drug is delivered)

fortably in solution at the moment of their application. Evaporative concentration can also upset the oil-to-water balance of emulsions, destabilizing them, and at times, causing them to break or invert. In a matter of hours, if not just minutes, a surface film or dry residue having a totally different delivery faculty than the bulk formulation may be all that is left of the application. Such precipitous changes, if out of control, can bring drug delivery to an abrupt halt.

The amounts of ointments and creams people apply are highly individualized. So are the techniques of application. Some patients use a vigorous inunction, whereas others just work the application until it is more or less uniform over the desired site and stop there. Although pharmacokinetic assessments of a system's delivery attributes are ordinarily done using normal skin (in vitro) or on healthy volunteers (in vivo), the site of its clinical deployment is usually anything but normal. Rather, it is determined by the skin condition to be treated. Clearly, the manufacturer is without control over how a disease is expressed on a particular patient. For many diseases, disease manifestation can be anywhere on the body. Moreover, from individual to individual it varies in intensity and vastness. Thus, more area may be involved in one person than in another, and the barrier function of the skin may be more or less intact in any instance. The net result of this creates a set of imponderables relative to delivery, efficacy, and safety.

The removal of the dermatological applications is rarely deliberate. Rather, some substance is usually transferred to clothing and such; some is absorbed; some evaporates; and some is inadvertently removed by bathing or other means. Applications can be deliberately washed from the skin if one wishes to terminate therapy. Partly because of their temporal inhabitancy, local applications tend to be short-acting relative to transdermal delivery systems. Other factors here are the finite doses that are actually administered and the oftentimes rapid evaporative concentration of such films to compositions that cease supporting dissolution of the drug and its diffusion to the skin's surface. Consider that the application of a topical product to the skin in a representative, 20-μm–thick layer places only 20 μg of drug over each square centimeter of skin when the drug is formulated at the relatively high concentration of 1%. Roughly 10 mg of stratum corneum covers each square centimeter of skin, enough for 20 μg of drug to effectively get lost in. Consequently, only a fraction of the drug that does enter the skin actually reaches the live tissues. Such finite doses do not sustain delivery and, thus, delivery wanes after several hours irrespective of the wearability of the application and of processes attending its evaporative shrinkage. Since all these attending processes defy quantification, there is precious little existing information to guide one concerning the fitting regimen of application for most topical dosage forms. Rather, dosing regimens have evolved historically from collective clinical experience. All in all, topical therapy is an extraordinarily complex operation.

Compositional changes following the application of certain topical systems are unavoidable. Many o/w creams contain as much as 80–85% external phase, usually primarily water. Lotions and gels also contain volatile constituents in large proportion. All rapidly evaporate down after their application and, consequently, the drug delivery system is the formed, concentrated film that develops on the skin and not the medium as packaged in the tube, jar, or bottle. Ingredients should be chosen to assure that compositional changes, as invariably occur, interfere as little as possible with delivery and therapy. The rate at which the volatile components evaporate to form the equilibrium film can itself be a factor in bioavailability [74]. It has been reported, for instance, that a thinly applied corticosteroid preparation produced greater vasoconstriction than did thicker applications of the same material [75]. Although the total amounts of drug per unit area were greater with the thick films, responses were less in their case because either evaporative concentration of the steroid proceeded more slowly or dilution by insensible perspiration was more rapid. Even without knowing the mechanistic details, we can conclude from this that less steroid was driven into the skin from the thick applications in the course of the test. It

has also be demonstrated that vasoconstriction is more pronounced at low concentrations when steroid is applied in volatile ethanol than when applied in propylene glycol [55]. Even though differences in solvency play their role here, it is also clear that the rapid evaporation of solvents such as ethanol drives drug into the skin. Such observations emphasize the importance of distinguishing between the system as packaged and the transitional system following application. Unfortunately, this distinction is not always made, and much topical delivery research aimed at assessing the relative abilities formulations have to deliver drug has been performed by placing extraordinarily thick layers of formulation over the skin. Such thick applications do not even remotely simulate the clinical release situation, especially when it comes to creams and gels. This area of drug delivery is in need of much research.

Knowledgeable formulators can use the tendency of creams, gels, and other systems to evaporatively concentrate to advantage. Solvents are chosen and blended so that the drug remains soluble in the formed film long after application is made. This can be accomplished by replacing a fraction of the water or other highly volatile solvent found in these systems with solvents of far lower volatility; and, as pointed out previously, propylene glycol is found in many topical corticosteroid creams and lotions just for this reason.

In summary, the way a topical drug is formulated has a great deal to do with its clinical effectiveness, a nonsurprising conclusion given what is known about the relations between bioavailability and formulation for other modes of administration. Yet, in the area of topical drug performance, antiquated concepts and approaches to system design linger on. In the days when topical bioavailability was little understood and, therefore, ignored, formulators concentrated on vehicle elegance and stability. Attempts were made to design vehicles compatible with all types of drugs, so-called universal vehicles. Universal vehicles are still discussed in many standard texts. Today's technology and science clearly indicate that the universal vehicle is akin to a unicorn: beautiful, but totally mythical. In the real world, each system must be designed around the drug it contains to optimize the clinical potential of the active ingredient. The duration of action will depend on how long the drugs remains appreciably in solution within its spread film.

B. Aspects of Physical and Chemical Stability

Concern for that physical and chemical integrity of topical systems is no different from that for other dosage forms. However, there are some unique and germane dimensions to stability associated with semisolid systems. A short list of some of the factors to be evaluated for semisolids is given in Table 12. All factors must be acceptable initially (within prescribed specifications), and all must remain so over the stated lifetime for the product (the product's *shelf life*).

The chemical integrities of drug, preservatives, and other key adjuvants must be assessed as a function of time to establish a product's useful shelf life from the chemical standpoint. Semisolid systems provide us with two special problems here. First, semisolids are chemically complex, to the point that just separating drug and adjuvants from all other components is an analyst's nightmare. Many components interfere with standard assays and, therefore, difficult separations are the rule before anything can be analyzed. Also, since semisolids undergo phase changes on heating, one cannot use high-temperature kinetics for stability prediction. Thus stability has to be evaluated at the storage temperature of the formulation, and this takes a long time. Under these circumstances, problematic stability may not be evident until studies have been in progress for a year or more. Be this as it may, stability details are worked out in the laboratories of industry, the pharmacist ordinarily accepting projected shelf lives as fact. Some qualitative indicators of chemical instability that the pharmacist might

Table 12 Factors for Evaluation of Semisolids

Stability of the active ingredient(s)
Stability of the adjuvants
Visual appearance
Color
Odor (development of pungent odor or loss of fragrance)
Viscosity, extrudability
Loss of water and other volatile vehicle components
Phase distribution (homogeneity or phase separation, bleeding)
Particle size distribution of dispersed phases
pH
Texture, feel upon application (stiffness, grittiness, greasiness, tackiness)
Particulate contamination
Microbial contamination and sterility (in the unopened container and under conditions of use)
Release and bioavailability

look for are the development of color (or a change in color or its intensity) and the development of an off odor. Often products yellow or brown with age as the result of oxidative reactions occurring in the base. Discolorations of this kind are commonly seen when natural fats and oils (e.g., lanolins) are used to build the vehicle. Extensive oxidation of natural fatty materials (rancidification) is accompanied by development of a disagreeable odor. One may also notice phase and texture changes in a suspect product. Pharmacists should take note of the appearances of the topical products they dispense, removing all those from circulation that exhibit color changes or become fetid. Changes in product pH also indicate chemical decompositions, most probably of a hydrolytic nature, and if somehow detected are reason to return a product.

Time-variable rheological behavior of a semisolid may also signal physical or chemical change. However, measures such as spreadability and feel on application are probably unreliable indicators of a changing rheology and more exacting measurements are necessary. A pharmacist does not ordinarily have the tools at hand to make accurate rheological assessments, but the equipment to do so is generally available and used within the development laboratories of the industry. One may find there exquisitely sensitive plate and cone research viscometers which, in principle, precisely quantify viscosity, or simply utilitarian rheometers. The latter include extrusion rheometers, which measure the force it takes to extrude a semisolid through a narrow orifice; penetrometers, which characterize viscosity in terms of the penetration of a weighted cone into a semisolid; and Brookfield viscometers, with spindle and helipath attachments, which measure the force it takes to drive a spindle helically through a semisolid. As used with semisolids, the utilitarian rheometers provide only relative, although quite useful, measures of viscosity. Increases (or decreases) in viscosity by any of these measuring tools indicate changes in the structural elements of the formulation. The gradual transformations in semisolid structure that take place are more often than not impermanent, in which event, the systems are restored to their initial condition simply by mixing them. Substantial irreversible rheological changes are a sign of poor physical stability.

Changes in the natures of individual phases of or phase separation within a formulation are reasons to discontinue use of a product. Phase separation may result from emulsion breakage, clearly a critical instability. More often, it appears more subtly as *bleeding*, the formation of visible droplets of an emulsion's internal phase in the continuum of the semisolid. This problem

is the result of slow rearrangement and contraction of internal structure. Eventually, here and there, globules of what is often clear liquid internal phase are squeezed out of the matrix. Warm storage temperatures can induce or accelerate such structural crenulation; thus, storage of dermatologicals in a cool place is prudent. The main concern with a system that has undergone such separation is that a patient will not be applying a medium of uniform composition. Because of unequal distribution between phases (internal partitioning), one phase will invariably have a high concentration of the drug relative to the other. Therefore, since semisolid emulsions, unlike liquid emulsions, cannot be returned to an even distribution by shaking, formulations exhibiting separation are functionally suspect and should be removed from circulation.

Pharmacists should also take a dim view of changes in the particle size, size distribution, or particulate nature of semisolid suspensions. They are the consequence of crystal growth, changes in crystalline habit, or the reversion of the crystalline materials to a more stable polymorphic form. Any crystalline alteration can lead to a pronounced reduction in the drug delivery capabilities and therapeutic usefulness of a formulation. Thus, products exhibiting such changes are seriously physically unstable and unusable.

A more commonly encountered change in formulations is the evaporative loss of water or other volatile phases from a preparation while it is in storage. This can occur as the result of inappropriate packaging or a flaw made in packaging. Some plastic collapsible tubes allow diffusive loss of volatile substances through the container walls. One will find this phenomenon occasionally in cosmetics, which are hurried to the market place without adequate stability assessment, but rarely in ethical pharmaceuticals, which are time-tested. However, a bad seal may occur in any tube or jar, irrespective of its contents, with eventual loss of volatile ingredients around the cap or through the crimp. Such evaporative losses cause a formulation to stiffen and become puffy, and its application characteristics change noticeably. There is corresponding weight loss. Under this influence the contents of a formulation may shrink and pull away from the container wall. These phenomena are most likely to be seen in creams and gels owing the high fractions of volatile components that characterize them. Problems here are exacerbated when products are stored in warm locations.

Gross phase changes are detectable by eye on close inspection of products. The package may get in the way of such analysis, but if a product is truly suspect, it should be closely examined by opening and inspecting the full contents of the container. A jar can be opened and its contents probed with a spatula without wrecking the container. Close inspection of the contents of a tube requires destruction of the package, however. The easy way to do this is to scissor off the seal along the bottom of the tube and then make a perpendicular cut up the length of the tube to the edge of the platform to which the cap is anchored. Careful further trimming a quarter of the way around the platform in each direction creates left and right panels that can be pealed back with tweezers to expose the tube's contents. Textural changes such as graininess, bleeding, and other phase irregularities are easily seen on the unfolded, flat surface. Normally it takes a microscope to reveal changes in crystalline size, shape, or distribution, but palpable grit is a sure sign a problem of the kind exists. Weight loss of a product, which is easily checked at the prescription counter, clearly indicates the loss of volatile ingredients (the weight of a suspect tube can be directly compared with the weight of a fresh tube). On the rare occasions when deteriorations such as these are noted by the pharmacist in the course of handling products, or are reported to the pharmacist by knowledgeable patients, the suspect packages should be removed from circulation, and the manufacturer informed of the action. If a problem seems general, rather than isolated (i.e., to a single bad package) the FDA should be notified as well to best safeguard the public. This agency will determine if a product has gone bad and general recall is warranted.

C. Freedom from Contamination

Particulates

Numerous topical preparations contain finely dispersed solids. Pastes, for example, contain as much or more than 50% solids dispersed in an ointment medium. Powders themselves are used topically. Many dermatological liquids and semisolids contain suspended matter. However present, the particles should be impalpable (i.e., incapable of being individually perceived by touch) so that the formulations do not feel gritty. The palpability of a particle is a function of its hardness, shape, and size. The pharmacist can manipulate only the latter; thus, it is important to prepare or use finely subdivided solids when making topical dosage forms. Individual particles larger than 50 μm in their longest dimension can be individually perceived by touch. The surface of the eye is substantially more sensitive, and a 10-μm particle can be distinguished here. Clearly, the presence of hard, palpable particulates in semisolids makes them abrasive, particularly when applied to disease- or damage-sensitized skin. Severe eye irritation is possible if ophthalmic ointments contain them. One particularly troublesome source of particulate contamination is flashings (tiny metals slivers and shavings) left over from the production of tin and aluminum collapsible tubes. These often adhere electrostatically and tenaciously to tubing walls following cutting of the containers down to a particular size. Some escape removal in washing and rinsing done to cleanse the empty containers. Consequently, a jet of exceedingly high-velocity air is blown into the open end of tubes just before their filling to remove all particulates. If this precaution is not taken, tiny metal slivers may be packaged with the product, posing the threat that they will become dislodged and instilled into the eye while the product is in use. For reasons as this, the *United States Pharmacopeia/National Formulary* (*USP/NF*) has a particulate test for ophthalmic ointments. In this test the ointments are liquefied in a petri dish at high temperature, 85°C for 2 hr, and then solidified by cooling. Particles that have settled to the bottom of the shallow glass container are counted by microscopic scanning at 30-times magnification. The requirements are met if the total number of particles 50 μm or larger in any dimension does not exceed 50 in the ten tubes tested and if not more than 8 particles are found in a single tube. Products that are put into the distribution channels have to meet this test. Nevertheless, the pharmacist should be on the lookout for particulate problems associated with commercial products. The pharmacist must also take measures to ensure that extemporaneously compounded formulations are free of particulates. Particular attention must be paid to the cleaning of collapsible tubes and other package parts before their use.

Microbial Specifications and Sterility

As of the *USP XIX*, it is legally required that ophthalmic ointments be prepared and dispensed as sterile products (until opened for use). Presently, in the United States, nonophthalmic topical preparations do not need to be sterile, although they cannot contain pathogens and must have low microbial counts. The reasons ophthalmic sterility requirements were broadened to cover ointments are enlightening. In the mid-1960s there was an outbreak of extremely serious pseudomona eye infections in the Scandinavian block of countries, in some instances with loss of sight. The source of the contamination was traced to antibiotic-containing ophthalmic ointments made by a regional manufacturer known for its high standards of manufacturing and quality control [76]. Pathogenic pseudomonads were found in both the products and in the manufacturing facilities where the ointments were prepared. It was widely believed up until this time that pathogens could not and would not survive and grow in ointments and similar media. The presence of antibiotics in the preparations could only have added to the false sense of security this company had. This incident sent shock waves throughout the pharmaceutical world and

spawned revisions in all world compendia. In the United States, ophthalmic ointments have to be sterile when dispensed. In Europe dermatological products that are to be used over broken skin also have to be sterile.

The foregoing incident has special meaning to the dispensing pharmacist. Unopened ophthalmic ointments should be dispensed for each condition and should be given very short datings. Patients should be advised to discard unused quantities of old preparations and to return for fresh supplies if and when chronic symptoms reappear. Similar advice and precautions are good practice with dermatologicals such as ointments that do not ordinarily contain microbial preservatives. Lotions, creams, and topical solutions that contain preservatives tend to remain pathogen-free after their packages have been opened, providing an extra measure of safety.

Preservatives have an important purpose in topical medications. Systems containing them tend to remain aseptic. Even if a few organisms subsist in the presence of the preservatives, these tend to be nonvegetative. Importantly, no pathogenic forms survive to cause problems. Preservatives are necessary for systems that have an aqueous phase, for water offers the most conducive environment for microbial growth. Therefore, all emulsions and aqueous solutions and suspensions should be preserved. However, choosing a preservative is no easy task, for the physical systems tend to be compositionally complex and polyphasic, affording many possible means for specific preservatives to be inactivated. In mass-produced products, the effectiveness of the preservation system of formulations is checked by the *USP* preservative challenge test.

D. Pharmaceutical Elegance

There are a number of attributes of the topical drug systems that may be classified as cosmetic, that make patients more or less willing to use their medications (compliant). These include the ease of application, the feel of the preparation once it is on the skin, and the appearance of the applied film. Ideally, the application should be undetectable to the eye and neither tacky nor greasy. Certain items, such as ointments and pastes, are intrinsically greasy, and suspensions of all types tend to leave an opaque, easily detectable film. Thus, the extent to which the cosmetic features can be idealized is dependent on the nature and purpose of the dosage form.

The ease of application and method of application of a formulation depend on the physicochemical attributes of the system involved. Solutions and other highly fluid systems may be swabbed on, sprayed on, or rolled on. A cotton pledget or other applicator is often necessary to obtain an even application. Soft semisolid systems, on the other hand, may be spread evenly and massaged into the skin with the fingers, a procedure technically referred to as inunction. The spreadability is a rheological quality related to the nature and degree of internal structure of the formulation. Formulations such as pastes that are very stiff tend to be hard to apply; their application over broken or irrigated skin can be disagreeable. The stiffness of a preparation can be up-regulated or down-regulated by manipulating the amounts of structure-building components of a vehicle and, in some instances, by adjusting the phase/volume ratio of semisolid emulsions. Thus, for ointments, increased spreadability can be obtained by decreasing the ratio of the waxy components (waxes and petrolatum) to fluid vehicle components (mineral oil, fixed oils). Greasiness of such preparations goes in the opposite direction. For o/w creams, decreasing the ratio of the internal phase to the external phase tends to make the systems more fluid. Substitution of more liquid oils for some of the high-melting waxy components of creams achieves the same end.

