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Pharmaceutical and Cosmetic Aerosols

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Keyphrases □ Aerosols, pharmaceutical and cosmetic—product formulation, components, manufacturing and packaging, testing, toxicity, and abuse, review □ Pharmaceutical aerosols—product formulation components, manufacturing and packaging, testing, toxicity, and abuse, review □ Cosmetic aerosols—product formulation components, manufacturing and packaging, testing, toxicity, and abuse, review □ Dosage forms, aerosols—literature review of pharmaceutical and cosmetic aerosols □ Toxicity—pharmaceutical and cosmetic aerosols, review

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Aerosol science and technology have been extended to numerous different products over the past 10–15 years, as evidenced by the fact that during 1973 over 2.9 billion aerosol units were produced in the United States and Canada (1). This amount, together with the over 1.5 billion units produced in the rest of the world, makes an impressive record based upon units produced (2). However, not so impressive when compared to these figures is the total production of pharmaceutical aerosols during the past years. In 1973 this production amounted to approximately 45 million units (1). Included were such products as antiasthmatic sprays, burn treatments, room vaporizers, antiseptics, oral anesthetics, contraceptives, fungicides, and various dermatological products. These product types are representative of the nature of pharmaceuticals packaged in aerosol form.

If one were to include in this category many of the products classified as "cosmetics," then the product figures as well as product categories present quite a different picture. Products such as antiperspirants and deodorants, feminine hygiene sprays, and various skin products accounted for over 500 million units during this same year (1). The development and formulation, as well as the manufacture and distribution of many of these cosmetic products, have come within the sphere of interest of the "pharmaceutical scientist" and the pharmaceutical industry due to diversification within the pharmaceutical industry as well as acquisition of pharmaceutical concerns by cosmetic companies and vice versa.

The first textbook devoted exclusively to the subject of aerosol science and technology appeared in 1958 and was authored by Herzka and Pickthall (3).

This was followed by the second edition in 1961 (4). In 1961, Shepherd (5) edited a comparable aerosol textbook, and other aerosol textbooks have appeared over the years (6–11). While all of these publications cover the aerosol field, the text by Johnsen *et al.* (10) is intended primarily as a reference to many practical aspects of aerosol technology such as crimping of valves, quality control systems, and container and valve specifications. The Sanders book (9) is intended as a teaching tool, while the Sciarra and Stoller text (11) covers the teaching aspects and serves as a reference for the development of various types of aerosol products. Many chapters on the subject of pharmaceutical and/or cosmetic aerosols have appeared in these as well as other books (12–21).

Aerosols as a dosage form have been accepted by both the USP (22) and the NF (23). In addition to containing definitions and test procedures in regard to aerosol dosage forms, the NF contains monographs for several commonly used propellants including trichloromonofluoromethane (24), dichlorodifluoromethane (25), and dichlorotetrafluoroethane (26).

Various medicinal agents have been formulated as aerosol dosage forms. These aerosols have been administered orally for either inhalation therapy or local activity in the lungs and externally to treat various skin conditions.

Several investigators have commented that pharmaceutical aerosols have not been developed and used to the same extent as other aerosols. According to a recent report, inhalation bronchial dilators are probably the largest single category of aerosol pharmaceuticals sold in pharmacies and hospitals, followed by antiseptic sprays and proprietary asthma control preparations. The fatalities that occurred in England and other European countries with these preparations and the ensuing unfavorable publicity probably accounted for a decrease in the sale of inhalation aerosol products (27). Stolley (28) indicated that these mortalities were due to the fact that most of these preparations contained a fairly high dosage of isoproterenol. The most frequently prescribed nebulizers in the United Kingdom contained a concentration of isoproterenol five times greater than that generally used in the United States. These preparations delivered a dose of active ingredient ranging from 0.08 to 0.40 mg/spray. Others (29, 30) have indicated different reasons for the difference in the mortality rate between these countries.

The development and growth of pharmaceutical aerosols have been, and always will be, relatively slow compared to the growth of other aerosols such as shave creams, insecticides, antiperspirants, deodorants, and room deodorants (31–34). According to Parisse (33): "Toxicological information concerning the inhalation of drugs is extremely sparse. Although a New Drug Application will most probably be required for any compound selected, it should be less burdensome to work with those drugs which have good toxicological histories in other dosage forms." He also indicated that the effective concentration for the drug when given by inhalation may be different from the concentration used in other dosage forms.

Other properties such as solubility of the drug in secretions, hygroscopicity of the drug, particle-size distribution, and selection of the propellant should also be considered. Pick (34) indicated that, with the exception of inhalation products for bronchospasms, the real potential for pharmaceutical aerosols has not been exploited. In addition, other problems such as the need for pharmaceutical grade components and FDA regulations resulted in a slower growth rate for pharmaceutical aerosols.

Research leading to the development and/or improvement of pharmaceutical aerosols has greatly increased during the past 10 years. This research has centered around several areas such as product formulation, aerosol components, propellant and product toxicity, and manufacturing and packaging technology including quality control and testing procedures.

PRODUCT FORMULATION

Pharmaceutical aerosols have been formulated as solutions, suspensions, emulsions, or semisolids (35–38).

Solution aerosols consist of solutions of active ingredients dissolved directly in the liquefied gas propellant or in a mixture of a cosolvent and propellant. These products are generally dispensed as a spray forming fairly small (about 0.5–1.0 μm) droplets to fairly large ones (about 50–100 μm), depending upon the valve characteristics and the nature and amount of the propellant.

Suspensions consist of dispersions or suspensions of the active ingredient in a mixture of the propellant, solvents, and suitable dispersing agents. These products are also dispersed as a fine spray with varying degrees of wetness, depending upon the solvents and propellants used. Emulsions can be dispensed either as a foam or spray, depending upon the specific formulation. Generally, water-in-oil-type emulsions (propellant is in the oil phase) are dispensed as fine droplets while oil-in-water types are dispensed as a foam. The stability of the foam can vary greatly, from very stiff to quick breaking. Semisolid formulations are generally dispersed in their original state, with the exception of some newer postfoaming gels.

Systems—Various systems have been used to dispense pharmaceutical aerosols. The use of conventional aerosol systems for various aerosol products is widespread and well known. These systems are capable of dispensing selected products as sprays or foams and depend upon the presence of from 5 to 95% of liquefied gas propellant. In certain instances, compressed gases have been utilized to accomplish the same end effect. While the liquefied gas propellant is chiefly of the fluorinated hydrocarbon type, hydrocarbons have been used to advantage in some systems.