Tackiness and greasiness are determined by physicochemical properties of the vehicle constituents that compose the formed film on the skin. A sticky film is extremely uncomfortable and, generally, considerable effort is directed to minimizing this inelegant feature. When creams are concerned, waxy ingredients, such as stearic and cetyl alcohol, produce noticeably nontacky

films. Stearic acid is the principal internal-phase component of vanishing creams, systems that are virtually undetectable visually or by touch after inunction. On the other hand, propylene glycol, which may be added to creams and gels to solubilize a drug, tends to make these systems tacky. The synthetic and natural gums used as thickening and suspending agents in gels and lotions tend to increase their tackiness and, therefore, these materials are used as sparingly as function allows.

Creams tend to be invisible on the skin. The same is true for ointments, although the oiliness of ointments causes them to glisten to an extent. Whatever opacity creams and ointments have is primarily due to the presence of insoluble solids. These often imbue applications with a powdery or even crusty appearance. Dispersed solids are usually functional, as in calamine lotion, zinc sulfide lotion, zinc oxide paste, and so on, and are an implacable feature of these preparations. However, sometimes insoluble solids are added as tints to match the color of the skin and to impart opacity. Since individual skins vary widely in hue (pigmentation) and texture, tinting to a single color and texture is generally unsuccessful.

Evaluation of the cosmetic elegance of topical preparations can be accomplished scientifically, but it is questionable whether physical experiments on system rheology and the like offer appreciable advantage over the subjective evaluations of the pharmacist, the formulator, or other experienced persons. Persons who use cosmetics are particularly adept and helpful as evaluators.

E. Skin Sensitivity: A Specific Toxicological Concern

One further problem of topical formulations associated with many ingredients, and of special concern with preservatives, is the development of skin sensitivities [77]. The skins of some individuals are particularly susceptible to an allergic conditioning to chemicals that is known as type IV contact hypersensitivity. Haptens (chemicals like urushiol found in poison ivy) are absorbed through the skin and, while in the local tissues, chemically react with local proteins. Langerhans cells, the local cells involved in immunological surveillance, identify these now denatured proteins as foreign (nonhost). The Langerhans cells then leave the dermis by way of the lymphatics and enter the draining lymph node, where they complete the sensitization process by passing the allergen message on to resident lymphocytes (antigen presentation). Once sensitized, subsequent contact with the offending chemical (hapten) leads to inflammation and skin eruption. Many of the preservatives used in pharmacy are phenols and comparably reactive substances, compounds that have a high propensity to sensitize susceptible individuals. The pharmacist should be alert to this possibility and prepared to recommend discontinuance of therapy and physician referral when allergic outbreak is evident or suspected. Moreover, the pharmacist should be ready to recommend alternative products that do not contain an allergically offending substance once it has been identified, assuming that a therapeutically suitable alternative exists.

Allergic incidents are widespread and, from an allergy standpoint, it is useful that the ingredients of dermatological medications are listed on the package or in the package insert. This allows the pharmacist to screen products for their suitability for individuals with known sensitivities. Over-the-counter medications and cosmetics also contain a qualitative listing of their ingredients. The pharmacist thus has access to critical information he or she needs to safeguard patients relative to their known hypersensitivities.

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12

Parenteral Products

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I. INTRODUCTION

The first official injection (morphine) appeared in the *British Pharmacopoeia* (*BP*) of 1867. It was not until 1898 when cocaine was added to the *BP* that sterilization was attempted. In this country, the first official injections may be found in the *National Formulary* (*NF*), published in 1926. Monographs were included for seven sterile glass-sealed ampoules. The *United States Pharmacopeia* (*USP*) published in the same year contained a chapter on sterilization, but no monographs for ampoules. The current *USP* contains monographs for over 400 injectable products [1].

Parenteral administration of drugs by intravenous (IV), intramuscular (IM), or subcutaneous (SC) routes is now an established and essential part of medical practice. Advantages for parenterally administered drugs include the following: rapid onset; predictable effect; predictable and nearly complete bioavailability; and avoidance of the gastrointestinal tract (GIT), and hence, the problems of variable absorption, drug inactivation, and GI distress. In addition, the parenteral route provides reliable drug administration in very ill or comatose patients.

The pharmaceutical industry directs considerable effort toward maximizing the usefulness and reliability of oral dosage forms in an effort to minimize the need for parenteral administration. Factors that contribute to this include certain disadvantages of the parenteral route, including the frequent pain and discomfort of injections, with all the psychological fears associated with "the needle," plus the realization that an incorrect drug or dose is often harder or impossible to counteract when it has been given parenterally (particularly intravenously), rather than orally.

In recent years, parenteral dosage forms, especially IV forms, have gained immensely in use. The reasons for this growth are many and varied, but they can be summed up as (a) new and better parenteral administration techniques; (b) new forms of nutritional therapy, such as intravenous lipids, amino acids, and trace metals; (c) the need for simultaneous administration of multiple drugs in hospitalized patients receiving IV therapy, (d) the extension of parenteral

therapy into the home; and (e) an increasing number of drugs that can be administered only by a parenteral route.

Many important drugs are available only as parenteral dosage forms. Notable among these are biotechnology drugs; insulin; several cephalosporin antibiotic products; and drugs such as heparin, protamine, and glucagon. In addition, other drugs, such as lidocaine hydrochloride and many anticancer products, are used principally as parenterals. The reasons that certain drugs are administered largely or exclusively by the parenteral route are very inefficient or unreliable absorption from the GIT, destruction or inactivation in the GIT, extensive mucosal or first-pass metabolism following oral administration, or clinical need in particular medical situations for rapid, assured high blood and tissue levels.

Along with this astounding growth in the use of parenteral medications, the hospital pharmacist has become a very knowledgeable, key individual in most hospitals, having responsibility for hospital-wide IV admixture programs, parenteral unit-dose packaging, and often central surgical supply. By choice, by expertise, and by responsibility, the pharmacist has accumulated the greatest fund of information about parenteral drugs—not only their clinical use, but also their stability, incompatibilities, methods of handling and admixture, and proper packaging. More and more, nurses and physicians are looking to the pharmacist for guidance on parenteral products.

To support the institutional pharmacist in preparing IV admixtures (which typically involves adding one or more drugs to large-volume parenteral fluids), equipment manufacturers have designed laminar flow units, electromechanical compounding units, transfer devices, and filters specifically adaptable to a variety of hospital programs.

The nurse and physician have certainly not been forgotten either. A wide spectrum of IV and IM administration devices and aids have been made available in recent years for bedside use. Many innovative practitioners have made suggestions to industry that have resulted in product or technique improvements, particularly in IV therapy. The use of parenteral products is growing at a very significant rate in nonhospital settings, such as outpatient surgical centers and homes. The reduction in costs associated with outpatient and home care therapy, coupled with advances in drugs, dosage forms, and delivery systems, has caused a major change in the administration of parenteral products [2].

II. ROUTES OF PARENTERAL ADMINISTRATION

The routes of parenteral administration of drugs are (a) subcutaneous, (b) intramuscular, and (c) intravenous; other more specialized routes are (d) intrathecal, (e) intracisternal, (f) intra-arterial, (g) intraspinal, (h) intraepidural, and (i) intradermal. The intradermal route is not typically used to achieve systemic drug effects. The similarities and differences of the routes or their definitions are highlighted in Table 1. The major routes will be discussed separately.

A. The Subcutaneous Route

Lying immediately under the skin is a layer of fat, the superficial fascia (see Fig. 1 in Chapter 8), that lends itself to safe administration of a great variety of drugs, including vaccines, insulin, scopolamine, and epinephrine. Subcutaneous (SC; also SQ or sub-Q) injections are usually administered in volumes up to 2 ml using a ½- to 1-in. 22-gauge (or smaller) needle. Care must be taken to ensure that the needle is not in a vein. This is done by lightly pulling back on the syringe plunger (aspiration) before making the injection. If the needle is inadvertently located in a vein, blood will appear in the syringe and the injection should not be made. The injection site may be massaged after injection to facilitate drug absorption. Drugs given by this

Table 1 Various Parenteral Routes of Drug Administration

Routes	Usual volume (ml)	Needle commonly used	Formulation constraints	Types of medication administered
Primary parenteral routes				
Small-volume parenterals				
Subcutaneous	2	⅝ in., 23 gauge	Need not be isotonic	Insulin, vaccines
Intramuscular	2	1½ in., 22 gauge	Can be solutions, emulsions, oils, or suspensions, isotonic preferably	Nearly all drug classes
Intravenous	50	Veinpuncture 1½ in., 22 gauge	Solutions and some emulsions	Nearly all drug classes
Large-volume parenterals	100 and larger (infusion unit)	Venoclysis 1½ in., 19 gauge	Solutions and some emulsions	Nearly all drug classes (see precautionary notes in text)
Other parenteral routes				
Intra-arterial: directly into an artery (immediate action sought in peripheral area)	2–20	20–22 gauge	Solutions and some emulsions	Radiopaque media, antineoplastics, antibiotics
Intrathecal (intraspinal; into spinal canal)	1–4	24–28 gauge	Must be isotonic	Local anesthetics, analgesics; neurolytic agents
Intraepidural (into epidural space near spinal column)	6–30	5 in., 16–18 gauge	Must be isotonic	Local anesthetics, narcotics, α_2-agonists, steroids
Intracisternal: directly into caudal region of the brain between the cerebellum and the medulla oblongata			Must be isotonic	
Intra-articular: directly into a joint, usually for a local effect there, as for steroid anti-inflammatory action in arthritis	2–20	1.5–2 in., 18–22 gauge	Must be isotonic	Morphine, local anesthetics, steroids, NSAIDs, antibiotics
Intracardial: directly into the heart when life is threatened (epinephrine stimulation in severe heart attack)	0.2–1	5 in., 22 gauge		Cardiotonic drugs, calcium
Intrapleural: directly into the pleural cavity or a lung (also used for fluid withdrawal)	2–30	2–5 in., 16–22 gauge		Local anesthetics, narcotics, chemotherapeutic agents
Diagnostic testing				
Intradermal	10	⅝ in., 26 gauge	Should be isotonic	Diagnostic agents

route will have a slower onset of action than by the IM or IV routes, and total absorption may also be less.

Sometimes dextrose or electrolyte solutions are given subcutaneously in amounts from 250 to 1000 ml. This technique, called hypodermoclysis, is used when veins are unavailable or difficult to use for further medication. Irritation of the tissue is a danger with this technique. Administration of the enzyme hyaluronidase can help by increasing absorption and decreasing tissue distention. Irritating drugs and vasoconstrictors can lead to abscesses, necrosis, or inflammation when given subcutaneously. Body sites suitable for SC administration include most portions of the arms and legs plus the abdomen. When daily or frequent administration is required, the injection site can and should be continuously changed or rotated, especially by diabetic patients self-administering insulin.

B. The Intramuscular Route

The IM route of administration is second only to the IV route in rapidity of onset of systemic action. Injections are made into the striated muscle fibers that lie beneath the subcutaneous layer. The principal sites of injection are the gluteal (buttocks), deltoid (upper arm), and vastus lateralis (lateral thigh) muscles. The usual volumes injected range from 1.0 to 3.0 ml, with volumes up to 10.0 ml sometimes being given (in divided doses) in the gluteal or thigh areas (see Table 1). Again, it is important to aspirate before injecting to ensure that the drug will not be administered intravenously. Needles used in administering IM injections range from 1 to 1½ in. and 19 to 22 gauge, the most common being 1½ in. and 22 gauge.

The major clinical problem arising from IM injections is muscle or neural damage, the injury normally resulting from faulty technique, rather than the medication.

Most injectable products can be given intramuscularly. As a result, there are numerous dosage forms available for this route of administration: solutions, oil-in-water (o/w) or water-in-oil (w/o) emulsions, suspensions (aqueous or oily base), colloidal suspensions, and reconstitutable powders. Those product forms in which the drug is not fully dissolved generally result in slower, more gradual drug absorption, a slower onset of action, and sometimes longer-lasting drug effects.

Intramuscularly administered products typically form a "depot" in the muscle mass from which the drug is slowly absorbed. The peak drug concentration is usually seen within 1–2 hr. Factors affecting the drug-release rate from an IM depot include the compactness of the depot (the less compact and more diffuse, the faster the release), the rheology of the product (affects compactness), concentration and particle size of drug in the vehicle, nature of the solvent or vehicle, volume of the injection, tonicity of the product, and physical form of the product.

C. The Intravenous Route

Intravenous medication is injected directly into a vein either to obtain an extremely rapid and predictable response or to avoid irritation of other tissues. This route of administration also provides maximum availability and assurance in delivering the drug to the site of action. However, a major danger of this route of administration is that the rapidity of absorption makes antidoting very difficult, if not impossible, in most instances. Care must also be used to avoid too rapid a drug administration by the IV route because irritation or an excessive drug concentration at the target organ (drug shock) can occur. The duration of drug activity is dependent on the initial dose and the distribution, metabolism, and excretion properties (pharmacokinetics) of the drug. For most drugs, the biological half-life is independent of the initial dose, because the elimination process is first-order. Thus, an intravenous drug with a short half-life would not

provide a sustained blood level. The usual method of administration for drugs with short half-lives is to use continuous IV drip. Intravenous injections (vein puncture) normally range from 1 to 100 ml and are given with either a 20- or 22-gauge 1½-in. needle, with an injection rate of 1 ml/10 sec for volumes up to 5 ml and 1 ml/20 sec for volumes over 5 ml. Only drugs in aqueous or hydroalcoholic solutions are to be given by the IV route.

Large proximal veins, such as those located inside the forearm, are most commonly used for IV administration. Because of the rapid dilution in the circulating blood and the general insensitivity of the venous wall to pain, the IV route may be used to administer drugs that would be too irritating or caustic to give by other routes (e.g., nitrogen mustards), provided that proper dosing procedures are employed. The risk of thrombosis is increased when extremity sites such as the wrist or ankle are used for injection sites, or when potentially irritating IV products are used, with the risk further increasing in patients with impaired circulation.

The IV infusion of large volumes of fluids (100–1000 ml) has become increasingly popular (Figs. 1 and 2). This technique, called *venoclysis*, utilizes products known as large-volume parenterals (LVPs). It is used to supply electrolytes and nutrients, to restore blood volume, to prevent tissue dehydration, and to dilute toxic materials already present in body fluids. Various parenteral drug solutions may often be conveniently added to the LVP products as they are being administered (Figs. 3 and 4), or before administration, to provide continuous and prolonged drug therapy. Such drug additions to LVP has become very common in hospitals. Combining parenteral dosage forms for administration as a unit product is known as *IV admixtures*. Pharmacists practicing such IV additive product preparation must be very knowledgeable to avoid physical and chemical incompatibilities in the modified LVP, creation of any therapeutic incompatibilities with other drugs being given parenterally or by any other route, or loss of sterility or addition of extraneous matter.

Commonly administered large-volume parenterals include such products as sodium chloride injection [USP] (0.9% saline), which replenish fluids and electrolytes, and 5% dextrose injection [USP], which provides fluid plus nutrition (calories) or various combinations of dextrose and saline. In addition, numerous other nutrient and ionic solutions are available for clinical use, the most popular of which are solutions of essential amino acids or lipid emulsions. These solutions are modified to be hypertonic, isotonic, or hypotonic to aid in maintaining both fluid, nutritional, and electrolyte balance in a particular patient according to need. Indwelling needles or catheters are required in LVP administration. Care must be taken to avoid local or systemic infections or thrombophlebitis owing to faulty injection or administration technique.

D. Other Parenteral Routes

Other more specialized parenteral routes are listed and described briefly in Table 1. The intra-arterial route involves injecting a drug directly into an artery. This technique is not simple and may require a surgical procedure to reach the artery. It is important that the artery not be missed, since serious nerve damage can occur to the nerves lying close to arteries. Doses given by this route should be minimal and given gradually, since, once injected, the drug effect cannot be neutralized. As shown in Table 1, the intra-arterial route is used to administer radiopaque contrast media for viewing an organ, such as the heart or kidney, or to perfuse an antineoplastic agent at the highest possible concentration to the target organ.

The intrathecal route is employed to administer a drug directly into the cerebrospinal fluid at any level of the cerebrospinal axis. This route is used when it is not possible to achieve sufficiently high plasma levels to accomplish adequate diffusion and penetration into the cerebrospinal fluid. This is not the same route used to achieve spinal anesthesia, for which the drug is injected within the dural membrane surrounding the spinal cord, or in extradural or

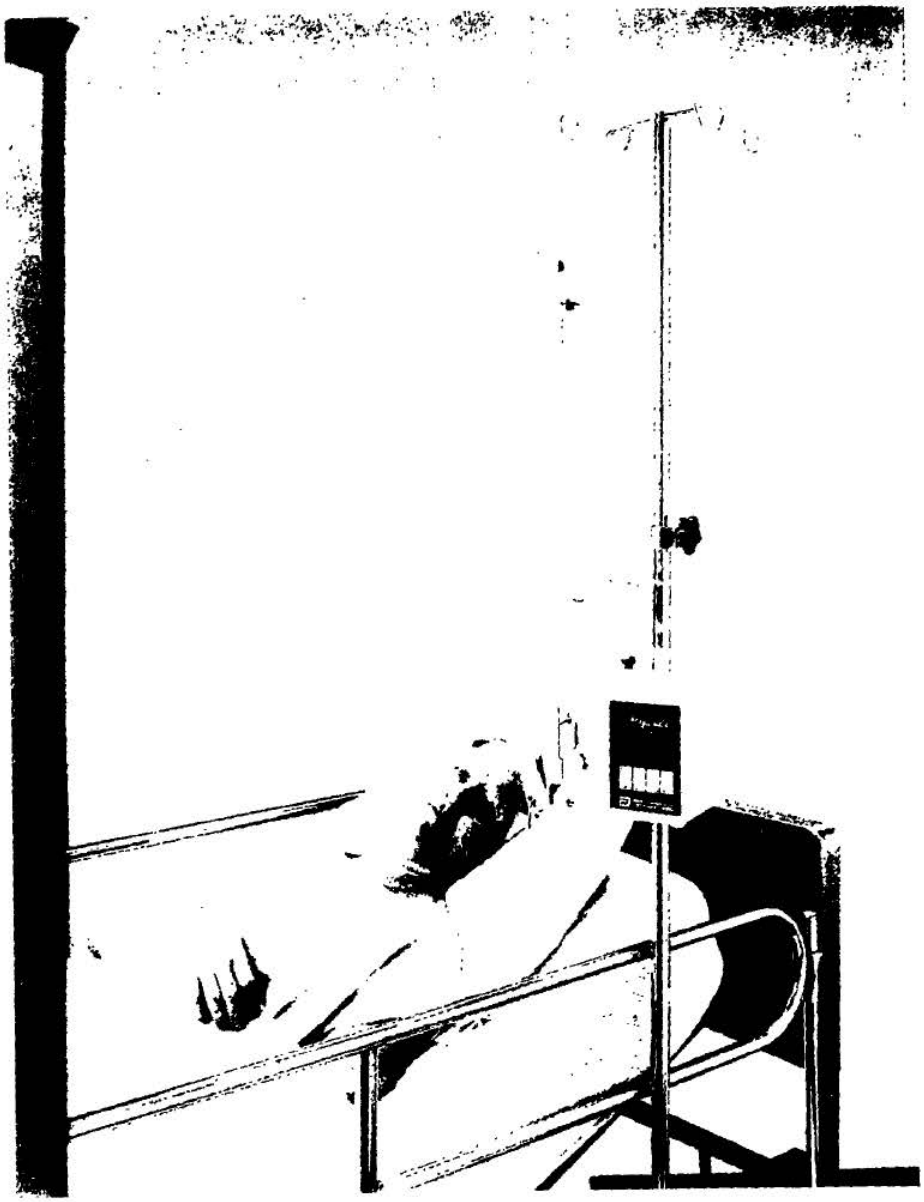

Fig. 1 Administration of an intravenous fluid by electronic flow control.

Fig. 2 Direct intravenous administration using gum rubber injection site.

epidural anesthesia (caudal or sacral anesthesia), for which the drug is deposited outside the dural membrane and within the body spinal caudal canals. Parenteral products administered by the intrathecal, intraspinal, and intracisternal routes must be especially carefully formulated, with ingredients of the highest purity because of the sensitivity of nerve tissue.

Intradermal (ID) administration involves injection into the skin layer (see Fig. 3 in Chapter 8). Examples of drugs administered by this route are allergy test materials. Since intradermal drugs are normally given for diagnostic purposes, it is important that the product per se be nonirritating. Volumes are normally given at 0.05 ml/dose and the solutions are isotonic. Intradermal medication is usually administered with a ½- or ⅝-in., 25- or 26-gauge needle, inserted at an angle nearly parallel to the skin surface. Absorption is slow and limited from this site, since the blood vessels are extremely small, although the area is highly vascular. The site should not be massaged after the injection of allergy test materials. Skin testing includes not only allergens, such as pollens or dust, but also microorganisms, as in the tuberculin or histoplasmin skin tests.

III. SPECIALIZED LARGE-VOLUME PARENTERAL AND STERILE SOLUTIONS

Large-volume parenterals designed to provide fluid (water), calories (glucose solutions), electrolytes (saline solutions), or combinations of these materials have been described. Several other specialized LVP and sterile solutions are also used in medicine and will be described

Fig. 3 Addition of intravenous medication directly to primary intravenous solution container.

here, even though two product classes (peritoneal dialysis and irrigating solutions) are not parenteral products.

A. Hyperalimentation Solutions

Parenteral hyperalimentation involves administration of large amounts of nutrients (e.g., carbohydrates, amino acids, and vitamins) to maintain a patient who is unable to take food orally, for several weeks, at caloric intake levels of 4000 cal/day or more. Earlier methods of parenteral alimentation, which involved IV administration, were not typically able to maintain patients without a weight loss and gradual deterioration in physical condition. Parenteral hyperalimentation involves continuous administration of the nutrient solution into the superior vena cava by an indwelling catheter. Available hyperalimentation solutions vary in various amino acids, vitamins, minerals, and electrolytes. The method permits administration of lifesaving or life-sustaining nutrients to comatose patients or to patients undergoing treatment for esophageal obstruction, GI diseases (including cancer), ulcerative colitis, and other disease states.

B. Peritoneal Dialysis Solutions

The sterile peritoneal dialysis solutions are infused continuously into the abdominal cavity, bathing the peritoneum (the semipermeable membrane covering the viscera of the abdominal cavity), and are then continuously withdrawn. The purpose of peritoneal dialysis is to remove toxic substances from the body, or to aid and accelerate the excretion function normal to the kidneys. The process is employed to counteract some forms of drug or chemical toxicity as

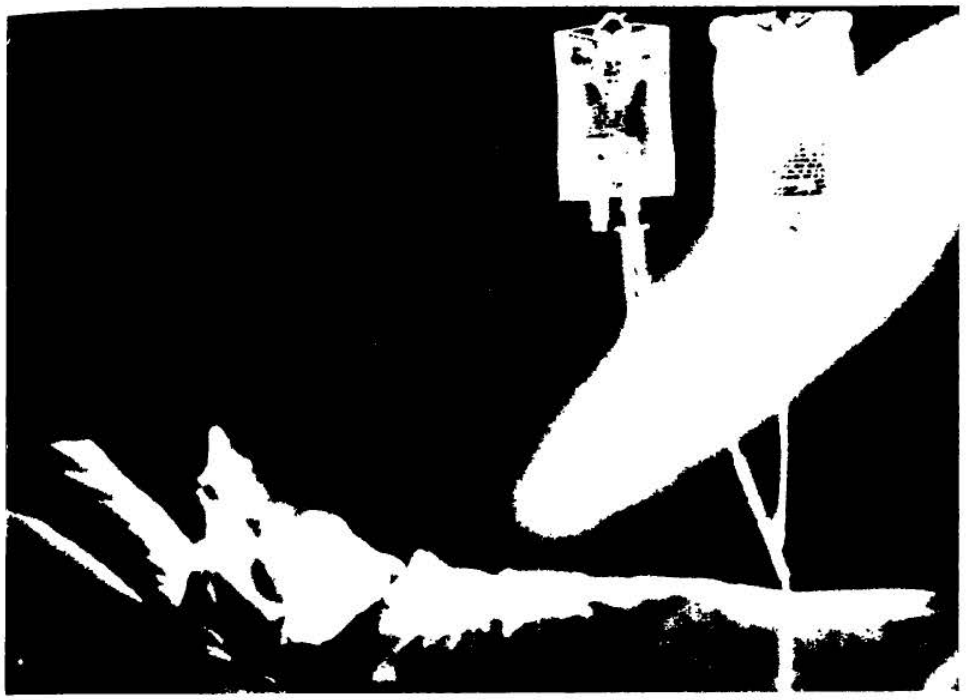

Fig. 4 "Piggybacking" of a small-volume intravenous fluid into the primary large-volume intravenous solution.

well as to treat acute renal insufficiency. Peritoneal dialysis solutions contain glucose and have an ionic content similar to normal extracellular fluid. Toxins or metabolites diffuse into the circulating dialysis fluid through the peritoneum and are removed. At the same time, excess fluid is removed from the patient if the glucose content renders the dialysis solution hyperosmotic. An antibiotic is often added to these solutions as a prophylactic measure.

C. Irrigating Solutions

Irrigating solutions are intended to irrigate, flush, and aid in cleansing body cavities and wounds. Although certain IV solutions, such as normal saline, may be used as irrigating solutions, solutions designed as irrigating solutions should not be used parenterally. Since irrigating solutions used in treatment of serious wounds infuse into the bloodstream to some degree, they must be sterile, pyrogen-free, and made and handled with the same care as parenteral solutions.

IV. PHYSICOCHEMICAL FACTORS AND COMPONENTS

Physicochemical properties of the active drug and the components used in a parenteral dosage form can significantly affect the availability of the drug substance. Other factors that influence drug availability are physiological (biological conditions and disease state of the patient), the route of administration, and the type of dosage form. Intramuscular and subcutaneous routes

of parenteral administration require drug absorption before blood or cerebrospinal fluid levels can be achieved. The rate at which the drug is absorbed has a significant influence on the concentration of the drug in the blood. With an IM suspension, drug dissolution is usually the rate-limiting step in the absorption of the drug at the injection site [3]. The absorption of the drug following IM administration is greatly influenced by the physicochemical properties of the drug.

Components that are incorporated into parenteral dosage forms may have very rigid specifications and standards. Because of these requirements, extensive analytical and toxicological testing is performed to ensure that a chemical is acceptable. Thorough toxicity testing is required of a new drug or other component not previously approved for parenteral use, and the accumulated data are evaluated. Testing may be done on the individual components as well as the final dosage forms. Given such explicit qualities as purity, safety, and lack of (or minimum) pharmacological effect required of parenteral additives, the formulator is restricted to a very few materials as excipients, preservatives, suspending agents, and surfactants. Because of the very extensive pharmacological and toxicological data required to obtain approval for any new additive, most formulators continue to depend on materials of known acceptability.

A. The Active Drug

A thorough evaluation of properties of the active drug or drugs is essential in developing a stable and safe parenteral dosage form. The physical and chemical factors that may significantly affect the development of a parenteral dosage form are discussed in Chapter 7 and by Motola and Agharkar [4]. Important properties include solubility and rate of solution. Factors that influence solubility include particle size; salt, ester, or other chemical form; solution pH; polymorphism; purity; and hydrate formulation.

Crystal Characteristics

Control of the crystallization process to obtain a consistent and uniform crystal form, habit, density, and size distribution is particularly critical for drug substances to be utilized in suspensions or powders. For example, when the crystallization of sterile ceftazidime pentahydrate was modified to significantly increase the density to reduce the volume of the fill dose, the rate of dissolution increased significantly. Many dry solid parenteral products, such as the cephalosporins, are prepared by sterile crystallization techniques.

To obtain a uniform product from lot to lot, strict adherence to the procedures developed for a particular crystallization must be followed, including control of pH, rates of addition, solvent concentrations and purity, temperature, and mixing rates. Each crystallization procedure has to be designed to ensure sterility and minimize particulate contamination. Changes, such as using absolute ethyl alcohol instead of 95% ethanol during the washing procedure, can destroy the crystalline structure if the material being crystallized is a hydrate structure.

Drugs that associate with water to produce crystalline forms are called hydrates. Water content of the hydrate forms of sodium cefazolin as a function of relative humidity is seen in Fig. 5. As shown in Fig. 5, the sesquihydrate is the most stable structure when exposed to extreme humidity conditions [5]. This figure also reveals the importance of choosing the proper combination of hydrate and humidity conditions when designing a manufacturing process or facility.

Chemical Modifications

Improvement of the properties of a drug may be achieved by the chemical modification of the parent drug. The preparation of an ester, salt, or employed other modification of the parent structure may be employed with parenteral drugs to increase stability, alter drug solubility,

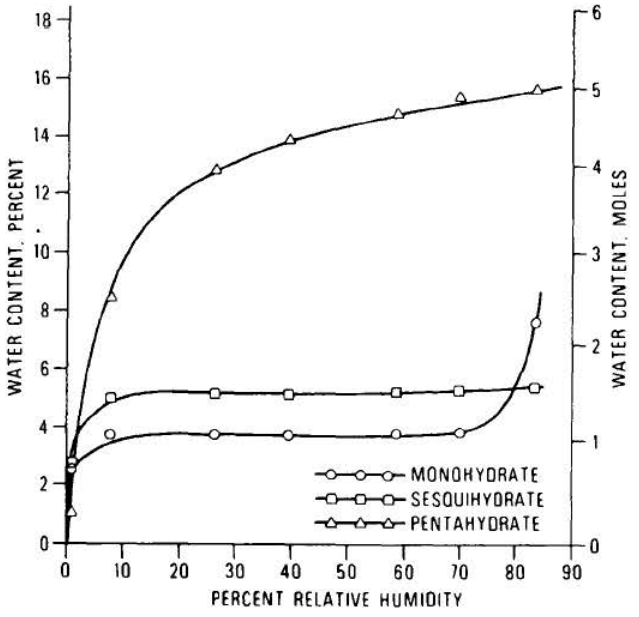

Fig. 5 Relative humidity versus water content of hydrate forms of sodium cefazolin. (From Ref. 5.)

enhance depot action, ease formulation difficulties, and possibly, decrease pain on injection. The molecularly modified drug that converts back to the active parent structure is defined as a *prodrug*. This conversion usually occurs within the body system or, for some drugs that are formulated as dry powders, occurs on reconstitution. The preparation of prodrugs is becoming a common practice with many types of drugs. Examples of antibiotic prodrugs include benzathine penicillin, procaine penicillin, metronidazole phosphate, and chloramphenicol sodium succinate.

The preparation of salts of organic compounds is one of the most important tools available to the formulator. Compounds for both IM and IV solutions require high solubility so that the drug may be incorporated into small volumes for IM administration and also be acceptable for IV use. Sodium and potassium salts of weak acids and hydrochloride and sulfate salts of weak bases are widely used in parenterals requiring highly soluble compounds, based on their overall safety and history of clinical acceptance.

If a drug's solubility is to be reduced to enhance stability or to prepare a suspension, the formulator may prepare water-insoluble salts. A classic example is procaine penicillin G, the decreased solubility (7 mg/ml) of which, when compared with the very soluble penicillin G potassium, is utilized to prepare stable parenteral suspensions. Another alternative to preparing an insoluble drug is to use the parent acidic or basic drug and to buffer the pH of the suspension in the range of minimum solubility.

Polymorphism

The literature lists numerous examples of polymorphism; that is, the existence of several crystal forms of a given chemical that exhibit different physical properties [6]. The conversion of one polymorph to another may cause a significant change in the physical properties of the drug.

Studies of polymorphs in recent years have pointed out the effects of polymorphism on solubility and, more specifically, on dissolution rates. The aspect of polymorphism that is of concern to the parenteral formulator is basically one of product stability [7]. Substances that form polymorphs must be evaluated so that the form used is stable in that particular solvent system. Physical stresses that occur during suspension manufacture may also give rise to changes in crystal form [8].

pH and pK_a

Profiles of pH versus solubility and pH versus stability are needed for solution and suspension formulations to help assure physical and chemical stability as well as to maximize or minimize solubility. This information is also valuable for predicting the compatability of drugs with various infusion fluids.

In summary, the physical and chemical data that should be obtained on the drug substance include the following:

Molecular structure and weight
Melting point
Thermal profile
Particle size and shape
Hygroscopicity potential
Ionization constant
Light stability
Optical activity
pH solubility profile
pH stability profile
Polymorphism potential
Solvate formation

B. Added Substances in Parenteral Formulations

To provide efficacious, safe, and elegant parenteral dosage forms, added substances must frequently be incorporated into the formula to maintain pharmaceutical stability, control product attributes, ensure sterility, or aid in parenteral administration. These substances include antioxidants, antimicrobial agents, buffers, bulking materials, chelating agents, inert gases, solubilizing agents, protectants, and substances for adjusting toxicity. In parenteral product development work, any additive to a formulation must be justified by a clear purpose and function. In addition, every attempt should be made to choose added substances that are accepted by regulatory agencies throughout the world, since most pharmaceutical development is international in scope.

Some of the added substances most commonly used are listed in Table 2. Pharmacists involved in IV additive programs must be aware of the types of additives that may be present in the products being combined.

Antioxidants

Salts of sulfur dioxide, including bisulfite, metasulfite, and sulfite, are the most common antioxidants used in aqueous parenterals. These antioxidants maintain product stability by being preferentially oxidized and gradually consumed over the shelf life of the product. Irrespective of which salt is added to the solution, the antioxidant moiety depends on the final concentration of the thio compound and the final pH of the formulation [9]. While undergoing oxidation

Table 2 Classes and Examples of Parenteral Additives

Additive class	Examples of parenteral additives	Usual concentration (%)
Antimicrobial	Benzalkonium chloride	0.01
	Benzyl alcohol	1–2
	Chlorobutanol	0.25–0.5
	Metacresol	0.1–0.3
	Butyl *p*-hydroxybenzoate	0.015
	Methyl *p*-hydroxybenzoate	0.1–0.2
	Propyl *p*-hydroxybenzoate	0.2
	Phenol	0.25–0.5
	Thimerosal	0.01
Antioxidants	Ascorbic acid	0.01–0.05
	Cysteine	0.1–0.5
	Monothioglycerol	0.1–1.0
	Sodium bisulfite	0.1–1.0
	Sodium metabisulfite	0.1–1.0
	Tocopherols	0.05–0.5
Buffers	Acetates	1–2
	Citrates	1–5
	Phosphates	0.8–2.0
Bulking agents	Lactose	1–8
	Mannitol	1–10
	Sorbitol	1–10
	Glycine	1–2
Chelating agents	Salts of ethylenediaminetetraacetic acid (EDTA)	0.01–0.05
Protectants	Sucrose	2–5
	Lactose	2–5
	Maltose	2–5
	Human serum albumin	0.5–2
Solubilizing agents	Ethyl alcohol	1–50
	Glycerin	1–50
	Polyethylene glycol	1–50
	Propylene glycol	1–50
	Lecithin	0.5–2.0
Surfactants	Polyoxyethylene	0.1–0.5
	Sorbitan monooleate	0.05–0.25
Tonicity-adjusting agents	Dextrose	4–5
	Sodium chloride	0.5–0.9

reactions, the sulfites may be converted to sulfate and other species. Sulfites can also react with certain drug molecules (e.g., epinephrine).