While most aerosol products in present day usage utilize one of these systems, many products cannot utilize these systems for numerous reasons. The viscosity of the product, the incompatibility of the product concentrate and propellant, and the desired dispensing characteristic of the finished product represent a few of the limitations of these systems. Several additional systems are available and are character-

Table I[a]—Ostwald Solubility Coefficient at 21.1°

Solvent	Solubility Coefficient: Nitrous Oxide	Solubility Coefficient: Carbon Dioxide
Water	0.6	0.85
Acetone	5.92	6.95
Ethanol	2.96	2.84
Methanol	3.20	3.51
Chloroform	5.54	3.6
Acetic acid	4.77	5.1
Methyl acetate	—	6.4
Ether	7.65	6.32
n-Pentane	4.13	1.94
Carbon tetrachloride	2.5	4.28
Ethylene bromide	2.7	2.1
Glycerin	1.2	0.03
Ethylene chloride	3.2	3.7

[a] From Ref. 52.

ized by providing for a physical separation of the propellant and product.

Many designs have been submitted for these systems, but only two basic ones have been accepted: the barrier packs and the siphon systems. Barrier packs utilize a plastic bag or piston to separate the product from the propellant, while siphon systems utilize a propellant cartridge and an outer nonpressurized container holding the product. While both systems separate the propellant from the product, they differ in several respects. In barrier packs, only the product is delivered and there is never any contact between the product and propellant (except for any propellant or product that may permeate through the plastic bag or piston). Since the propellant is located within the product container in siphon systems, the outer container no longer needs to be made from the materials used in the manufacture of conventional aerosol containers. With the absence of pressure, this container can be made of plastic and other similar materials in addition to metal and glass and there is a greater freedom in design. These systems and their potential application to pharmaceutical systems have been reviewed extensively in the literature (39–46).

Sciarra (47) discussed the potential application of codispensing systems for pharmaceuticals. Any reaction resulting in precipitation, liquefication, oxidation–reduction, hydrolysis, or the evolution of a gas is a candidate for codispensing. This system was developed during the late 1960's (48) and has been used to dispense two incompatible ingredients, such as hydrogen peroxide and a reducing agent, resulting in the liberation of sufficient heat. When combined with a shave cream formulation, a hot foam is produced. Figure 1 illustrates the temperature rise noted using different concentrations of reducing agent (49).

At the present time, shave foams are heated by the reaction of an oxidizing agent with a reducing agent. The reducing agent, such as a sulfite, thiosulfate, urea, or thiourea, is placed with the external phase consisting of soap solution and propellant while the oxidizing agent, such as hydrogen peroxide, is kept within a plastic bag attached to the valve.

Hair dyes have also been developed in this system where the dye and propellant are in the external phase and the ammonium hydroxide is kept within

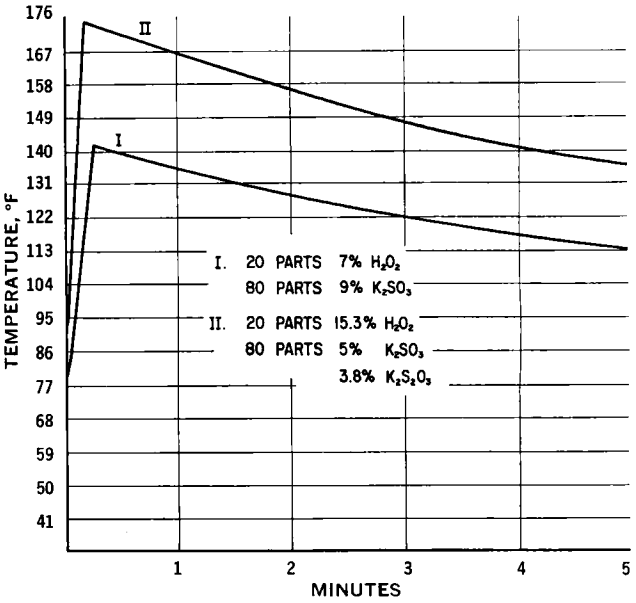

Figure 1—*Heat production from hydrogen peroxide (H_2O_2) reacted with potassium sulfite (K_2SO_3) and potassium thiosulfate ($K_2S_2O_3$). (From Ref. 49.)*

the bag. An antiperspirant preparation containing a high concentration of aluminum salt also utilizes this system. One phase contains the aluminum salt while the other phase contains the solvents and propellant.

Propellants—One important component of the aerosol dosage form is the propellant. Even though investigations were carried out using compressed gases as possible propellants for aerosols, liquefied gases and, in particular, fluorinated hydrocarbons still remain the propellant of choice for most applications. Hostier (50) described the various classifications of propellants along with methods for determining gas concentration, solubility, temperature effect, and the influence of pressure. Holzner (51) suggested the use of carbon dioxide and nitrous oxide in combination with fluorinated hydrocarbons. Since these gases are somewhat soluble in different aerosol systems, they tend to give a fine dispersion of the product and also to compensate partially for the drop in pressure brought about by a change in volume as the product is dispensed.

Hsu and Campbell (52) developed several equations which can be used to calculate the solubility of compressed gases in a given formulation. Based upon the Ostwald solubility coefficient (λ) for a particular solvent:

$$\lambda = \frac{\text{volume of gas dissolved}}{\text{volume of liquid}} \qquad \text{(Eq. 1)}$$

the volume of compressed gas dissolved in a given volume of liquid can be determined. Table I gives the Ostwald solubility coefficient for some commonly used solvents. The coefficient can easily be determined using a pressure container partially filled with a known volume of the liquid. A sufficient amount of gas is added to saturate the liquid, and the Ostwald coefficient is calculated from the following equation:

$$\lambda = \frac{1}{X}\left(\frac{WRT}{V_c MP} + X - 1\right) \qquad \text{(Eq. 2)}$$

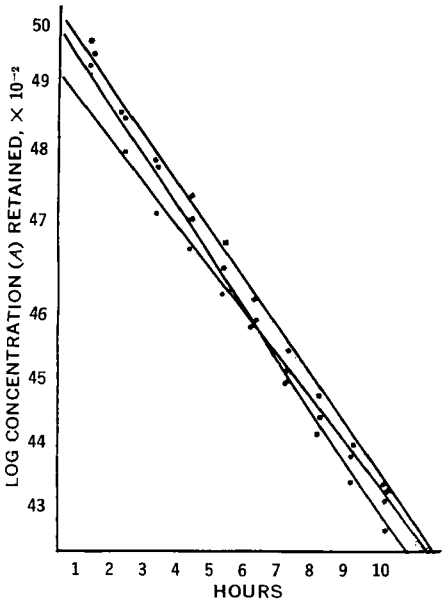

Figure 2—*Release of gentian violet into different solvents (Emerez 1533 film containing hexadecyl alcohol, 10% w/w). Key: ●, desorbing solvent, 0.45% sodium chloride solution; □, desorbing solvent, 0.45% sodium sulfate anhydrous solution; and *, desorbing solvent, potassium phosphate buffer solution, pH 7. (From Ref. 53.)*

where λ = Ostwald solubility coefficient, X = volume of liquid/volume of container, W = weight of propellant gas (grams), R = gas constant (82.06 ml atm mol^{-1} deg^{-1}), T = temperature (°K), V_c = volume of container (milliliters), M = molecular weight of the propellant, and P = total pressure (atmospheres).