Sulfite levels are determined by the reactivity of the drug, the type of container (glass seal versus rubber stopper), single- or multiple-dose use, container headspace, use of inert gas purge, and the expiration dating period to be employed. Upper limits for sulfite levels are specified in most pharmacopeias; for example, the *USP* allows 3.2 mg of sodium bisulfite per millimeter of solution, whereas the French pharmacopeia (*Pharmacopée Française*) allows only 1.6

mg/ml. Allowances on upper limits are made for concentrated drugs that are diluted extensively before use. An oxygen-sensitive product to be used in France might require a smaller container (less headspace) or a glass seal ampoule to maintain product stability because of the reduced bisulfite level.

Sulfites have been reported to precipitate an allergic reaction in some asthmatics. If possible, alternative antioxidants should be considered or the product should be manufactured and packaged in a manner such as to eliminate or minimize the concentration of bisulfite required. Deoxygenation of the makeup water, maintaining the solution under a nitrogen atmosphere throughout the manufacturing process, and purging the filled vials with an inert gas could significantly reduce the amount of antioxidant required.

Antimicrobial Agents

A suitable preservative system is required in all multiple-dose parenteral products to inhibit the growth of microorganisms accidentally introduced during withdrawal of individual doses. Preservatives may be added to single-dose parenteral products that are not terminally sterilized as a sterility assurance measure; that is, to prevent growth of any microorganisms that could be introduced if there were any inadvertent breach of asepsis during filling operations. However, the inclusion of a preservative in single-dose parenteral products must be weighed against the need to develop formulations that are acceptable to regulatory bodies worldwide. Inclusion of a preservative can be a difficult challenge here, given the wide range of viewpoints concerning which preservatives are acceptable and when it is appropriate to include them in a formulation. Partly because of this, there is a trend in parenteral product development to eliminate preservatives wherever it is practical to do so. This may require added measures in manufacturing to improve sterility assurance—such as using barrier technology to provide positive separation of personnel from product during aseptic filling and transfer steps.

The formulation scientist must be aware of interactions between preservatives and other components of a formulation that could compromise the efficacy of the preservative. For example, proteins can bind thimerosal, reducing preservative efficacy. Partitioning of preservative into a micellar phase or an oil phase (in an emulsion) can also reduce the effective concentration of preservative available for bactericidal or bacteriostatic action. Preservative efficacy testing should be done on the proposed formulation to assure an effective preservative concentration.

Several investigators have published research on incompatibilities of preservatives with rubber closures and other packaging components, particularly polymeric materials [10]. Again, challenging the product with selected microorganisms to measure bacteriostatic or bactericidal activity is necessary, including evaluation of efficacy as a function of time throughout the anticipated shelf life of the product.

More subtle effects of preservatives on injectable formulations are possible. Formulation of insulin is an illustrative case study. Insulin is usually formulated as a multiple-dose vial, since individual dosage varies among patients. Preservation of zinc insulin with phenol causes physical instability of the suspension, whereas methylparaben does not. However, the presence of phenol is required for obtaining protamine insulin crystals [8].

Buffers

Many drugs require a certain pH range to maintain product stability. As discussed previously, drug solubility may also be strongly dependent on the pH of the solution. An important aid to the formulator is the information contained in a graph of the solubility profile of the drug as a function of pH (Fig. 6). The product can then be buffered to approach maximum or minimum solubility, whichever is desired.

Parenteral products should be formulated to possess sufficient buffer capacity to maintain proper product pH. Factors that influence pH include product degradation, container and stopper

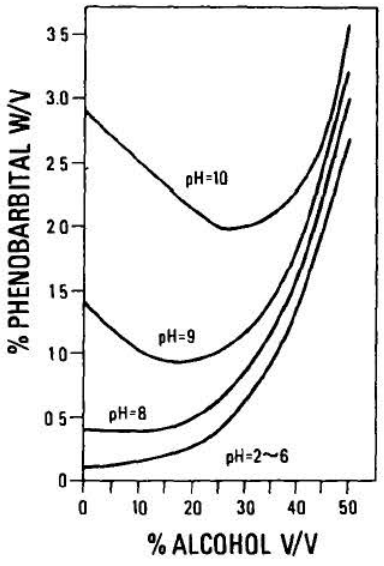

Fig. 6 Interdependence of pH and alcohol concentration on the solubility of phenobarbital. (From Ref. 11.)

effects, diffusion of gases through the closure, and the effect of gases in the product or in the headspace. However, the buffer capacity of a formulation must be readily overcome by the biological fluids; thus, the concentration and ratios of buffer ingredients must be carefully selected.

Buffer systems for parenterals consist of either a weak base and the salt of a weak base or a weak acid and the salt of a weak acid. Buffer systems commonly used for injectable products are acetates, citrates, and phosphates (see Table 2). Amino acids are receiving increased use as buffers, especially for polypeptide injectables.

Chelating Agents

Chelating agents are added to complex and, thereby, inactivate metals such as copper, iron, and zinc that generally catalyze oxidative degradation of drug molecules. Sources of metal contamination include raw material impurities; solvents, such as water, rubber stoppers and containers; and equipment employed in the manufacturing process [12]. The most widely used chelating agents are ethylenediaminetetraacetic acid (edetic acid; EDTA) derivatives and salts. Japan does not allow the use of these particular chelating agents in any parenteral products. Citric and tartaric acids are also employed as chelating agents.

Inert Gases

Another means of enhancing the product integrity of oxygen-sensitive medicaments is by displacing the air in the solution with nitrogen or argon. This technique may be made more effective by first purging with nitrogen or boiling the water to reduce dissolved oxygen. The container is also purged with nitrogen or argon before filling and may also be topped off with the gas before sealing.

Glass-seal ampoules provide the most impervious barrier for gas transmission. A butyl rubber stock is used with rubber-stoppered products that are sensitive to oxygen because it provides better resistance to gas permeation than other rubber stocks.

Solubilizing Agents and Surfactants

Drug solubility can be increased by the use of solubilizing agents, such as those listed in Table 2, and by nonaqueous solvents or mixed solvent systems, to be discussed shortly. When using solubilizing agents, the formulator must consider their effect on the safety and stability of the drug.

A surfactant is a surface-active agent that is used to disperse a water-insoluble drug as a colloidal dispersion. Surfactants are used for wetting and to prevent crystal growth in a suspension. Surfactants are used quite extensively in parenteral suspensions for wetting powders and to provide acceptable syringability. They are also used in emulsions and for solubilizing steroids and fat-soluble vitamins.

Tonicity Adjustment Agents

It is important that injectable solutions that are to be given intravenously are isotonic, or nearly so. Because of osmotic pressure changes and the resultant exchange of ionic species across red blood cell membranes, nonisotonic solutions, particularly if given in quantities larger than 100 ml, can cause hemolysis or crenation of red blood cells (owing to hypotonic or hypertonic solutions, respectively). Dextrose and sodium chloride or potassium chloride are commonly used to achieve isotonicity in a parenteral formula.

Protectants

A protectant is a substance that is added to a formulation to protect against loss of activity caused by some stress that is introduced by the manufacturing process or to prevent loss of active ingredients by adsorption to process equipment or to primary packaging materials. Protectants are used primarily in protein and liposomal formulations. For example, cryoprotectants and lyoprotectants are used to inhibit loss of integrity of the active substance resulting from freezing and drying, respectively. Compounds that provide cryoprotection are not necessarily the same as those that provide lyoprotection. For example, polyethylene glycol protects lactate dehydrogenase and phosphofructokinase from damage by freezing, but does not protect either protein from damage by freeze-drying. Compounds such as glucose and trehalose are effective lyoprotectants for both proteins [13]. Effective cryo- and lyoprotectants must be determined on a case-by-case basis, but sugars and polyhydroxy compounds are usually the best candidate compounds. These same types of compounds also tend to markedly improve the stability of proteins against inactivation by thermal denaturation.

Another type of protectant is used to prevent loss of active substance—again, usually a protein and usually present at a very low concentration—by adsorption to materials or equipment in the manufacturing process or to components of the primary package. In manufacturing, particular attention should be given to adsorption of the active entity to filters (especially nylon) and to silicone tubing used for transfer operations. For packaging materials, rubber closures and other polymeric materials should be examined carefully for adsorptive potential. The same consideration applies to infusion equipment, particularly considering that most materials in modern IV infusion therapy are polymeric.

Human serum albumin (HSA) is commonly used as a protectant against adsorptive loss. HSA is present at higher concentration than the active substance, and is preferentially adsorbed, coating the surface of interest and preventing adsorption of the drug. For example, insulin is subject to adsorptive loss to hydrophobic materials. Addition of 0.1–1.0% HSA has been reported to prevent adsorptive loss [8].

C. Vehicles

Aqueous Vehicles

"Water for injection" (WFI) is the most widely used solvent for parenteral preparations. The requirements for WFI are generally the same throughout the world. Companies involved in international markets must be assured that their products comply with the applicable standards. The most common means of obtaining WFI is by the distillation of deionized water. Water for injection must be prepared and stored in a manner to ensure purity and freedom from pyrogens.

Microorganisms, dissolved organic and inorganic substances, and foreign particles are the most common contaminants found in water. New purification methods and systems are continually being investigated to improve the quality of water for parenteral use. Inorganic compounds are commonly removed by distillation, reverse osmosis, deionization, or a combination of these processes. Membrane and depth filters are used to remove particulate contaminants, and charcoal beds may be used to remove organic materials. Filtration, chilling or heating, or recirculation of water are used to reduce microbial growth and to prevent pyrogen formation that will occur in a static deionization system. To inhibit microbial growth, WFI must be stored at either 5°C or 60–90°C if it is to be held for over 24 hr.

The *USP* also lists sterile water for injection and bacteriostatic water for injection, which unlike WFI, must be sterile. Higher levels of solids are allowed in these vehicles because of the possible leaching of glass constituents into the product during high-temperature sterilization and subsequent storage. Bacteriostatic water for injection must not be placed in containers larger than 30 ml. This is to prevent the administration of large quantities of bacteriostatic agents (such as phenol) that could become toxic if large volumes of solution were administered. Other aqueous vehicles that may be used in place of sterile water for injection or bacteriostatic water for injection for reconstitution or administering drugs include 5% dextrose, 0.9% sodium chloride, and a variety of other electrolyte and nutrient solutions, as noted earlier.

Nonaqueous and Mixed Vehicles

A nonaqueous solvent or a mixed aqueous–nonaqueous solvent system may be necessary to stabilize drugs, such as the barbiturates, that are readily hydrolyzed by water, or to improve solubility (e.g., digotoxin). Nonaqueous solvents must be carefully screened and tested to ensure that they exhibit no pharmacological action, are nontoxic and nonirritating, and are compatible and stable with all ingredients of a formulation.

A major class of nonaqueous solvents is the fixed oils. The *USP* [1] recognizes the use of fixed oils as parenteral vehicles and lists their requirements. The most commonly used oils are corn oil, cottonseed oil, peanut oil, and sesame oil. Because fixed oils can be quite irritating when injected and may cause sensitivity reactions in some patients, the oil used in the product must be stated on the label.

Sesame oil is the preferred oil for most of the official injections in oil. This is because it is the most stable (except in light) and, thus, will usually meet the official requirements. Fixed oils must never be administered intravenously and are, in fact, restricted to IM use.

The *USP* usually does not specify an oil, but states that a suitable vegetable oil can be used. The main use of such oils is with the steroids, with which they yield products that produce a sustained-release effect. Sesame oil has also been used to obtain slow release of fluphenazine esters given intramuscularly [4]. Excessive unsaturation of an oil can produce tissue irritation. The use of injections in oil has diminished somewhat in preference to aqueous suspensions,

which generally have less irritating and sensitizing properties. Benzyl benzoate may be used to enhance steroid solubility in oils if desired.

Water-miscible solvents are widely used in parenterals to enhance drug solubility and to serve as stabilizers. The more common solvents include glycerin, ethyl alcohol, propylene glycol, and polyethylene glycol 300. A common example of an injectable product formulated with nonaqueous solvents is IV Valium, which contains 40% propylene glycol and 10% ethanol. Mixed-solvent systems do not exhibit many of the disadvantages observed with the fixed oils, but may also be irritating or increase toxicity, especially when present in large amounts or in high concentrations. A solution containing a high percentage of ethanol will produce pain on injection.

The formulator should be aware of the potential of nonaqueous solvents in preparing a solubilized or stable product that may not have been otherwise possible. The reader is directed to comprehensive reviews of nonaqueous solvents for additional information [15,16].

V. DOSAGE FORMS

A. Solutions

The most common of all injectable products are solutions. Solutions of drugs suitable for parenteral administration are referred to as *injections*. Although usually aqueous, they may be mixtures of water with glycols, alcohol, or other nonaqueous solvents. Many injectable solutions are manufactured by dissolving the drug and a preservative, adjusting the pH, sterile filtering the resultant solution through a 0.22-μm–membrane filter and, when possible, autoclaving the final product. Most solutions have a viscosity and surface tension very similar to water, although streptomycin sulfate injection and ascorbic acid injection, for example, are quite viscous.

Sterile filtration, with subsequent aseptic filling, is common because of the heat sensitivity of most drugs. Those drug solutions that can withstand heat should be terminally autoclave-sterilized after filling, since this better assures product and package sterility.

Large-volume parenterals (LVPs) and small-volume parenterals (SVPs) containing no antimicrobial agent should be terminally sterilized. It is standard practice to include an antimicrobial agent in SVPs that cannot be terminally sterilized or are intended for multiple-dose use. The general exceptions are products that pass the *USP* Antimicrobial Preservative Effectiveness Test [1] because of the preservative effect of the active ingredient, vehicle, pH, or a combination of these. For example, some barbiturate products have a pH of 9–10 and a vehicle that includes glycol and alcohol.

Injections and infusion fluids must be manufactured in a manner that will minimize or eliminate haze and color. Parenteral solutions are generally filtered through 0.22-μm–membrane filters to achieve sterility and remove particulate matter. Prefiltration through a coarser filter is often necessary to maintain adequate flow rates, or to prevent clogging of the filters during large-scale manufacturing. A talc or carbon filtration aid (or other filter aids) may also be necessary. If talc is used, it should be pretreated with a dilute acid solution to remove surface alkali and metals.

The formulator must be aware of the potential for binding when filtering protein solutions. Because of the cost–availability of most protein materials, a membrane should be used that minimizes protein adsorption to the membrane surface. Typical filter media that minimize this binding include hydrophilic polyvinylidene difluoride and hydroxyl-modified hydrophilic polyamide membranes [17]. Filter suppliers will evaluate the compatibility of the drug product with their membrane media and also validate the selected membrane.

The total fluid volume that must be filled into a unit parenteral container is typically greater than the volume that would contain the exact labeled dose. The fill volume is dependent on the viscosity of the solution and the retention of the solution by the container and stopper. The *USP* [1] provides a procedure for calculating the fill dose that is necessary to ensure the delivery of the stated dose. It also provides a table of excess volumes that are usually sufficient to permit withdrawal and administration of the labeled volume.

B. Suspensions

One of the most difficult parenteral dosage forms to formulate is a suspension. It requires a delicate balance of variables to formulate a product that is easy to fill, ships without caking or settling, and ejects through an 18- to 21-gauge needle through its shelf life. To achieve these properties it is necessary to select and carefully maintain particle size distribution, zeta potential, and rheological parameters, as well as the manufacturing steps that control wettability and surface tension. The requirements for, limitations in, and differences between the design of injectable suspensions and other suspensions have been previously summarized [18,19].

A formula for an injectable suspension might consist of the active ingredient suspended in an aqueous vehicle containing an antimicrobial preservative, a surfactant for wetting, a dispersing or suspending agent, and perhaps a buffer or salt.

Two basic methods are used to prepare parenteral suspensions: (a) sterile vehicle and powder are combined aseptically, or (b) sterile solutions are combined and the crystals formed in situ. Examples of these procedures may be illustrated using sterile penicillin G procaine suspension (*USP*) and sterile testosterone suspension (*USP*).

In the first example, procaine penicillin, an aqueous vehicle containing the soluble components (such as lecithin, sodium citrate, povidone, and polyoxyethylene sorbitan monooleate) is filtered through a 0.22-μm–membrane filter, heat sterilized, and transferred into a presterilized mixing–filling tank. The sterile antibiotic powder, which has previously been produced by freeze-drying, sterile crystallization, or spray-drying, is gradually added to the sterile solution aseptically while mixing. After all tests have been completed on the bulk material, it is aseptically filled.

An example of the second method of parenteral suspension preparation is testosterone suspension. Here, the vehicle is prepared and sterile-filtered. The testosterone is dissolved separately in acetone and sterile-filtered. The testosterone–acetone solution is aseptically added to the sterile vehicle, causing the testosterone to crystallize. The resulting suspension is then diluted with sterile vehicle, mixed, the crystals allowed to settle, and the supernatant solution siphoned off. This procedure is repeated several times until all the acetone has been removed. The suspension is then brought to volume and filled in the normal manner.

The critical nature of the flow properties of parenteral suspensions becomes apparent when one remembers that these products are frequently administered through 1¼-in. or longer needles having internal diameters in the range of only 300–600 μm. In addition, microscopic examination shows a very rough interior needle surface, further hindering flow. The flow properties of parenteral suspensions are usually characterized on the basis of syringeability or injectability. The term *syringeability* refers to the handling characteristics of a suspension while drawing it into and manipulating it in a syringe. Syringeability includes characteristics such as ease of withdrawal from the container into the syringe, clogging and foaming tendencies, and accuracy of dose measurement. The term *injectability* refers to the properties of the suspension during injection; it includes such factors as pressure or force required for injection, evenness of flow, aspiration qualities, and freedom from clogging. The syringeability and injectability characteristics of a suspension are closely related to viscosity and to particle characteristics.

C. Emulsions

An emulsion is a heterogeneous dispersion of one immiscible liquid in another. This inherently unstable system is made possible through the use of an emulsifying agent, which prevents coalescence of the dispersed droplets. Parenteral emulsions are rare because it is necessary (and difficult) to achieve stable droplets of less than 1 μm to prevent emboli in the blood vessels, and it is not usually necessary to achieve an emulsion for drug administration.

Parenteral emulsions have been used for several purposes, including (a) water-in-oil emulsions of allergenic extracts (given subcutaneously), (b) oil-in-water sustained-release depot preparations (given intramuscularly), and (c) oil-in-water nutrient emulsions (given intravenously). Formulation options are severely restricted through a very limited selection of stabilizers and emulsifiers, primarily owing to the dual constraints of autoclave sterilization and parenteral injection. Additionally, unwanted physiological effects (e.g., pyrogenic reaction and hemolysis) have further limited the use of intravenous emulsions.

An increasingly popular class of intravenous emulsions is fat emulsions. These preparations have been available in Europe for over 20 years and in the United States since 1975. Fat is transported in the bloodstream as small droplets called chylomicra. Chylomicra are 0.5- to 1.0-μm spheres consisting of a central core of triglycerides and an outer layer of phospholipids. Intravenous fat emulsions usually contain 10% oil, although they may range up to 20% (Table 3). These emulsions yield triglycerides that provide essential fatty acids and calories during total parenteral nutrition of patients who are unable to absorb nutrients through the gastrointestinal tract. The products commercially available in the United States range from 0.1 to 0.5 μm and have a pH of 5.5–8 (blood plasma has a pH of 7.4). Glycerol and glucose are added to make the product isotonic.

D. Dry Powders

Many drugs are too unstable—either physically or chemically—in an aqueous medium to allow formulation as a solution, suspension, or emulsion. Instead, the drug is formulated as a dry powder that is reconstituted by addition of water before administration. The reconstituted product is usually an aqueous solution; however, occasionally it may be an aqueous suspension (for example, ampicillin trihydrate and spectinomycin hydrochloride are sterile powders that are reconstituted to form a sterile suspension).

Dry powders for reconstitution as an injectable product may be produced by several methods—filling the product into vials as a liquid and freeze-drying, aseptic crystallization followed by powder filling, and spray-drying followed by powder filling. A brief discussion of each follows.

Freeze-Drying

The most common form of sterile powder is a *freeze-dried* or *lyophilized*, powder. The advantages of freeze-drying are that (a) water can be removed at low temperature, avoiding damage to heat-sensitive materials; (b) if freeze-drying is done properly, the dried product has a high specific surface area, which facilitates rapid, complete rehydration (or "reconstitution") of the solid; and (c) from an operations point of view, freeze-dried dosage forms allow drug to be filled into vials as a solution. This makes control of the quantity filled into each vial more precise than filling drug into vials as a powder. In addition, since drug is filled as a solution, there is minimal concern with airborne particulate matter and potential cross-contamination as is the problem with powder filling.

Despite the advantages of freeze-drying, there are some limitations that must be kept in mind.

Table 3 Intravenous Fat Emulsions

Component (g/100 ml)	Intralipid[a]		Liposyn II[b]		Infonutrol[c]	Lipofundin[d]	Lipihysan[e]	
	10%	20%	10%	20%	15%	10%	10%	15%
Soybean oil	10	20	5	10				
Safflower oil			5	10				
Cottonseed oil					15	10	10	15
Egg phospholipids	1.2	1.2	1.2	1.2				
Soybean phospholipids					1.2	1.2		
Soybean lecithin							1.5	2
Glycerol	2.25	2.25	2.5	2.5				
Glucose					4			
Sorbitol						5	5	5
Pluronic F-68					0.3			
DL-α-Tocopherol							0.05	0.05
Water for injections q.s. ad	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml	

[a]Kabi-Vitrum A. G., Stockhold, Sweden.
[b]Abbott Laboratories, North Chicago, IL.
[c]Astra-Hewlett, Södertäye, Sweden
[d]Braun. Melsunger, West Germany
[e]Egic, L'Equilibre Biologique S. A., Loiret, France

1. Some proteins are damaged by freezing, freeze-drying, or both. Although the damage can often be minimized by using protective agents in the formulation, the problem is still substantial.
2. Often the stability of a drug in the solid state depends on its physical state (i.e., crystalline or amorphous [20]). If freeze-drying produces an amorphous solid, and the amorphous form is not stable, then freeze-drying will not provide an acceptable product.
3. Freeze-drying is a relatively expensive drying operation. Although this is not an issue for many high-cost drug products, it may become an issue for more cost-sensitive pharmaceutical products.

In freeze-drying, a solution is filled into vials, a special slotted stopper is partially inserted into the neck of the vial (Fig. 7), and trays of filled vials are transferred to the freeze-dryer (Fig. 8). The solution is frozen by circulation of a fluid, such as silicone oil, at a temperature in the range of −35° to about −45°C through internal channels in the shelf assembly. When the product has solidified sufficiently, the pressure in the freeze-dry chamber is reduced to a pressure less that the vapor pressure of ice at the temperature of the product, and heat is applied to the product by increasing the temperature of the circulating fluid. Under these conditions, water is removed by *sublimation* of ice, or a phase change from the solid state directly to the vapor state without the appearance of an intermediate liquid phase. The phase diagram in Fig. 9 illustrates the difference between freeze-drying and conventional drying methods, during which drying takes place by a phase change from the liquid state to the vapor state. Freeze-drying takes place below the triple point of water, at which solid, liquid, and vapor all coexist in equilibrium. As freeze-drying proceeds, a receding boundary can be observed in the vial as the thickness of the frozen layer decreases. This phase is called *primary drying*, during which ice is removed by direct sublimation through open channels created by prior sublimation of ice. After primary drying, additional drying is necessary to remove any water that did not

Fig. 7 Vials typically used for lyophilization showing special slotted stopper.

freeze during the freezing process, but instead remained associated with the solute. This is called *secondary drying* and consists of water removal by diffusion and desorption of water from the partially dried solid phase. The phases of a typical freeze-dry cycle—freezing, primary drying, and secondary drying—are illustrated by means of a plot of shelf temperature, chamber pressure, and product temperature in Fig. 10.

The most important objective in developing a freeze-dried product is to assure that critical quality attributes are met initially and throughout the shelf life of the product. Examples of critical quality attributes are recovery of original chemical or biological activity after reconstitution, rapid and complete dissolution, appropriate residual moisture level, and acceptable cake appearance. In addition, process conditions should be chosen to maximize process efficiency; that is, those conditions that minimize drying time without adversely affecting product quality. The driving force for sublimation is the vapor pressure of ice, and the vapor pressure of ice is highly temperature-dependent as shown below:

Temperature (°C)	Vapor pressure (mm Hg)
−40	0.096
−30	0.286
−20	0.776
−10	1.950
0	4.579

Therefore, freeze-drying should be carried out at the highest allowable product temperature that maintains the appropriate attributes of a freeze-dried product. This temperature depends

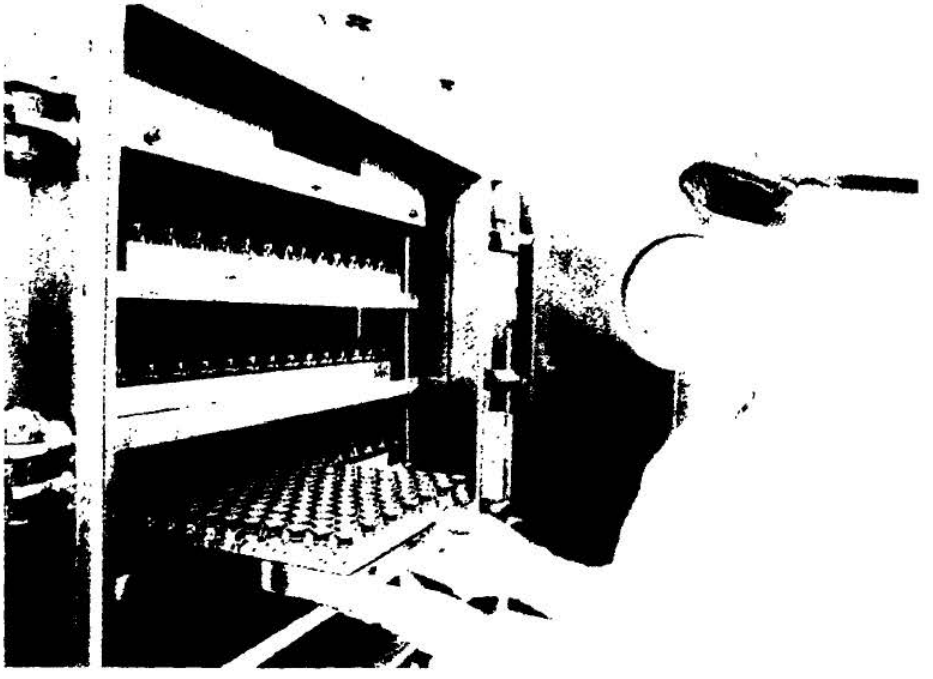

Fig. 8 Filled vials being transferred to freeze dryer.

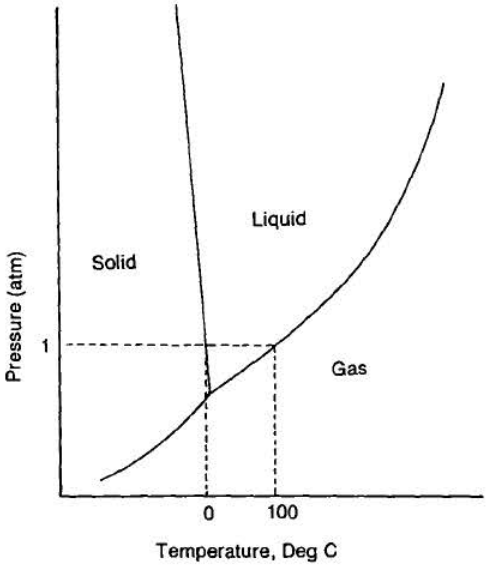

Fig. 9 Phase diagram of water.

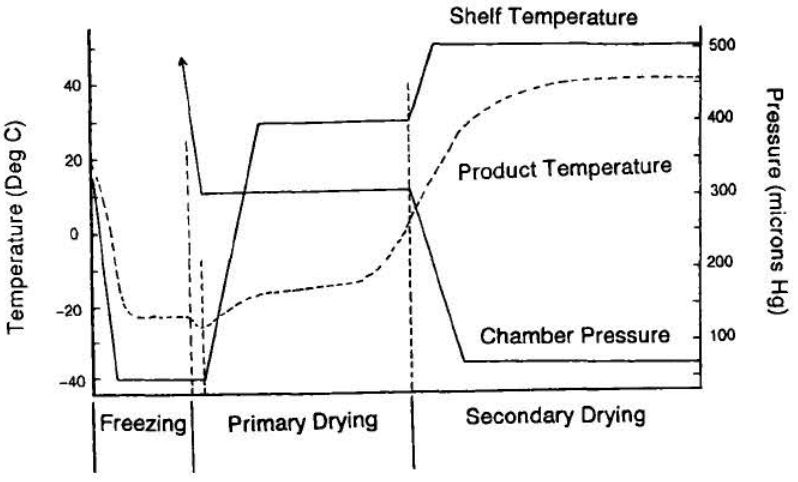

Fig. 10 Process variables during a representative freeze-dry cycle.

on the nature of the formulation. Process development and validation requires characterizing the physical state of the solute, or solutes, that result from the freezing process and identifying a maximum allowable product temperature for the primary drying process [21,22].

The term *eutectic temperature* is often misused in reference to freeze-drying. A eutectic phase—an intimate mixture of ice and crystals of solute that melts as if it were a single, pure compound—is present only if the solute crystallizes when the solution is frozen. Eutectic melting can often be detected by a thermal analysis technique, such as differential scanning calorimetry DSC [23,24]. An example of a eutectic system is neutral glycine in water. The presence of a eutectic phase is indicated by a melting endotherm in the DSC thermogram of the solution (Fig. 11) in addition to the melting endotherm for ice. In this example, the theoretical maximum allowable product temperature during primary drying is the eutectic melting temperature at −3.5°C. In practice, the product temperature should be maintained a few degrees below this temperature to assure that melting does not occur during the process. Examples of some other common solutes that form eutectics, along with the eutectic temperature, are shown below (24):

Solute	Eutectic temperature (°C)
Calcium chloride	−51.0
Citric acid	−12.2
Mannitol	−1.0
Potassium chloride	−10.7
Sodium carbonate	−18.0
Sodium chloride	−21.5
Sodium phosphate, dibasic	−0.5

However, many solutes do not crystallize during the freezing process, but instead, remain amorphous. Examples include sugars, such as sucrose, lactose, maltose, and many polymers. In this case, no eutectic phase is formed. Instead, the freeze concentrate becomes more concentrated and more viscous as the temperature is lowered and ice crystals grow. This process

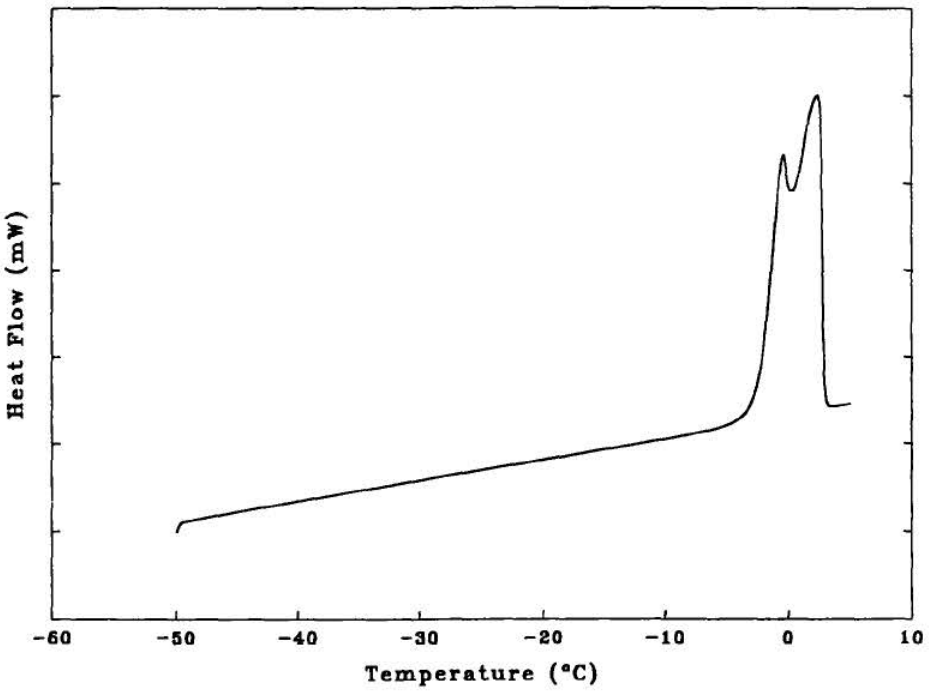

Fig. 11 DSC thermogram of neutral glycine in water.

continues until a temperature is reached at which the viscosity of the freeze concentrate increases dramatically with only a small change in temperature, and ice crystal growth ceases on a practical time scale. This temperature is a *glass transition temperature*, and is an important characteristic of amorphous systems. Below the glass transition temperature, the freeze concentrate exists as a rigid glass. Above the glass transition temperature, the freeze concentrate behaves as a viscous liquid. The significance of the glass transition temperature of the freeze concentrate (commonly referred to as Tg') is that it is closely related to the *collapse temperature* in freeze-drying. If drying is carried out above the collapse temperature, the freeze concentrate will flow and lose the microstructure established by freezing, once the supporting structure of ice crystals is removed. Collapse can be observed in a variety of forms, from a slight shrinkage of the dried cake (where the cake has pulled away from the wall of the vial) to total loss of any cake structure.