By rearranging Eq. 2 and solving for W, the weight of compressed gas required to saturate the liquid at a given pressure can be calculated:

$$W = \frac{V_c MP}{RT}(X\lambda + 1 - X) \qquad \text{(Eq. 3)}$$

These equations are applicable to the formulation of emulsion systems where a foam is desired using a soluble compressed gas. The pressure drop from compressed gas systems as the contents are utilized can be calculated from a modification of Eq. 3 to yield:

$$P_2 = P_1 \Big/ \left(1 + \frac{\Delta X}{X\lambda - \Delta X\lambda + 1 - X}\right) \qquad \text{(Eq. 4)}$$

where P_1 = pressure in container before dispensing (atmospheres), and P_2 = pressure in container after dispensing (atmospheres).

Formulation—*Solutions*—Various studies have been conducted on materials used in the aerosol dosage form. Sciarra and Gidwani (53) determined the influence of polymeric films such as ethylcellulose, polyamide resins, and acrylic resins together with plasticizers, including hexadecyl alcohol and tributyl citrate, upon the rate of release of gentian violet. The films were prepared from an aerosol and cast upon a mercury surface. They determined that this release followed first-order kinetics (Fig. 2). The polyamide film was successful in producing a timed-release film, while several of the other films showed a delay in the release of gentian violet. These properties were then related to film hardness, modulus of elasticity and flexibility, and alkali resistance. The effect of electrolytes upon this release is shown in Fig. 3.

Proposed kinetics for the release of cetylpyridinium chloride and benzalkonium chloride were discussed (54). These drugs were dissolved in films cast from solutions of several film-forming agents. The dried films were then exposed to a desorbing solution of demineralized water and demineralized water–sodium chloride; the rate of the release is shown in Figs. 4–6.

All data presented in this study (54), with the exception of data on the mixed polymer, showed that the drug release followed first-order kinetics. For *in vitro* drug release to be exponential, the plot of log A *versus* time should yield a straight line, and the y-intercept at zero time should correspond to the initial concentration. But the typical apparent first-order profiles show that the values of the y-intercepts are, in fact, less than the predicted values. It seemed apparent from the drug release profiles that one portion of the drug is released immediately and the other portion exponentially. The initial release is faster than the remainder, which follows first-order kinetics, because of the presence of surface drug which may be ignored. There is, therefore, a lag time before the rate follows a first-order process. Hence the linear portion of the curve is the rate-determining step for the drug release. Since the rate release during the first 60 min (lag time) was indeterminate, the rate-limiting step permitted the determination of relative rate constants and half-lives for the drugs studied. Two processes possibly may be involved: transportation of the drug by hydration followed by release of drug from the film surface.

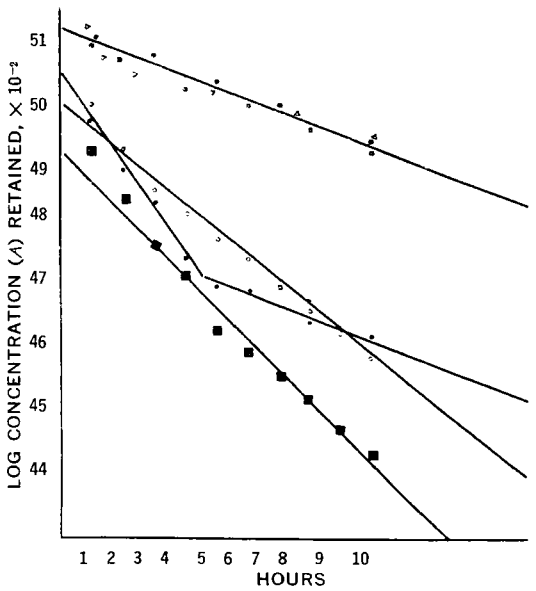

Figure 3—*Release of gentian violet from various films (solvent, 0.45% sodium chloride solution). Key: ●, Emerez 1540, hexadecyl alcohol, 10% w/w; ■, Emerez 1540, hexadecyl alcohol, 30% w/w; □, Emerez 1540, Citroflex-4, 10% w/w; *, Emerez 1540, Amerchol-L 101, 10% w/w; ○, Emerez 1536, unplasticized; and △, Carboset 525, unplasticized. (From Ref. 53.)*

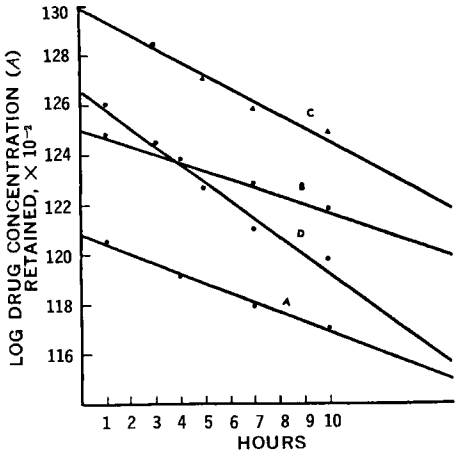

Figure 4—*Apparent first-order profile for ethylcellulose film containing hexadecyl alcohol, 30 PHR (parts of plasticizer per 100 parts of polymer). Key: A, cetylpyridinium chloride/demineralized water; B, cetylpyridinium chloride/0.225% sodium chloride; C, benzalkonium chloride/0.225% sodium chloride; and D, benzalkonium chloride/demineralized water. (From Ref. 54.)*

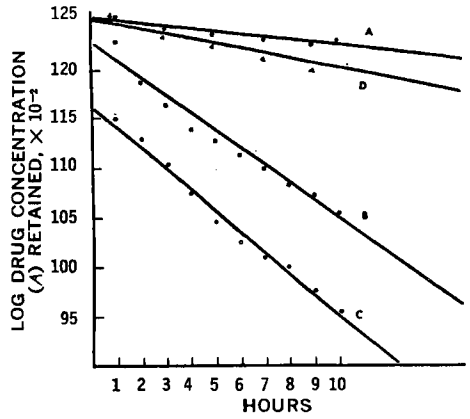

Figure 5—*Apparent first-order profile for cetylpyridinium chloride. Key: A, hexadecyl alcohol, 10 PHR/0.45% sodium chloride; B, hexadecyl alcohol, 10 PHR/demineralized water; C, tributyl citrate, 10 PHR/demineralized water; and D, tributyl citrate, 10 PHR/0.45% sodium chloride. (From Ref. 54.)*

Such drug release may be expressed mathematically by the following equations:

$$\text{total amount released} = \text{amount released immediately} + \text{amount released exponentially} \quad \text{(Eq. 5)}$$

$$C_t = A_0 C_i + A C_e \quad \text{(Eq. 6)}$$

where C_t = total amount of drug released at any time t, A_0 = original amount of drug in the film, C_i = fraction of original amount of drug released immediately, A = amount of drug remaining in the film, and C_e = fraction of remaining drug released exponentially.

Further studies (55) were concerned with the effect of plasticizer concentration on the water vapor transmission of film-forming agents.

The selection of a polymeric film for application as a protective film to the skin is determined by considering various physicochemical and biological properties. These include hardness, modulus of elasticity, alkali resistance, water vapor transmission, and stability to degradation from exposure to UV radiation. These properties were evaluated to determine the use of certain film plasticizers for application to the body *via* an aerosol spray.

A film-forming polymer suitable for application to injured skin should be permeable to water vapor so as to decrease the possibility of anaerobic bacterium growth in the wound vicinity. However, some conditions may require the use of an occlusive dressing. Components added to film-forming agents as a part of the formulation may affect the rate of water vapor transmission. The effects of several plasticizers, such as diacetin, ethyl phthalate (diethyl phthalate), triethyl citrate, and acetyltriethyl citrate, on the water vapor transmission of cellulose acetate films were reported (56).

The rate of water vapor transmission *(WVT)* of a film between two specified parallel surfaces is dependent upon the film, the plasticizer and its concentration, and film thickness. The water vapor transmission can be calculated from the following:

$$WVT = (g)(24/t)(a) \quad \text{(Eq. 7)}$$

where g = weight of loss or gain (grams), t = time (hours) during which loss or gain in g was observed, a = exposed area of the specimen (square inches), and WVT = rate of water vapor transmission (expressed in g/in^2/24 hr).

Flux *(F)* can be calculated from:

$$F = \frac{W \times T}{A \times 0.1} \quad \text{(Eq. 8)}$$

where W = weight of water vapor permeating (milligrams), T = film thickness, and A = effective area of exposed film.

The permeability coefficient *(P_c)* is defined as the milligrams of water vapor that permeates through a 0.1-mm thick film, per unit area in square centime-

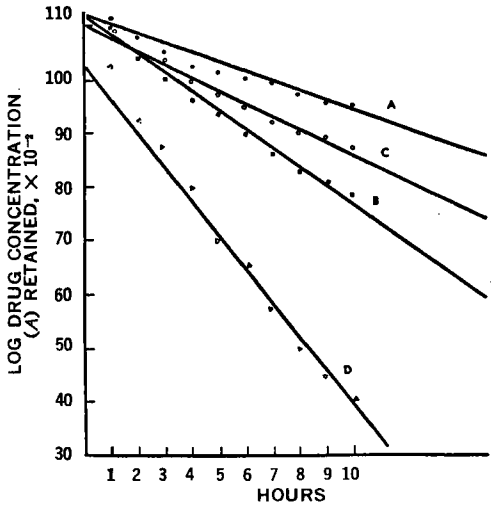

Figure 6—*Apparent first-order profile for benzalkonium chloride. Key: A, hexadecyl alcohol, 10 PHR/0.45% sodium chloride; B, hexadecyl alcohol, 10 PHR/demineralized water; C, tributyl citrate, 10 PHR/0.45% sodium chloride; and D, tributyl citrate, 10 PHR/demineralized water. (From Ref. 54.)*

Table II[a]—Water Vapor Transmission of Films Prepared from Ethylcellulose at 37°

Plasticizer[b]	Hours	Flux (*F*) I, mg	II, mg	Mean, mg
Unplasticized	24	151.3	151.5	151.4
	48	275.9	277.6	276.8
	72	410.9	412.0	411.4
	96	537.0	547.8	542.4
Tributyl citrate, 10 PHR	24	84.0	84.9	84.4
	48	162.7	162.4	162.5
	72	220.0	221.4	220.7
	96	281.0	279.5	280.3
Tributyl citrate, 20 PHR	24	120.2	121.1	120.6
	48	269.6	270.6	270.1
	72	450.2	451.8	450.5
	96	645.8	647.4	646.6
Tributyl citrate, 10 PHR; hexadecyl alcohol, 10 PHR	24	254.5	253.7	254.1
	48	572.1	573.9	573.0
	72	869.5	871.6	870.6
	96	1177.0	1179.6	1178.3
Tributyl citrate, 15 PHR; hexadecyl alcohol, 15 PHR	24	110.0	93.4	101.7
	49	219.6	176.4	198.0
	72	343.5	270.7	307.1
	96	473.5	338.0	405.7

[a] From Ref. 55. [b] PHR indicates parts of plasticizer per 100 parts of polymer.

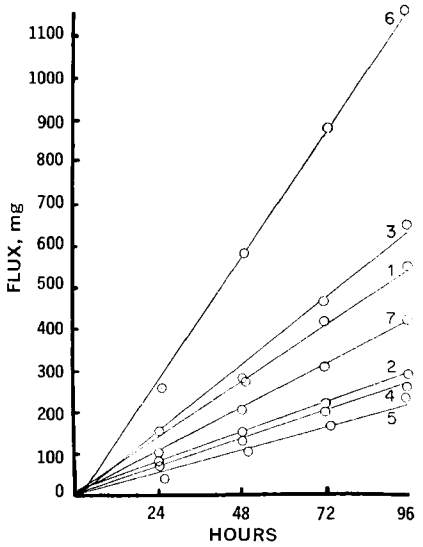

Figure 7—*Water vapor transmission of ethylcellulose films. Key: 1, unplasticized; 2, tributyl citrate (10 PHR); 3, tributyl citrate (20 PHR); 4, hexadecyl alcohol (10 PHR); 5, hexadecyl alcohol (20 PHR); 6, tributyl citrate (10 PHR)/hexadecyl alcohol (10 PHR); and 7, tributyl citrate (15 PHR)/hexadecyl alcohol (15 PHR). (From Ref. 55.)*

ters, per unit pressure drop every 24 hr, following a steady state of diffusion under the experimental conditions of temperature and pressure. The water vapor transmission of films prepared from two film-forming agents is given in Tables II and III and Figs. 7 and 8.

The hardness and tackiness of various film-forming agents were also studied using a pendulum hardness tester (57). The films of uniform thickness required for this type of determination were prepared with the aid of a centrifugal apparatus. Eckardt (57) examined various acid esters of ethylcellulose, polyvinylpyrrolidone–vinyl acetate, and other substances. In addition to moisture, the results suggested that sebum, plasticizer, and fragrance can greatly affect the hardness of these film formers used in aerosols.