The glass transition of solutes that remain amorphous during and after the freezing process can often be seen in the DSC thermogram as a shift in the baseline toward higher heat capacity. This is illustrated in the DSC thermogram of sucrose solution in Fig. 12, in which the glass transition is observed at −34°C. Glass transition (Tg') values of some other solutes common to freeze drying are shown below (24):

Solute	Glass transition (Tg')
Dextran	−9
Gelatin	−10

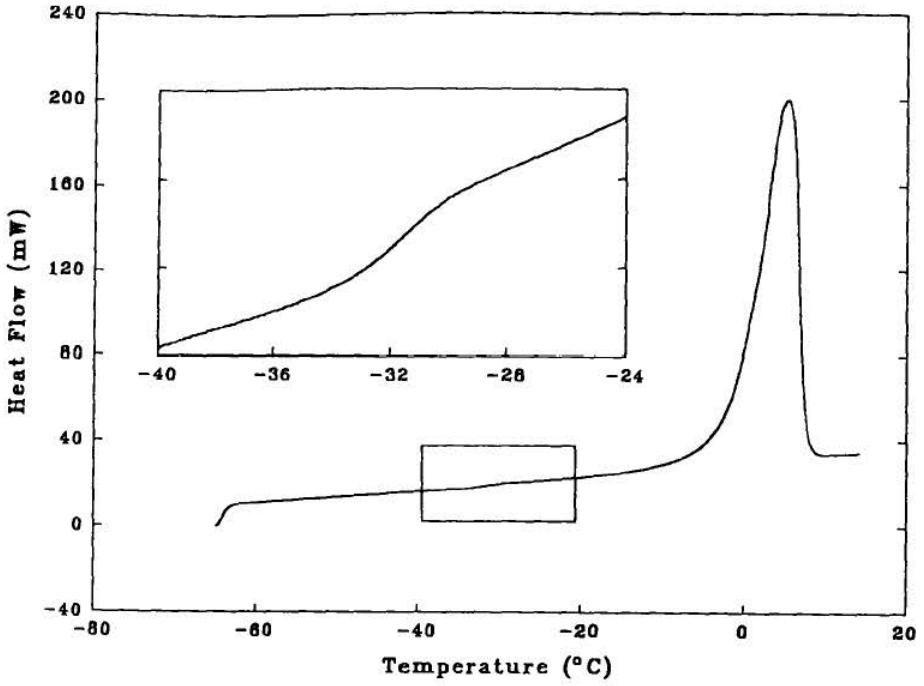

Fig. 12 DSC thermogram of sucrose solution.

Glucose	−43
Lactose	−32
Maltose	−32
Polyvinylpyrrolidone	−24
Sorbitol	−48

Some solutes may first form a metastable amorphous phase initially on freezing and then crystallize when the material is heated. This is the basis for *thermal treatment*, or *annealling*, in the freeze-dry process, during which the product is frozen to perhaps −40°C, the product is then heated to some temperature below the melting point of ice, held for a few hours, then cooled before starting the drying process. Some cephalosporins are known to crystallize by thermal treatment [20], and mannitol is a common excipient which frequently forms a metastable amorphous phase that crystallizes with subsequent heating [26].

In general, crystallization of the solute is desirable in terms of freeze-drying properties, as well as quality attributes of the final product, for several reasons. First, when the solute crystallizes, nearly all of the water is present as ice in the frozen matrix, and it is removed by direct sublimation during primary drying. Therefore, there is little water to be removed by secondary drying. This improves process efficiency, since water removed during secondary drying must be removed primarily by the process of diffusion, rather than by bulk flow. Second, eutectic temperatures are usually higher than collapse temperatures, which allows higher product temperatures and more efficient drying. Eutectic temperatures of most organic compounds are in the range of −1° to about −12°C, whereas collapse temperatures commonly are −30°C

or lower. Third, the chemical and physical stability of a compound in crystalline form is generally better than that of the same compound in an amorphous form [20,27]. This can be a critical aspect of determining the feasibility of a freeze-dried dosage form.

An understanding of the effect of formulation on freeze-drying behavior is important to the pharmaceutical scientist involved in the development of freeze-dried products. Mixtures of components should be expected to behave differently from single-component systems. For example, a compound that crystallizes readily from aqueous solution when it is the only solute present may not crystallize at all when other solutes are present. For solutes that remain amorphous on freezing, the glass transition temperature is affected by the presence of other solutes. Subtle variations in the composition of the formulation, such as changes in ionic strength or pH, may have a significant effect on the physical chemistry of the freezing and freeze-drying processes.

Many drugs are present in a dose too small to form a well-defined freeze-dried cake, and must be formulated with a *bulking agent*, the purpose of which is to provide a dried matrix in which the active ingredient is dispersed. Common bulking agents are mannitol, lactose, glycine, and mixtures of these compounds. Buffers are commonly used, such as sodium or potassium phosphate, acetate, citrate, or tris-hydroxymethylaminomethane (THAM). Formulations of proteins, liposomes, or cells generally require the presence of a *protectant*, or a substance that protects the active compound from damage by freezing, by drying, or both. Disaccharides, such as sucrose, lactose, and maltose, are, in general, the most effective protectants [28]. Trehalose, a disaccharide of glucose, is also a well-known protectant, but is not currently used in freeze-dried products for use in humans.

In addition to the effects of formulation factors on freeze-drying behavior, it is important for the pharmaceutical scientist to understand basic principles of heat and mass transfer in freeze-drying [29,30]. Because of the high heat input required for sublimation—670 calories/g—transfer of heat from the heated shelf to the sublimation front is often the rate-limiting step in the coupled heat and mass transfer process. There are three basic mechanisms for heat transfer: conduction, convection, and radiation. *Conduction* is the transfer of heat by molecular motion between differential volume elements of a material. *Convection* is the transfer of heat by bulk flow of a fluid, either from density differences (natural convection) or because an external force is applied (forced convection). Because of the relatively low pressures used in freeze-drying, convection is probably not a large contributing factor in heat transfer. Heat transfer by *thermal radiation* arises when a substance, because of thermal excitation, emits radiation in an amount determined by its absolute temperature. Of these mechanisms, heat transfer by conduction is the most important. Heat transfer by conduction takes place through a series of resistances—the bottom of the vial, the frozen layer of product, the metal tray (if used), and through the vapor phase caused by lack of good thermal contact between the vial and the shelf. The thermal conductivity of the vapor phase at the pressures used in freeze-drying is dependent on pressure in the chamber. Therefore, to maintain consistent drying conditions from batch to batch, it is as important to control the chamber pressure as it is to control shelf temperature [31]. In addition, changes in the geometry of the system that will affect heat transfer will also affect process consistency. Examples include changing from molded to tubing vials, changing the depth of fill in the vials, and changing from trays with metal bottoms to those without bottoms. Thermal radiation is a small, but significant, contributor to the total quantity of heat transferred to the product. This can be a significant issue in scale-up of cycles from pilot dryers to production-scale equipment.

Mass transfer in freeze-drying refers to the transfer of water vapor from the sublimation front through open channels in the partially dried layer, created by prior sublimation of ice, through the headspace of the vial, past the lyostopper, through the chamber, to the condenser.

The reader is referred to basic studies of mass transfer in freeze-drying by Pikal and co-workers for in-depth treatment of the theoretical and practical aspects of mass transfer [30,32]. Briefly, the rate-limiting step in mass transfer is transfer of water vapor through the partially dried matrix of solids. Resistance of the dried layer increases in a more or less continuous fashion as the depth of the dried layer increases, and the resistance also increases with the concentration of solids in the dried layer. Other factors can also affect the resistance of the dried layer, such as the method of freezing; faster freezing tends to create a higher resistance in the dried layer.

Mass transfer of the "unfrozen" water through a glassy phase during secondary drying occurs slower than bulk flow of water vapor by direct sublimation, since no open channels are present in the glassy phase. The high resistance of the solid material to mass transfer is why secondary drying can be the most time-consuming phase of the freeze-dry cycle for amorphous solutes containing a large percentage of unfrozen water. According to studies reported by Pikal, shelf temperature is the most critical process variable, affecting the rate of secondary drying and final moisture level [32]. Chamber pressure had no measurable influence on secondary drying kinetics.

The quantity of residual water is frequently a critical product characteristic relative to chemical and physical stability of freeze-dried products, particularly amorphous solids. Water acts as a plasticizer of the solid material, lowering the glass transition temperature. A low glass transition temperature, relative to the storage temperature, can result in physical instability, such as cake shrinkage or collapse, or accelerated rates of chemical reactions leading to instability. Often, a small change in moisture content can result in a large change in the glass transition temperature; therefore, careful consideration of appropriate limits on residual moisture is often an important part of the product development process.

Aseptic Crystallization and Dry Powder Filling

Aseptic crystallization is primarily used for manufacture of sterile aqueous suspensions. However, if the physical form of the drug is critical to quality of the final product, better control over physical form can be attained by aseptic crystallization because a large variety of organic solvents can be used to control the crystallization process. In aseptic crystallization, the drug is dissolved in a suitable solvent and sterile filtered through an appropriate membrane filter. A second solvent—a sterilely filtered nonsolvent for the drug—is then added at a controlled rate, causing crystallization and precipitation of the drug. The crystals are collected on a funnel, washed if necessary, and dried by vacuum drying. After drying, it may be necessary to mill or blend the drug crystals. The powder is then transferred to dry-powder-filling equipment and filled into vials. Although simple in principle, there are obvious drawbacks to this approach. Batch-to-batch variability in crystal habit and crystal size and the resulting variability in physical properties can be troublesome for consistent product quality. Maintenance of asepsis between sterile crystallization and filling of the powder is a challenge during material handling, and will usually result in decreased sterility assurance. Also, since the drug is filled into vials as a powder, maintenance of fill weight uniformity is generally more troublesome than when filling with a liquid.

Spray-Drying

A solution of drug is sterile filtered and metered into the drying chamber, where it passes through an atomizer that creates an aerosol of small droplets of liquid (Fig. 13). The aerosol comes into contact with a stream of hot sterile gas—usually air. The solvent evaporates quickly, allowing drug to be collected as a powder in the form of uniform hollow spheres. The powder is then filled into vials using conventional powder-filling equipment. Spray-drying may be more economical than freeze-drying, but challenges in the use of this technique include sterile fil-

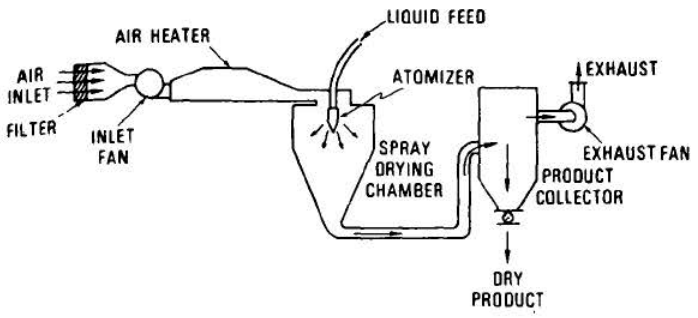

Fig. 13 Schematic drawing of spray-dryer.

tration of very large volumes of air, constructing and maintaining a spray dryer that can be readily sterilized, aseptic transfer of powder from the spray dryer to the powder-filling line, and precise control of the drying conditions to prevent overheating of the product while providing adequate drying. Probably because of these limitations, the technique is not widely used.

E. Protein Formulations

The first biotechnology-derived therapeutic agent to be approved by FDA in the United States was human insulin (Humulin, Eli Lilly) in 1982. The number of such products has grown steadily since then, and now accounts for roughly 3 billion dollars in sales in the United States. This growth is expected to continue during the next decade. Because biotechnology-derived pharmaceuticals are generally proteins and glycoproteins, they require special consideration in formulation and processing.

Special problems with formulation and processing of proteins arise from the hierarchy of structural organization of proteins. In addition to primary structure (the amino acid sequence), proteins have secondary structure (interactions between peptide bonds, resulting in helical or sheetlike structures), tertiary structure (folding of chain segments into a precise three-dimensional arrangement), and in some, quaternary structure (association of individual protein subunits into a multimeric structure). Disruption of this higher-order structure can lead to loss of the biologically active, or native, conformation which, in turn, causes physical instability and may accelerate reactions that are characteristic of chemical instability of proteins.

Loss of the native conformation of a protein generally exposes hydrophobic amino acid residues that are normally buried on the inside of the self-associated structure and are shielded from the aqueous environment. This leads to association between the exposed hydrophobic residues of neighboring proteins (aggregation), or between these exposed residues and hydrophobic surfaces that the protein may encounter either in the manufacturing process or in the primary package.

Processing variables, usually are not critical for traditional low molecular weight drugs, may be critical for protein formulations. For example, vigorous agitation of a protein solution can cause foaming, generating a large air–water interface that is an excellent site for denaturation, aggregation, and perhaps precipitation of protein. Loss of protein by adsorption to surfaces, such as tubing and filters used in manufacturing, can result in subpotent product. Other potentially critical factors in maintenance of the native structure during processing include temperature, pH, the presence of organic solvents, and ionic strength of the formulation.

Disruption of the native structure of a protein can also contribute to chemical instability by accelerating the rates of a variety of degradation routes, including deamidation, hydrolysis, oxidation, disulfide exchange, β-elimination, and racemization.

Formulation strategies for stabilization of proteins commonly include additives such as other proteins (e.g., serum albumin), amino acids, and surfactants to minimize adsorption to surfaces (see Sec. IV.B). Modification of protein structure to enhance stability by genetic engineering may also be feasible, as well as chemical modification such as formation of a conjugate with polyethylene glycol.

Most proteins are not sufficiently stable in aqueous solution to allow formulation as a sterile solution. Instead, the protein is freeze-dried and reconstituted before use. Development of a freeze-dried protein formulation often requires special attention to the details of the freezing process (potential pH shifts and ionic strength increase with freezing) as well as to potential loss of activity with drying. Formulation additives, such as sugars and polyhydroxy compounds, are often useful as cryoprotectants and lyoprotectants (see also Sec. IV.B). Residual moisture may also be critical to the stability of the dried preparation [33].

F. Novel Formulations

A summary of sustained- and controlled-release parenteral dosage forms is included in Chapter 16. This subject is also covered extensively by Chien [34].

Concepts in drug delivery that have received increasing attention include drug carrier systems, implants, intravenous infusers, and implantable infusion pumps. Carrier systems include microspheres, liposomes, monoclonal antibodies, and emulsions. Drugs are incorporated into these systems to increase the duration of drug action and to provide selective delivery of the drug to a specific target site or organ. Implants are used for the same reason. Unwanted side effects and adverse reactions are usually reduced because of selective delivery, which also results in a lower concentration of drug required to achieve the desired therapeutic effect. Infusion pumps provide a delivery system with uniform, continuous flow. A specific dose of a drug, such as insulin, may be administered to a patient on a continual or intermittent basis.

VI. PACKAGING

Container components for parenteral products must be considered an integral part of the product because they can dramatically affect product stability, potency, toxicity, and safety. Parenteral dosage forms, especially solutions, usually require more detailed evaluation of packaging components for product compatability and stability than do other pharmaceutical dosage forms. Common container components in direct contact with the product include various types of glass, rubber, plastic, and stainless steel (needles)—all of which may react with the drug. Maintenance of microbiological purity and product stability, adaptability to production operations and inspections, resistance to breakage and leakage, and convenience of clinical use are factors that must be evaluated when selecting the container.

Parenteral packaging includes ampoules (glass-seal), rubber-stoppered vials and bottles, plastic bags and bottles, glass and plastic syringes, and syringe–vial combinations. Glass containers have traditionally achieved widespread acceptability for parenteral products because of their relative inertness. In recent years, hospital preference for unit-dose and clinical convenience has resulted in an increase in products packaged in disposable syringes and the development of polyvinyl chloride, polyester, and polyolefin plastic containers for IV fluids. Package systems, such as the dual chamber plastic container and Add-Vantage, have been developed for

Fig. 14 Dual-chamber Nutri-Mix container for amino acid and dextrose solutions.

combining unstable mixtures of drugs and solutions (Figs. 14 and 15). Several antibiotics that are unstable in solution are now available as a frozen product in a plastic container. These systems are designed for convenience and cost efficiency as well as minimizing the potential of contamination when preparing the admixture. Parenteral packaging materials are discussed in Chapter 18.

Fig. 15 Add-Vantage drug-diluent admixture system.

VII. STABILITY

A formal stability program is needed to assure that all critical attributes of any drug product are maintained throughout the shelf life of the product. A validated stability-indicating assay is essential to measure chemical or biological activity, and acceptance criteria should be established before initiating stability studies. Particular attention should be given to developing a detailed protocol for a stability study before preparing stability samples, including assays to be performed, storage conditions, and sampling intervals.

In general, expiration dating is based on the estimated time required for the active compound to reach 90–95% of labeled potency at the specified storage temperature. However, other considerations may limit the shelf life of the product. For example, the shelf life of products containing a preservative may be determined by adsorption of preservative to a rubber closure or another elastomeric component of the container–closure system. The drug substance itself may be subject to physical instability such as adsorption. The stability program should include placing enough units at the specified storage conditions to allow inspection of a statistically valid number of units to verify acceptable appearance of the product, such as the development of haze or discreet particulate matter in solution products, as well as to check for discoloration or any other physical attribute that would result in unacceptable pharmaceutical elegance. Formulation pH is often a critical attribute that must be monitored during a stability study, since pH may be affected both by chemical reactions in solution or by interactions between the formulation and the container–closure system.

Sterile powders may require special attention to identify which tests are required to assure adequate physical and chemical stability. The stability of many dried products is often sensitive to small differences in the amount of residual water present, requiring monitoring of residual moisture by Karl Fisher titration or loss on drying. This is particularly important for protein formulations. Special efforts may be needed to minimize the residual moisture in rubber stoppers, since water vapor can transfer from the closure to the powder during prolonged storage. Reconstitution time—the amount of time required after addition of diluent until all solids are dissolved—should be measured routinely. For freeze-dried products, cake shrinkage with time is not uncommon. This may be accompanied by discoloration, increased reconstitution time, or crystallization of one or more component of the formulation. The physical state of the drug—crystalline or amorphous—has an important influence on stability, particularly for cephalosporins. Periodic examination of stability samples by x-ray diffraction may be valuable to identify changes in physical state of either drug or excipients that could influence critical quality attributes. For some solid dosage forms subject to oxidative degradation, it is critical to exclude oxygen from the vial headspace. The headspace of selected vials should be analyzed periodically for oxygen. Many freeze-dried powders are stoppered under vacuum or an inert gas. Testing selected vials during the stability study for presence of vacuum in the headspace of the vial is a useful method of verifying container–closure integrity.

Sterile suspensions can be challenging for physical stability, and this should be reflected in the stability protocol. Examples of physical stability issues for suspensions include (a) caking, which causes poor resuspendability; (b) changes in the particle size distribution, particularly growth of large crystals of drug, which can cause poor syringeability; and (c) polymorphic transformations, which can result in changes in dissolution characteristics and, therefore, the bioavailability of the drug.