Table III[a]—Water Vapor Transmission of Films Prepared from Polyamide Resin at 37°

Plasticizer[b]	Hours	Flux (*F*) I, mg	II, mg	Mean, mg
Unplasticized	24	4.91	4.74	4.83
	48	10.95	11.00	10.96
	72	14.81	14.86	14.79
	96	20.06	19.90	19.90
Tributyl citrate, 10 PHR	24	8.94	9.90	9.02
	48	17.36	17.49	17.37
	72	29.21	28.60	28.90
	96	41.90	42.17	41.98
Tributyl citrate, 20 PHR	24	8.03	8.23	8.13
	48	16.88	17.09	16.86
	72	27.64	27.85	27.45
	96	35.84	36.25	36.04
Hexadecyl alcohol, 20 PHR	24	7.39	6.46	6.88
	48	15.66	14.87	15.23
	72	22.09	22.02	22.05
	96	32.37	32.11	32.19
Tributyl citrate, 10 PHR; hexadecyl alcohol, 10 PHR	24	12.17	12.28	12.22
	48	24.19	24.38	24.28
	72	37.97	38.18	38.03
	96	50.06	50.22	50.14

[a] From Ref. 55. [b] PHR indicates parts of plasticizer per 100 parts of polymer.

The spreading of hair spray resins when applied to hair was discussed from the point of view of the wettability of hair fibers (58). The wettability depends on the magnitude of the surface tension of the solution compared with the critical surface tension of the hair fibers. Measurements of both of these quantities showed that, for the commonly employed hair spray solvents, complete wettability (zero contact angle) invariably occurs, giving rise to spontaneous spreading on the fiber surface. The rate of spreading was shown to depend mainly on the viscosity of the solution, the rate of evaporation of the solvent, and the rate of increase in the solution viscosity with concentration due to evaporation. The Washburn equation describing the rate of capillary penetration of liquids into porous systems was also shown to be insufficient when dealing with volatile fluids. A new equation, a modification of the Washburn equation, allowing for the effects of solvent evaporation and increasing solution viscosity with evaporation, was described and shown to be in good agreement with experimental data for various resin solutions spreading in a bundle of human hairs.

Dispersions and Powders—Very few references have appeared in the pharmaceutical literature regarding the development of inhalation aerosols. For the most part, epinephrine bitartrate or isoproterenol sulfate or hydrochloride has been used as a dispersion in the propellant. Epinephrine hydrochloride has also been used in solution form for this purpose. Not until 1960 were several reports published concerning the development and evaluation of these products (59, 60). These reports were concerned with the uniformity of dispensing each dose from the aerosol package, particle-size distribution, and analytical control methods, and they represent an early attempt

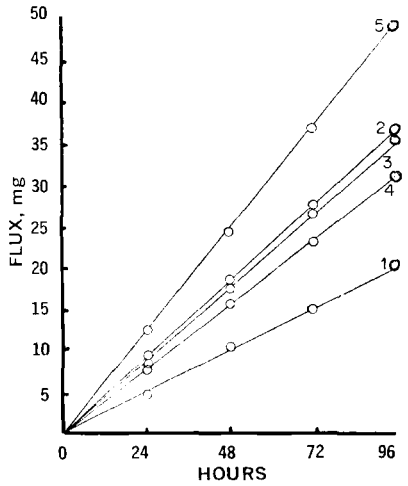

Figure 8—*Water vapor transmission of polyamide resin films. Key: 1, unplasticized; 2, tributyl citrate (10 PHR); 3, tributyl citrate (20 PHR); 4, hexadecyl alcohol (20 PHR); and 5, tributyl citrate (10 PHR)/hexadecyl alcohol (10 PHR). (From Ref. 55.)*

to establish some standards for this dosage form. Several of these procedures and suggested standards were reflected in NF XIII specifications and standards.

Various epinephrine salts were investigated as alternatives to the bitartrate and hydrochloride (61). The maleate, malate, and fumarate were synthesized and formulated as both suspension and solution-type aerosols. The solubility and stability of each salt were determined. The bitartrate and malate were the least soluble in the fluorocarbon propellant, while the maleate and fumarate showed a higher degree of solubility. The decomposition that took place followed first-order kinetics, and epinephrine maleate and bitartrate seemed to be more stable than the other salts of epinephrine studied.

Additional studies (62) showed the development and pharmacological action of epinephrine bitartrate in the rabbit eye. A formulation consisting of 0.5% epinephrine bitartrate in 0.5% hydroxypropyl methylcellulose was compared to a 0.5% epinephrine bitartrate preparation in a fluorocarbon propellant. Figure 9 illustrates the effect of each preparation upon intraocular pressure and pupil size. Based upon chemical analysis, it was noted that only 13% of the calculated dose of epinephrine was delivered to the eye by the aerosol adaptor used, even though similar pharmacological effects were obtained with the aerosol. This was taken as an indication that more epinephrine than was actually needed was being used. Modified Draize eye irritation studies did not reveal any signs of irritation following aerosol administration of the vehicle or the drug. The investigators concluded that this lack of irritation, along with the desired pharmacological effect, indicates the possible usefulness of administering ophthalmic drugs by means of an aerosol dosage form.

Most aerosols intended for inhalation therapy contain a fairly low concentration of solid particles. In many instances, the maximum concentration rarely exceeds 1%. Other solids have been dispensed in aerosol form and include the so-called powder aerosols. The concentration of powder in these cases is about 10–15%, although it is possible to produce a system with from 85 to 90% powder. Several reviews on this subject have appeared over the past few years. Most authors agree that powder aerosols have the potential of presenting serious formulation problems in the areas of valve clogging, particle-size growth and agglomeration, caking and sedimentation, and ease of redispersion (63–65).

According to Herzka (64), the three basic reasons for the most serious problem, valve clogging, are large and/or needle-shaped particles, the presence of only partially soluble resinous or crystalline materials in the product, and the agglomerative sedimentation of the products. The design of the valve was also discussed. Isopropyl myristate, in a concentration of 0.5–2.0%, was suggested as a lubricating agent to prevent valve clogging as well as agglomeration of particles. According to Elvin (65), needle- and plate-shaped particles tend to present a greater clogging potential than spherical ones. These particles should generally be in the 35–40-μm range, while spherical particles can be as large as 75 μm. To aid in resuspending the powders, a bulking agent such as a silica gel can also be added. In this investigation, various silica derivatives were studied to determine the relative effect of each.

Many studies with powder systems utilize aluminum chlorhydroxide formulations as antiperspirants. Crotty *et al.* (66) investigated the physical behavior of this solid in aerosol formulations. Their study in-

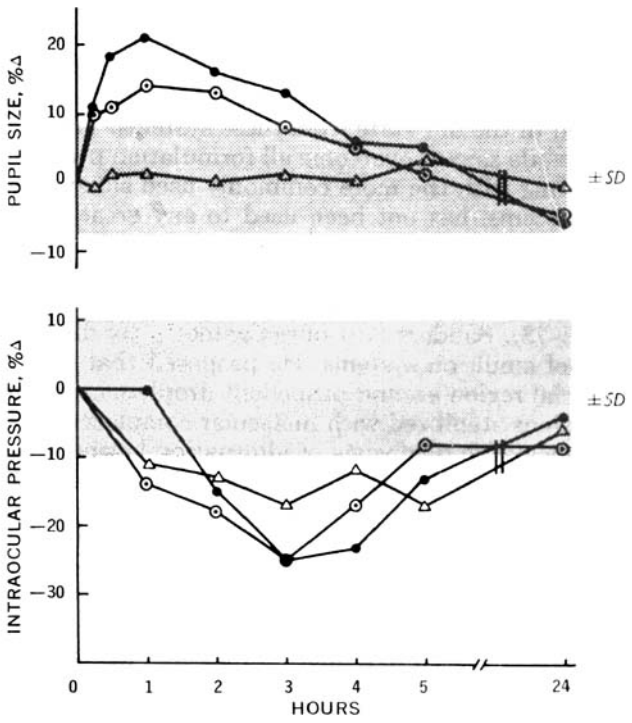

Figure 9—*Intraocular pressure and pupil size after drug administration [epinephrine bitartrate (0.5%) in: ●, hydroxypropyl methylcellulose; ⊙, fluorocarbon; and △, saline]. Each point represents the percent change of the mean values of from six to 12 eyes for each time period. The standard deviation about the control mean is based on 54 observations. (From Ref. 62.)*

Table IV[a]—Stability of Aqueous Aerosol Systems[b] by Polyoxyethylene Fatty Ethers

Composition: Polyoxyethylene Fatty Ether	Water Solubility	Weight Percent in Aqueous Phase	Hydrophilic–Lipophilic Balance Value	Stability, min: Emulsion[c]	Stability, min: Foam[d]
Polyoxyethylene (4) lauryl ether	Dispersible	1.8	9.7	<1	<5
Polyoxyethylene (23) lauryl ether	Soluble	6.0	16.9	>1	<5
Polyoxyethylene (3) cetyl ether	Insoluble	1.6	5.3	>30	>120
Polyoxyethylene (10) cetyl ether	Dispersible	3.3	12.9	<1	<15
Polyoxyethylene (20) cetyl ether	Soluble	5.4	15.7	<1	<5
Polyoxyethylene (2) stearyl ether	Insoluble	1.8	4.9	>30	>120
Polyoxyethylene (10) stearyl ether	Dispersible	3.4	12.4	<1	<15
Polyoxyethylene (20) stearyl ether	Dispersible	5.5	15.3	<5	<5

[a] From Ref. 79. [b] Aerosol formulation: 90% aqueous phase–10% Freon 12/Freon 114 (40:60) propellant. Freon is du Pont's registered trademark for its fluorocarbons. [c] Time to initial phase separation after shaking. [d] Time to first indication of foam collapse.

cluded the use of fuming silica as a dispersing agent for aluminum chlorhydroxide. The effects of moisture, polarity, and particle size of the substituents upon viscosity and homogeneity were also studied.

The use of hexadecyl alcohol and other emollients to aid in the suspension and redispersion of the aluminum chlorhydroxide was suggested (67), as was the use of colloidal silica and isopropyl myristate along with passing the slurry through a colloid mill (68). The conclusion in the latter study was that the use of this mill would prevent agglomeration of the aluminum chlorhydroxide particles and avoid valve clogging. The use of alcohol-soluble aluminum salts as deodorants and antiperspirants was studied, and it was concluded that such use was not feasible or involved a great deal of uncertainty as to formulation and stability (69, 70).

While most aerosol powder systems contained a fairly low percentage of solids (up to 15%) and a large amount of propellant, a system containing a minor portion of liquefied gas propellant and a major portion of powder was developed (71). The powder is delivered in the dry state from these systems. This system, while said to overcome all formulation problems occurring with the more commonly used slurry powder systems, has not been used to any great extent (72).

Emulsions—The formulation of emulsions for dispensing as aerosol foams has been studied extensively (73–78). Sanders (79) investigated many different aerosol emulsion systems. He proposed that the interfacial region around propellant droplets in aerosol emulsions stabilized with molecular complexes is polymolecular and consists of alternating layers of oriented water molecules and bimolecular layers of the molecular complex. He further noted that the molecular complex has a liquid crystal structure which is insoluble in any of the phases, resulting in its concentration at the interface. According to Sanders, this phenomenon has a stabilizing effect upon the foam. He further stated that these liquid crystals in aqueous systems are often responsible for the pearlescence occurring in creams.

The relationship between the solubility of a series of polyoxyethylene fatty ethers and their effectiveness as stabilizers for aerosol emulsions and foams is shown in Table IV. The polyoxyethylene ethers producing the most stable foam were polyoxyethylene (2) stearyl and polyoxyethylene (2) cetyl ethers. These were the only ethers found to be insoluble in water. Sanders concluded that the best stabilizers for aerosol foams were those with a low solubility in the aqueous phase and low solubility or insolubility in the propellant phase. However, the stabilizers must be dispersible to some extent in the propellant phase. For systems containing an aqueous alcohol phase, Sanders also noted the importance of solubility of the surfactant in the aqueous alcohol phase. Since increasing the concentration of ethanol in these systems increases the solubility of the surfactant, the more stable foams are produced at low alcohol concentrations. However, this technique is used to produce the quick-breaking foam systems.

Emulsions containing mineral oil or glycol as the nonaqueous phase were also investigated. Table V illustrates the relationship between foam stability and solubility of the surfactant in polyethylene glycol 400 while Table VI shows this same relationship with mineral oil foam systems. Mineral oil foam systems differed from the glycol systems in that the propellant was soluble in mineral oil. For the most part, however, it seems that the most stable foams were produced with surfactants that were least soluble in either polyethylene glycol 400 or mineral oil.

Table V[a]—Foam Stability and Surfactant Solubility in Polyethylene Glycol 400 Foams[b]

Surfactant	Solubility of Surfactant Glycol	Foam Stability
Ethoxylated stearyl alcohol	Insoluble	Stable foam
Polyoxyethylene (4) lauryl ether	Soluble	No foam
Polyoxyethylene (23) lauryl ether	Insoluble	Stable foam
Polyoxyethylene (2) cetyl ether	Insoluble	Stable foam
Polyoxyethylene (10) cetyl ether	Soluble	No foam
Polyoxyethylene (20) cetyl ether	Insoluble	Stable foam
Polyoxyethylene (2) stearyl ether	Insoluble	Stable foam
Polyoxyethylene (10) stearyl ether	Insoluble	Stable foam
Poloxyethylene (2) oleyl ether	Soluble	No foam
Polyoxyethylene (10) oleyl ether	Soluble	No foam

[a] From Ref. 79. [b] Aerosol formulation: 86% polyethylene glycol 400–4% surfactant–10% Freon 12/Freon 114 (40:60) propellant.