For parenteral emulsions, the formulation scientist must be particularly aware of changes in particle size distribution of the oil phase. Droplet coalescence results in increased droplet size. As a general rule, average droplet size should be less than 1 μm. Droplet sizes more than about 6 μm can cause adverse effects.

VIII. STERILIZATION METHODS

Five sterilization processes are described in the *USP* [1]: steam, dry-heat, filtration, gas, and ionizing radiation. All are commonly used for parenteral products, except gas and ionizing radiation, which are widely used for devices and surgical materials. To assist in the selection of the sterilization method, certain basic information and data must be gathered. This includes determining (a) the nature and amount of product bioburden, and (b) whether the product and container–closure system will have a predominately moist or dry environment during sterilization. Both of these factors are of critical importance in determining the conditions (time and temperature) of any sterilization method chosen.

The natural bioburden in a well-maintained pharmaceutical parenteral manufacturing plant is quite low, often to the point that it is difficult to isolate and propagate plant bioburden for sterilization studies. Nevertheless, it is still important to characterize the microbiological bioburden in the process and then monitor it at regular intervals.

For sterilization purposes, microorganisms can be categorized into three general categories: (a) easy to kill with either dry or moist heat; (b) susceptible to moist heat, but resistant to dry heat (e.g., *Bacillus subtilis*); or (c) resistant to moist heat but susceptible to dry heat (e.g., *Clostridium sporogenes*). Organisms such as *B. Subtilis* and *C. sporogenes* are often used as biological indicators because they are spore formers of known heat resistance. When used in a known concentration, they will be killed at a reproducible rate. In this manner, when a product has a low bioburden, biological indicator organism(s) can be used at a concentration of 1×10^3 in kill studies to simulate 10^6 kills of natural (environmental) bioburden. Processing and design of container–closure systems for individual products must be reviewed carefully to ascertain whether moist or dry conditions predominate, particularly in difficult-to-reach inner portions of closures. A good review of the use of biological indicators in validating parenteral container–closure systems may be found in Ref. 35.

The *USP* also recommends the use of biological indicators, whenever possible, to monitor all sterilization methods except sterile filtration. Biological indicators are generally of two types. If a product to be sterilized is a liquid, microorganisms are added directly to carefully identified representative samples of the product. When this is not practical, as with solids or equipment to be sterilized, the culture is added to strips of filter paper. The organism chosen varies with the method of sterilization.

Sterilization tests are performed to verify that an adequate sterilization process has been carried out. Validation of the sterilization cycle also gives assurance of process. Sterility is not assured simply because a product passes the *USP* sterility test. As outlined in the *USP*, the sterility test is described in considerable detail, including procedures for sampling, general conditions of the test, and specific procedures for testing solids and liquids. In addition, guidelines for the design of an aseptic work environment are outlined in some detail. Sample limitations, plus the impossibility of cultivating and testing all viable microorganisms that may be present, affect the reliability of sterility tests. Because of these problems, it is necessary to monitor and test sterilization equipment continuously. Reference 35 provides a good review of validation of sterile products.

A. Sterilization by Steam

When drug solutions and containers can withstand autoclaving conditions, this method is preferred to other sterilization methods because moist heat sterilizes quickly and inexpensively. However, judgment must be exercised and experiments run to ensure that the solution and container are permeable to steam. Oils and tightly closed containers, for example, are not normally sterilizable by steam.

Autoclave steam sterilization is a well-established and widely used procedure. Normally, steam enters through the top of the chamber (Fig. 16). Being lighter than air, it remains at the top of the chamber, but steadily and continuously drives the air out of the chamber through the bottom vent throughout the sterilization cycle. The velocity of steam entering the autoclave, the efficiency of water separation from incoming steam, the size of the drain, and the amount of vacuum applied, all are examples of factors that must be controlled to obtain efficient and reproducible steam sterilization in an autoclave. A thorough description of steam sterilization variables and theory can be found in Ref. 36.

With the widespread use of flexible packaging for LVP products, the use of steam sterilization has increased. Compared with the traditional LVP glass bottles closed with rubber stoppers, flexible LVP plastic containers (polyvinyl chloride, polyester, or polyolefin) offer autoclaving advantages. Specifically, (a) a larger surface area is available for heating per unit volume of liquid; (b) if held in a "flattened" position during sterilization, the heat penetration depth required is reduced, resulting in a more uniform thermal mapping of the contents; and (c) shorter heat-up and cool-down periods are required. The net effect is to allow a much shorter sterilization cycle for LVP products packaged in flexible containers, thus exposing the product to less heat, less potential for degradation, and reduced manufacturing costs.

B. Sterilization by Dry Heat

Dry heat is widely used to sterilize glassware and equipment parts in manufacturing areas for parenteral products. It has good penetration power and is not as corrosive as steam. However, heat-up time is slow necessitating long sterilization periods at high temperatures. It is important to allow sufficient circulation around the materials to be sterilized. Metal cans are often used to contain the parts or containers that are to be sterilized.

The two principal methods of dry-heat sterilization are infrared and convection hot air. Infrared rays will sterilize only surfaces. Sterilization of interior portions must rely on conduction. Convection hot-air sterilizers are normally heated electrically and are of two types: gravity or mechanical. In gravity convection units, a fan is used to promote uniformity of heat distribution throughout the chamber.

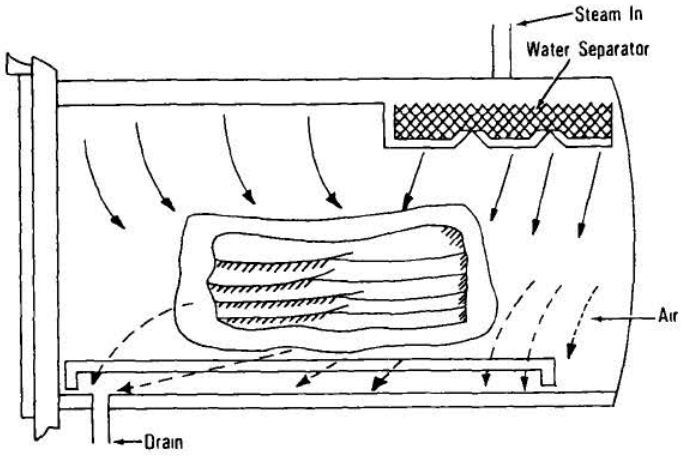

Fig. 16 Gravity displacement steam sterilizer.

Dry-heat processes kill microorganisms primarily through oxidation. The amount of moisture available to assist sterilization in dry-heat units varies considerably at different locations within the chamber and at different time intervals within the cycle. Also, the amount of heat available, its diffusion, and the environment at the spore–air interface all influence the microorganism kill rate. Consequently, cycles tend to be longer and hotter than would be expected from calculations, to ensure that varying conditions do not invalidate a run. In general, convection dry-heat sterilization cycles are run above 160°C [37].

C. Sterilization by Ethylene Oxide

Ethylene oxide (ETO), a colorless gas, is widely used as a sterilant in hospitals and industry for items that cannot be sterilized by steam. It is often diluted with carbon dioxide, or sometimes fluorocarbons, to overcome its flammable and explosive nature. The mechanism by which ETO kills microorganisms is by alkylation of various reactive groups in the spore or vegetative cell. One of the more resistant organisms to ETO is *B. subtilis* var. *niger* (*globigii*). It is the *USP* biological indicator for monitoring the effectiveness of ETO sterilization cycles. Several factors are important in determining whether ETO is effective as a sterilizing gas: gas concentration, temperature, humidity, spore water content, and substrate for the microorganisms. Ethylene oxide should be present at a concentration of about 500 ml/liter for maximum effectiveness. Once gas concentration is not a limiting factor, the inactivation rate of spores by ETO doubles for each 10°C rise in temperature. Relative humidity plays an important role, in that the sensitivity of spores to ETO largely depends on the water content of the spore.

A "typical" ETO sterilization cycle is shown in Fig. 17. As discussed at the beginning of this section, it is important to determine and monitor the bioburden level of the product entering the sterilizer. Also, the load configuration in the sterilizer is important in achieving uniform and reliable sterilization. Unfortunately, commercially available biological indicators used in ETO sterilization are often unreliable. Hopefully, progress will be made in this field in the years ahead.

Unlike other methods, it is necessary to posttreat the product, either through vacuum purging or by allowing the product to remain at ambient conditions for a time, to allow removal of residual ETO and ethylene chlorhydrin/ethylene glycol by-products before use by the consumer.

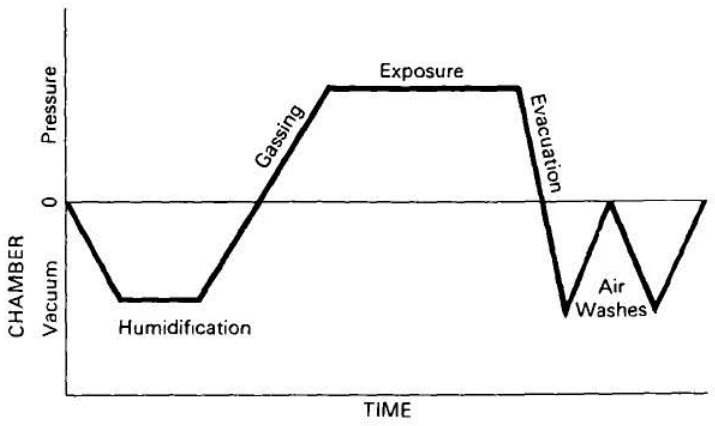

Fig. 17 Ethylene oxide sterilization cycle.

In addition, in 1984 OSHA lowered the maximum permissible operator 8-hr exposure level from 50 ppm in air to 1 ppm (on a time-weighted average) [38].

D. Sterilization by Filtration

It has been only in the past 20 years that filters have become sufficiently reliable to use them on a wide scale to sterilize injectable solutions. Even now, it is prudent to use filtration to sterilize only those products that can not be terminally sterilized.

Filters are of two basic types, depth and membrane. Depth filters rely on a combination of tortuous pathway and adsorption to retain particles or microorganisms. They are made from materials such as diatomaceous earth, inorganic fibers, natural fibers, and porcelain. They carry a nominal rating; that is, a particle size above which a certain percentage of particles is retained. The major advantage of depth filters is their ability to retain large quantities of particles, including many below the nominal rating of the particular filter. Disadvantages of depth filters include grow-through and reproduction of microorganisms, tendency of the filter components to slough during line surges, and retention of some liquid in the filter. Membrane filters rely on sieving and, to a lesser degree, absorption to prevent particles from passing. Although all pores in a membrane filter are not of the same size, nevertheless, the filter can retain all particles larger than the stated size.

Similar to depth filters, membrane filters are made from a variety of materials, although filters made from cellulose ester derivatives are by far the most common. The advantages of membrane filters include no retention of product, no media migration, and efficiency independent of flow-rate pressure differential. The major disadvantages are low capacity before clogging and the need to prewash the filters to remove surfactants. Given the advantages and disadvantages of each type of filter, when large quantities of liquids are to be sterile filtered, such as in industrial applications, it is very common to use a relatively coarse depth filter (1–5 μm) to remove the great majority of particles and, subsequently, use a membrane filter to remove the remaining particles and microorganisms down to a predetermined size (0.22 μm).

Filter cartridges are used for filtering large volumes of solution or more viscous products because of the large surface area that is available through the pleated design. Hydrophobic filters are also available for sterile filtering of gases and solvents [39].

IX. CLINICAL CONSIDERATIONS IN PARENTERAL PRODUCT DESIGN

The formulator must take into consideration all the factors that will improve the clinical acceptability and safety of a product. To minimize tissue damage and irritation and to reduce hemolysis of blood cells and prevent electrolyte imbalance, isotonic solutions should be formulated, if possible. This is not always feasible as a result of the high concentrations of drugs used and the low volumes required for some injections; the wide variety of dose regimens and methods of administration; or because of product stability considerations. Historically, there has been concern over the osmolarity or tonicity of IV fluids. There has also been interest in the osmolarity of other parenteral dosage forms. As mentioned previously, sodium or potassium chloride and dextrose are commonly added to adjust hypotonic solutions.

The effect of isotonicity on reducing pain on injection is somewhat vague, although it may at least reduce tissue irritation. Pain on injection may occur during and immediately following the injection, or it may be a delayed or prolonged type of pain that becomes more severe after subsequent injections. The actual cause of the pain is often unknown and will vary significantly

among patients and according to the product. In some cases, pain may be reduced by minor formulation changes, such as adjusting tonicity and pH, or by adding on anesthetic agent, such as benzyl alcohol or lidocaine hydrochloride. In other cases, pain is more inherent to the drug, and pain reduction is more difficult or impossible to resolve. Pain, soreness, and tissue inflammation are often encountered in parenteral suspensions, especially those containing a high amount of solids.

Thrombophlebitis, which is an inflammation of the venous walls, may occur during IV administration and may be related to the drugs being infused, the administration techniques, the duration of the infusion, and the tonicity, and possibly, the pH of the infusion fluid [40]. It has been difficult to define the relative importance of each because of the interplay of all these variables. Some drugs do cause a more significant amount of phlebitis than others. Perhaps the most important factor is administration technique. Proper cleaning of the injection site, the type of cannula employed, strict adherence to aseptic techniques when one is preparing and administering the fluid, and the duration of the infusion are factors that influence the degree of phlebitis that may occur.

The formulator should be aware of the types of clinical use of a drug when designing the dosage forms. Specific examples are pediatric dosage forms and unit dosage forms—including disposable syringes and special packages for hospital, office, or home administration. Hospital packages can take several forms, depending, for example, on whether the package is to be unit-dose, reconstituted by a nurse, bulk dispensed in the pharmacy, or administered as a secondary "piggyback" IV container.

Drugs that affect tissue properties, particularly blood flow at the absorption site, may be used to control the rate of absorption. Reduced drug absorption may be achieved physiologically with an IM preparation by incorporating epinephrine, which causes a local constriction of blood vessels at the site of injection. Increased muscular activity may enhance drug absorption because of increased drug flow.

When preparing preparations for IV and IM use, the formulator must be aware of the effect of added substances when unusually large doses of the drug are administered. Although the *USP* limits the use of some added substances (Table 4), these types of problems cannot always be anticipated. The *USP* urges special care when administering over 5 ml [1]. When effects do become apparent, the formulator should consider additional dosage sizes or formulation changes. Sometimes during the life of a drug product, new uses and larger doses make the original formula unsatisfactory. When this happens, a new dosage form should be designed and the appropriate cautionary statements placed on the respective labels. The "precautions,

Table 4 Maximum Amounts of Added Substances Permitted in *USP* Injectable Products

Substance	Maximum (%)
Mercury compounds	0.01
Cationic surfactants	0.01
Chlorobutanol	0.5
Cresol	0.5
Phenol	0.5
Sulfur dioxide	0.2
or sodium bisulfite equivalent	0.2
or sodium sulfite equivalent	0.2

problems, hazards, and complications associated with parenteral drug administration'' are discussed extensively by Duma and Akers [41].

All parenteral dosage forms must be sterile, pyrogen-free and essentially free from particles that can be detected by visual inspection. Sources of particulate matter include the drug substance, other components or the vehicle; the manufacturing process, which includes the personnel, environment, equipment; and the packaging components. The *USP* provides methods and standards for a microscopic and an electronic liquid-borne particle counting system for large-volume and small-volume parenterals.

The preparation of a new drug substance or dosage form for evaluation in clinical trials must meet the same regulatory requirements and controls as a marketed product. The cGMP requirements for clinical trial products are outlined by the FDA and are discussed in Chapter 21.

The formulator of a new product must consider the manufacturing process to be used for full-scale production of the product. Many new product failures or deficiencies occur because of the inability to resolve or foresee production-related problems, rather than poor product development per se. Therefore, the scientist who has formulated the product must be involved in the development of its manufacturing process and testing. For example, at scale-up, it was found that there was a loss of preservative in the portion of solution/suspension that was in prolonged contact with the transfer tubing during ''down'' time. This was not observed on a small-scale process with less down time and minimum tubing exposure.

The use of clinical trial manufacture as trial production runs provides valuable information and experience for evaluating the scale-up of the formulation and the process. If validated bulk-drug substance is available during the latter stages of the clinical studies (Phase III), this provides an ideal time to validate the manufacturing process. By using this approach, stability data are included in the validation package, thereby reducing the total amount of stability studies. Also, the validated lots can be used in clinical studies. This also permits a thorough evaluation of the process and specifications before submission of the NDA or the registration document.

A. Toxicity Studies

In toxicity studies, acute toxicity tests are usually carried out in the rat, mouse, cat, and dog. Subacute toxicity studies for IM products are performed by giving SC injections to rats and IM injections to dogs. In IV studies the rat tail vein or a front leg is used. Deliberate overdosing usually ''washes out'' metabolism differences between species. In dogs it is common to give an IV dose five times that intended for humans. In rats this is increased to ten times.

Irritation studies are done in rabbits. Each rabbit serves as its own control. The concentration selected for the irritation studies is that intended for humans.

B. Clinical Evaluation

Clinical evaluation of the dosage form is the most expensive and critical phase of product development. All that has been done before this point has been done in an effort to ensure a safe and reliable product for the clinician.

A drug company normally assigns one of its staff physicians as ''monitoring'' physician for the clinical trial (CT) program. The monitoring physician has the key role in the conduct of the CT program (Fig. 18). He or she coordinates the establishment of clinical protocols, the awarding of grants, the gathering and ''in-house'' evaluation of clinical data, and preparation of the FDA submission.

The monitoring physician must first establish what the clinical protocol is going to be. With injectable products, this involves both a clinical pharmacology safety test and a dose-ranging

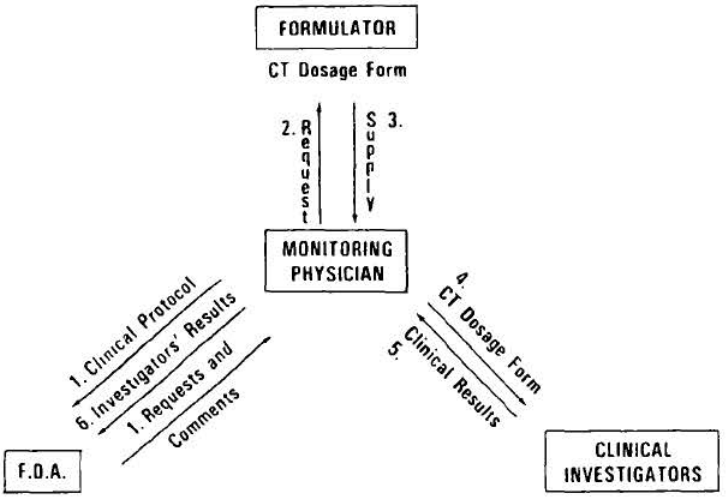

Fig. 18 Clinical trial scheme.

study in humans. These studies are normally a single IM injection in several patients. Depending on the drug, clinical studies may proceed eventually to controlled double-blind studies. Care must be exercised to involve a sufficient number of patients to make the studies statistically meaningful. If it is intended that treatment of several clinical conditions is to be claimed for the product, each must be evaluated separated. Throughout the course of the studies, there is a continuing dialogue between the FDA and the monitoring physician.

When the clinical program has been approved by a peer review committee and filed with the FDA, the monitoring physician requests a sufficient amount of material from the formulator to initiate the clinical program. Before the dosage form is released to the custody of the monitoring physician, the new drug substance and the formulated product must be thoroughly evaluated to ensure proper potency, purity, and safety. Stability studies must also be initiated so that, if the product becomes subpotent or physically unstable during the course of the clinical trial, it can be recalled before any harm can result to the patients in the study.

After release of CT material, the monitoring physician supplies it to the clinical investigators with whom the clinical program has previously been discussed. As the clinical investigators use the product, they begin sending in reports to the monitoring physician, who evaluates them and sends them to the FDA. Although the concept shown in Fig. 18 is oversimplified, it does convey the principal framework under which the clinical trials are conducted.

X. QUALITY ASSURANCE

The terms *quality assurance* and *quality control* are sometimes used interchangeably, but there is an important difference in meaning. Quality control generally refers to testing of raw materials, packaging components, and final product for conformance to established requirements. Quality assurance is a term that includes quality control, but has broader meaning to also include written operating procedures, personnel training, record keeping, and facility design and monitoring. The philosophy of a quality assurance program is to build quality into the product, rather than to rely only on final product testing to cull out defective product.

Although principles of quality control and quality assurance are important to all pharmaceutical dosage forms, they are especially critical when considering the unique attributes of parenteral dosage forms–sterility, absence of pyrogens, and freedom from extraneous particulate matter. Quality control is generally divided into three areas: (a) raw materials, (b) in-process controls, and (c) product specifications. However, numerous attributes for a product have to be considered throughout all phases of development, evaluation, production, and storage to guarantee good quality.

The factors necessary to achieve quality in a product during the developmental stage have been discussed. The formulator of a new product must consider the manufacturing process to be used for full-scale production of the product. Many new product failures or deficiencies occur because of inability to resolve or foresee production-related problems, rather than to poor product development per se. Therefore, the scientist involved in the development of a product must be involved in development of its manufacturing process and testing. Standards must be carefully established for all raw materials and packaging components used in the product so that the quality of the product will be maintained. Trial production runs should be performed on a new product for stability testing and process evaluation.

A. Regulatory and Compendial Requirements

The manufacture and sale of parenteral products is regulated by federal and state laws, as well as by the *USP*. Federal drug regulations are discussed in detail in Chapter 21. The *USP* provides specifications, test procedures, standards, and so on. for parenteral products and their packaging components. In addition to individual monographs, the *USP* limits the use of certain additives (see Table 4), limits the size of multiple-dose containers to 30 ml, and requires a suitable preservative to be added to containers intended for multiple use.

The current Good Manufacturing Practice (cGMP) regulations are guidelines that the FDA requires a pharmaceutical manufacturer to meet. Compliance with the cGMPs is a prerequisite for the approval of NDAs, INDs, and antibiotic forms. General areas in which GMP guidelines must be established and adhered to include:

Organization and personnel
Buildings and facilities
Control of drug components, packaging, and materials
Production and process control
Equipment
Packaging and labeling control
Holding and distribution
Laboratory control
Records and reports

Parenteral formulation and the preparation of parenterals for clinical trial use obviously require adherence to cGMPs. A development group that generates CT materials should have guidelines and written procedures covering such areas as equipment (validation, maintenance, and cleaning), environment (monitoring and cross-contamination), instruments (maintenance and monitoring), housekeeping, documentation, training, and material handling and storage. Sterilization methods, aseptic processing, and filling techniques and methods, all must be validated to assure product sterility and quality. *Validation* is the process of proving that a process or equipment does what it is supposed to do within the established limits. All individuals performing an aseptic process must periodically pass a test to verify their aseptic technique.

B. Monitoring Programs

Process Facilities

Continual evaluation of manufacturing processes are necessary to maintain "good manufacturing practices." Facilities, buildings, and equipment used in the production of parenteral products must be specially designed for this purpose. Factors to be considered when designing a new plant include environmental conditions, work flow, equipment, choice of materials, personnel, organization, process, documentation, production hygiene, and process controls [42,43]. Thorough planning and engineering of a parenteral facility will not only help maintain the quality of the manufactured products, but will simplify cleanup and maintenance requirements. Contamination of a product is minimized by maintaining a clean facility.

Production Areas

Production areas can be separated into seven general classes: cleanup area, preparation area for packaging materials, preparation area for drug products, sterilization facilities, aseptic filling and processing areas, sorting and product holding areas, and a labeling section.

The exact identity of all packaging components, the bulk and filled product, labels, and so on, must be carefully maintained. The production ticket must be written so that it is easily understood and followed by the appropriate production personnel. All procedures should be clearly outlined and limits established for all operators, (e.g., "Heat water to 35–45°C" or "Autoclave sterilize for 15–20 min at 121–124°C).

All production processes, such as ampoule washing and sterilization, solution filtration, equipment setup and operation, sorting, and freeze-drier cleaning and operation, should be covered in detail in a procedure manual to ensure that all operations are understood as well as carried out properly and uniformly. Cleaning, sterilization, sterile filtration, filling, and aseptic processing operations must be validated.

Personnel

People are the principal source of contamination in clean room operations. All personnel involved throughout the development and production of a parenteral product must be aware of those factors that influence the overall quality of a product as well as those factors on which they directly impinge. It is of particular importance that production personnel be properly trained so that human error is minimized. They should be made aware of the use of the products with which they are involved and the importance of following all procedures, especially proper aseptic techniques. Procedures must be set up to check and verify that the product is being manufactured as intended. After manufacture of a batch, production tickets must be carefully checked, sterilization charts examined, and labels verified for correctness and count.

Environmental Monitoring

Control of environmental factors is important to product quality. Air quality and air movement, care and maintenance of the area, and personnel movement and attire are of particular importance.

The air quality in preparation and aseptic areas can be one of the greatest sources of product contamination. However, this problem can be minimized by use of the effective equipment currently available to provide clean air essentially free from microorganisms and dirt particles. Depth-type filters, electrostatic filters, and dehumidification systems are used to remove the major portion of the airborne contaminants. Air for aseptic areas is then passed through high-efficiency particulate air (HEPA) filters, which remove 99.97% of all particles 0.3 μm or larger. To prevent outside air from entering aseptic areas, a positive pressure is maintained relative to corridors.

A laminar flow enclosure provides a means for environmental control of a confined area for aseptic use. Laminar flow units utilize HEPA filters, with the uniform movement of air along parallel lines. The air movement may be in a horizontal or vertical direction and may involve a confined area, such as a workbench, or an entire room. Laminar flow modules are suspended above filling lines, vial- and stopper-washing equipment, and other processes to provide an aseptic and particulate-free environment.

Regardless of the methods used to obtain a clean air environment, unless the parenteral operator is made completely aware of the limits of laminar flow, uses careful, planned movements, and is wearing proper clothing, he or she can be a source of product contamination. Operator movement within aseptic rooms should be minimized. The rooms must be disinfected regularly and thoroughly before setting up for aseptic operation.

Commonly used environmental monitoring techniques include the following:

Passive Air Sampling. Petri dishes containing microbiological growth media are placed in aseptic areas for specified lengths of time, the "settling plates" are then incubated and colonies are counted and identified. This is a qualitative test, since there is no way of knowing the volume of air represented by a given number of colonies.

Active Air Sampling. Active air sampling provides quantitative data because air at a known flow rate is impacted on a strip of nutrient media, followed by incubation of the nutrient strips and enumeration of colonies. Common active air sampling instruments include the slit-to-agar impact sampler and the centrifugal (Reuter) sampler.

Air Classification Measurement. Electronic airborne particle monitoring instruments count and size particulate matter in the sampled air with no consideration of whether the particles are viable or nonviable. Air classification is defined as the number of particles per cubic foot of air that are larger than 0.5 μm in diameter. Climet and HIAC-Royco are common instruments for airborne particulate monitoring).

Surface Monitoring. Contact (or Rodac) plates of growth media are applied to surfaces such as bench tops, walls, and personnel, then incubated. Colony-forming units (CFUs) are counted and identified.

Differential Pressure Measurement. Differential manometers are instruments that measure the difference in pressure between two adjacent rooms. Cleaner environments must have a higher pressure than adjacent less clean environments to prevent flow of relatively dirty air into the cleaner environment. This differential pressure must be monitored and controlled.

C. Product Testing and Evaluation

Quality control testing and evaluation is involved primarily with incoming raw materials, the manufacturing process, and the final product. Testing of incoming raw materials includes routine testing on all drugs, chemicals, and packaging materials.

Process controls include daily testing of water for injection (USP), conformation of fill doses and yields, checking and approving intermediate production tickets, and checking label identity and count. Finished product control includes all the tests necessary to ensure the potency, purity, and identity of the product. Parenteral products require additional tests, which include those for sterility, pyrogens, clarity, and particulate analysis; and for glass-sealed ampoules, leaker testing.

Sterility Testing

The purpose of a sterility test is to determine the probable sterility of a specific batch. The *USP* lists the procedural details for sterility testing and the sample sizes required [1]. The *USP*

official tests are the direct (or culture tube inoculation) method and the membrane filtration method.

The interpretation of sterility results is divided into two stages by the *USP* relative to the type of sterility failure if one occurs. If sterility failure of the test samples occurred because of improper aseptic technique or as a fault of the test itself, stage 1 may be repeated with the same sample size. Sample size is doubled in a stage 2 testing, which is performed if microbial growth is observed in stage 1 and there is no reason that the test was invalid. The only absolute method to guarantee the sterility of a batch would be to test every vial or ampoule.

There is a probability of non-product-related contamination in the order of 10^{-3} when performing the sterility test because of the aseptic manipulations necessary to carry out the procedure. This level (10^{-3}) is comparable with the overall efficiency of an aseptic operation. Confidence in the sterility test is dependent on the fact that the batch has been subjected to a sterilization procedure of proved effectiveness. Records of all sterility tests must be maintained, as well as temperature recordings and records from autoclaves, ovens, or other equipment used during the manufacturing process. All sterilizing equipment must be validated to ensure that the proper temperatures are obtained for the necessary time period. These validations are obtained by the use of thermocouples, chemical and biological indicators, sealed ampoules containing culture medium with a suspension of heat-resistant spores, and detailed sterility testing.

Pyrogen Testing

Pyrogenic substances are primarily lipid polysaccharide products of the metabolism of microorganisms; they may be soluble, insoluble, or colloidal. Pyrogens produced by gram-negative bacilli are generally the most potent. Minute amounts of pyrogens produce a wide variety of reactions in both animals and humans, including fever, leukopenia, and alterations in blood coagulation. Large doses can induce shock and eventually death.

Pyrogens readily contaminate biological materials because of their ability to withstand autoclaving as well as to pass through many filters. Several techniques are used to remove them from injectable products. The ideal situation is one in which there are no pyrogens present in the starting materials. This is achieved by strict control of the cleanliness of equipment and containers, distillation of water, and limited processing times. In general, pyrogens may be destroyed by being subjected to prolonged heating. Other pyrogen-removal techniques, which are generally less effective or applicable, include filtration, absorption or adsorption, chemical (oxidation), aging, or a combination of these.

One pyrogen test is a qualitative biological test based on the fever response of rabbits. If a pyrogenic substance is injected into the vein of a rabbit, a temperature elevation will occur within 3 hr. Many irritative medical agents will also cause a fever.

A preferred method for the detection of pyrogens is the limulus amebocyte lysate (LAL) test. A test sample is incubated with amebocyte lysate from the blood of the horseshoe crab, *Limulus polyphemus*. A pyrogenic substance will cause a gel to form. This is a result of the clottable protein from the amebocyte cells reacting with the endotoxins. This test is more sensitive, more rapid, and easier to perform than the rabbit test.

Leaker Testing and Sealing Verification

Ampoules that have been sealed by fusion must be tested to ensure that a hermetic seal was obtained. The leaker test is performed by immersing the ampoules in a dye solution, such as 1% methylene blue, and applying at least 25 in. (ca. 64 cm) of vacuum for a minimum of 15 min. The vacuum on the tank is then released as rapidly as possible to put maximum stress on weak seals. Next, the ampoules are washed. Defective ampoules will contain blue solution.

Another means of testing for leakers is a high-frequency spark test system developed by the Nikka Densok Company of Japan, which detects the presence of pinholes in ampoules.

Some advantages of this system include higher inspection accuracy, higher processing speed, and eliminating the possibility of product contamination [44].

Bottles and vials are not subjected to such a vacuum test because of the flexibility of the rubber closure. However, bottles that are sealed under vacuum may be tested for vacuum by striking the base of the bottle sharply with the heel of the hand to produce a "water hammer" sound. Another test is the spark test, in which a probe is applied outside the bottle. When it reaches the air space of the bottle, a spark discharge occurs if the headspace is evacuated.

The microbiological integrity of various packages, such as vials and stoppers, disposable syringes, and plastic containers, should be determined. A microbiological challenge test is performed by filling the package with a sterile medium and then exposing the sealed container to one of the following tests that is appropriate for the package system: (a) static-aerosol challenge, (b) static-immersion challenge, (c) static-ambient challenge, or (d) dynamic-immersion challenge. The static-immersion challenge test is used commonly with new package combinations. The sealed containers are periodically challenged by immersion into a suspension of challenge organisms. Storing the containers at 5° or 40–50°C, or both, before immersion provides additional stress.

Clarity Testing and Particulate Analysis

Clarity is defined as the state or quality of being clear or transparent to the eye. Clarity is a relative term subject to the visual acuity, training, and experience of the sorter. Clarity specifications are not given in the *USP*, other than to state that all injections be subjected to visual inspection.

Particulate matter is defined in the *USP* as extraneous, mobile, undissolved substances, other than gas bubbles, unintentionally present in parenteral solutions. Test methods and limits for particulates are stated in the *USP* for large-volume injections and small-volume injections.

The development of sorting standards is the responsibility of the manufacturer. Parenteral solutions are sorted for foreign particles, such as glass, fibers, precipitate, and floaters. The sorter also checks for any container deficiency and improper dose volume when feasible. All products containing clear solutions should be inspected against a black and sometimes a white background using a special light source. Although manual visual inspection is the most common means of inspection, electronic particle detection equipment and computer-controlled electro-optic systems are replacing manual inspection and use a light source or camera, or both, positioned behind, above, or below the units being inspected.

Instruments that measure scattered light, such as the Photo-Nephelometer (Coleman Instruments, Oak Brook, IL) are used to evaluate and set clarity standards for parenteral preparations. It is not possible to establish an overall standard value for all products (e.g., 30 nephelos) because the value itself is relative and influenced by many factors, including concentration, aging, stopper extracts, and the solubility characteristics of the raw materials. Nephelometer readings are insensitive to contamination by large (visible) particulates.

The significance of particulate contamination in all parenteral preparations and devices has received much attention. Although it has not been established that particles can cause toxic effects, the pharmaceutical industry, the medical profession, hospital pharmacists, and the FDA, all realize the importance of reducing particulate levels in all parenteral products and devices.

Sources of particulate matter include the raw materials, processing and filling equipment, the container, and environmental contamination. Several methods have been developed for identifying the source of particulates in a product so that they may be eliminated or reduced. The most effective method is that of collecting the particulates on a membrane filter and identifying and counting them microscopically. However, this method is time-consuming and not adaptable to in-line inspection. Several video image projection methods for in-line detection

of particles have been developed that provide potential for mechanizing inspection. Electronic particulate counters have been applied to parenterals because of the rapidity at which they do particulate analysis. Their main disadvantages are the lack of differentiation of various types of particulates including liquids such as silicones, and the fact that particle size is measured differently from microscopic analysis. The *USP* tests for particulate matter in injections utilizes both the microscopic and light obscuration methods [1].

Labeling

The package and, in particular, the labeling for parenteral dosage forms are integral and critical parts of the product. The labeling must be legible and clearly identify the drug, its concentration, handling or storage conditions, and any special precautions. The dose or concentration must be prominently displayed when other concentrations of the same drug are marketed. Proper labeling is difficult with the space limitation dictated by small containers used for many parenteral products. Smaller containers have become increasingly popular because of the unit-dose concept.

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