Table VI[a]—Surfactant Solubility and Foam Stability in Mineral Oil Systems[b]

Surfactant	Surfactant Solubility in Mineral Oil	Foam Stability
Ethoxylated stearyl alcohol	Insoluble	Stable
Polyoxyethylene (4) lauryl ether	Soluble	No foam
Polyoxyethylene (2) cetyl ether	Soluble	No foam
Polyoxyethylene (10) cetyl ether	Insoluble	No foam
Polyoxyethylene (2) stearyl ether	Insoluble	Stable
Polyoxyethylene (10) stearyl ether	Insoluble	No foam
Polyoxyethylene (2) oleyl ether	Soluble	No foam

[a] From Ref. 79. [b] Aerosol formulation: 79% mineral oil–6% surfactant–15% Freon 12 propellant.

An emulsifier system of octanoic acid and 1-aminooctane was used in a study of liquid crystalline phases in aerosol formulations (80). Both propellant and acid showed complete solubility in the system containing the least amount of water. A two-phase area was formed, showing the immiscibility of the propellant, dichlorotetrafluoroethane, with the water–amine solution. As the water content was increased, similar solubility relationships were seen, except that the two-phase area of immiscibility between the propellant and the water–amine layer increased. This two-phase portion representing the area of immiscibility of propellant with the water–amine layer was referred to as the liquid crystalline phase (Fig. 10). In going from a low water content to a higher water content, the liquid crystalline phase increases (Fig. 11).

Further studies along these same lines (81) revealed the fact that emulsion compositions containing both a liquid crystalline phase and a liquid phase gave rise to foams with high stability compared to foams produced from compositions where only a liquid phase was present. According to Friberg and coworkers (82, 83), foam stability is related to the presence of liquid crystalline phases in which the emulsifiers, water, and oil phases are all associated into an ordered structure, and not as indicated by Sanders (79). Sanders indicated that the foam stability was related to the formation of a molecular complex. Sanders evaluated the foams on the basis of phase separation and ultimate collapse of the foam, while Jederström *et al.* (81) evaluated the foam on the basis of foam height. Differences in the type of surfactant used as well as the composition of aqueous phase–surfactant–propellant phase could have influenced the results.

Based upon the results of this latest study (81), it is suggested that emulsifiers and stabilizers for aerosol foams be evaluated by noting the composition of the emulsion prior to the addition of the propellant. A liquid crystalline phase should be present, and this phase should show some miscibility with the propellant.

The pearlescence occurring with certain water-soluble polyoxyethylene fatty ethers and fatty alcohols

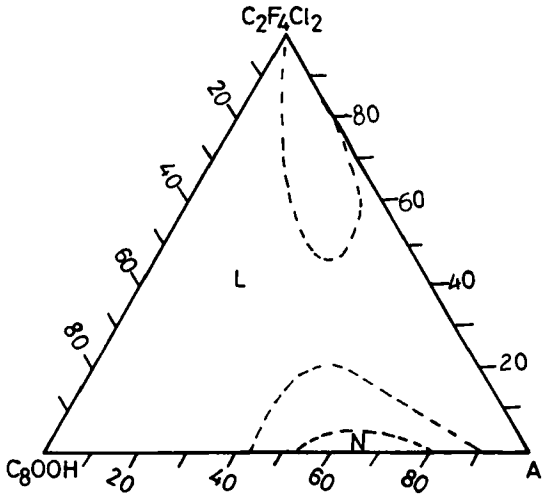

Figure 10—*Phase regions in the system of octanoic acid–propellant–water/amine [water (19%), 1-aminooctane (81%)] (C_8OOH–$C_2Cl_2F_4$–A). Key: L, isotropic solution; and N, liquid crystalline phase, "neat phase." (From Ref. 80.)*

was also studied (84) and took place only when the surfactant would concentrate in the aqueous phase. The incompatibility of certain pearlescent structures with fluorinated hydrocarbon propellants was observed. The triethanolamine myristate–propellant system was also investigated (85). The properties of the foam produced from two emulsions with different degrees of stability were compared to those of the emulsion. A glass pressure cell was developed so that the emulsions could be viewed microscopically. Microscopic and visual observations of the two systems showed that the surfactant system producing emulsified propellant droplets with the smaller diameters also produced foams with an initially smaller bubble size and a slower increase in bubble size after discharge. Greater stability was noted in systems that showed a smaller emulsified droplet.

Various methods for the production of these emul-

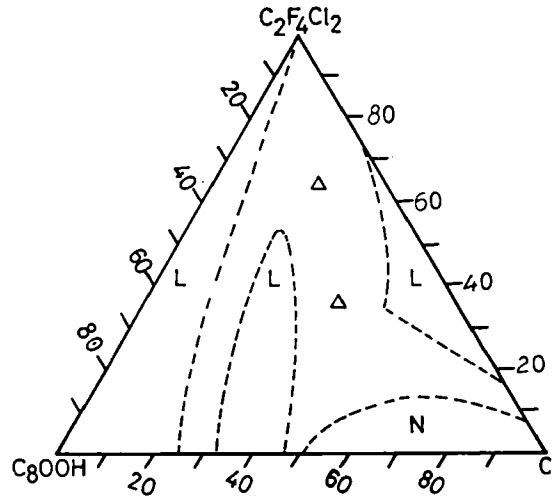

Figure 11—*Phase regions in the system of octanoic acid–propellant–water/amine [water (33%), 1-aminooctane (67%)] (C_8OOH–$C_2Cl_2F_4$–C). Key: L, isotropic solution; N, liquid crystalline phase, "neat phase"; and Δ, three-phase area indication. (From Ref. 80.)*

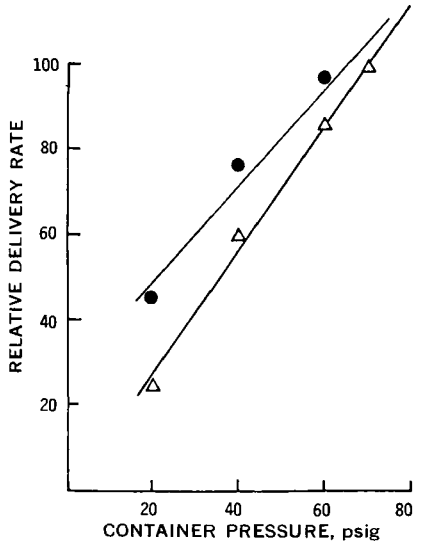

Figure 12—*Plot of the relative delivery rate* versus *container pressure for selected sodium carboxymethylcellulose solutions* (●, *2%; and* △, *3%*). (*From Ref. 93.*)

sions were also studied (86). Photomicrographs and phase separation times were used to judge the quality of the emulsion. Aerosols were prepared for the best and the poorest emulsions produced by adding the propellant to the concentrate. Concentrates with the smallest droplet size and the longest separation times produced the most stable aerosols. These stable aerosols also produced the most stable foams. Sanders (86) accounted for this stability on the basis of the formation of a triethanolamine myristate–myristic acid complex during the initial addition of the aqueous phase.

Depending upon the nature of the propellant, surfactant, and aqueous or nonaqueous phase, foams of differing viscosity and consistency could be produced. In addition, such foams described as sparkling, shiny, expanding, collapsing, periscoping, and crackling could be produced (87). These foams are described as being suitable for use for a variety of cosmetic and pharmaceutical products. The aerosol

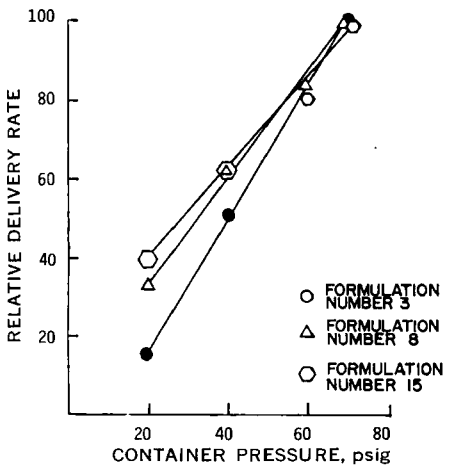

Figure 13—*Plot of the relative delivery rate* versus *container pressure for selected formulations. Formulation Number 3 is representative of a typical cream, Number 8 is a lotion, and Number 15 is a suspension.* (*From Ref. 93.*)

quick-breaking foam is based upon a system consisting of alcohol, water, surfactant, and propellant (88). As the propellant vaporizes, the foam is formed since the surfactant comes out of solution due to the loss of propellant. Under the action of skin heat, the surfactant partially dissolves, causing the foam to collapse. Rubbing of the foam destroys the crystal lattice and results in the same effect. A more detailed study of aqueous alcohol aerosol foams reports on the solubility of the propellant in water–ethanol solutions and the effect of various surfactants upon this solubility. Other solvents such as acetone, diethylene glycol, ethylene glycol, glycerin, propylene glycol, and isopropyl myristate were also studied (89).

Lemlich (90) reviewed the physical aspects of foam. Bubble size, shape, fit, and movement, along with methods for measuring the liquid content and bubble size, were indicated.

The effect of nonionic emulsifiers, buffer, pH, and hydrophilic–lipophilic balance values in the stability of emulsions used to produce aerosol foams was studied (91). A series of emulsions containing a high water content was prepared and studied for stability. These workers noted that the Sorenson buffer system was superior to an acetate buffer system as related to emulsion stability. Evidence indicated the existence of an unfavorable pH-dependent acetate-ion effect on emulsion stability.

Semisolids—Semisolids are dispensed from pressurized systems. Generally, ointments, creams, gels, and similar materials make up this dosage form. Recently, these products have been successfully dispensed from "barrier pack" pressurized systems. The flow properties of the semisolid as it passes from the container and through the valve openings is especially critical. Fisher and Sheth (92, 93) studied the effect of product rheology and pressure upon the delivery rate of a model cream, lotion, suspension, and polymer solution from one such barrier pack[1]. Flow curves were developed for each model system studied. The delivery rate was also determined in terms of grams discharged per second. As one would predict, the delivery rate increased with pressure, although the rate of increase was not linear with the increase in pressure. The concept of relative delivery rate was proposed by these workers and included comparing the delivery rate at a specific pressure to the delivery rate at the highest test pressure. In this study, 70 psig was used as the highest pressure and the equation used was:

$$R = \frac{\text{delivery rate at a specific pressure}}{\text{delivery rate at 70 psig}} \times 100 \quad \text{(Eq. 9)}$$

where R = relative delivery rate.

Plots of these values for each model are shown in Figs. 12 and 13. The rheological properties of the polymer solution were determined at different pressures (Fig. 14).

A novel approach to the dispensing of gels from

[1] Consisting of an accordian-like pleated plastic bag placed inside a standard three-piece aerosol can (Continental Can Co., New York, N.Y.).

Table VII[a]—Mean Dose Delivered (Milligrams) from Meter Valves at Various Levels of Container Emptying

Level of Emptying	Type of Meter Valve[b]				
	E501	V501	V501-DA	R501-EC	S501-EC
			Formulation I		
Initial	68.0	69.0	73.0	68.3	87.6
10%	68.1	69.2	75.2	68.7	88.7
50%	68.5	69.7	76.2	69.6	91.3
80%	68.9	69.8	77.4	70.5	92.9
Total mean	68.3	69.4	76.1	69.3	90.1
Coefficient of variation, %	2.08	4.90	5.73	2.22	3.80
			Formulation II		
Initial	65.4	65.8	75.4	69.7	89.4
10%	66.0	65.6	76.2	70.6	90.8
50%	68.0	67.4	77.3	71.6	92.9
80%	68.5	67.2	78.3	72.3	94.6
Total mean	66.9	66.5	76.7	71.0	91.9
Coefficient of variation, %	2.48	5.26	1.51	2.43	2.87
			Formulation III		
Initial	38.4	41.0	43.4	40.1	43.3
10%	37.4	38.7	43.0	39.3	47.8
50%	37.3	37.9	41.8	37.8	46.9
80%	36.8	36.9	40.0	36.8	45.5
Total mean	37.5	38.9	42.0	38.5	47.1
Coefficient of variation, %	5.01	3.78	3.33	3.94	5.41
			Formulation IV		
Initial	64.2	71.1	79.6	72.7	96.7
10%	64.1	70.7	79.2	73.0	97.7
50%	64.0	70.2	79.0	72.8	97.1
80%	63.9	70.1	79.4	72.8	97.6
Total mean	64.1	70.5	79.3	72.8	97.0
Coefficient of variation, %	1.5	1.73	1.28	1.61	1.42

[a] From Ref. 96. [b] E501 = 50 μl, Emson Research, Inc.; V501 = 50 μl, VCA (upright); V501-DA = 50 μl, VCA (inverted); R501-EC = 50 μl, Riker Labs. (inverted); and S501-EC = 50 μl, experimental valve (inverted).

pressurized systems was developed (94) and consisted of a gel packaged in an enclosed bag. In addition to the gel, a liquid with a low boiling point, such as dichlorotetrafluoroethane[2] or pentane, is incorporated into the gel. A propellant such as dichlorodifluoromethane[3] or a mixture of isobutane–propane is added on the outside of the bag and supplies the dispensing pressure. When emitted, the gel is in a ribbon-like structure but foams as the low boiling solvent escapes due to the warmth of the hand or by rubbing. This principle has been used for foaming shave gels.

AEROSOL COMPONENTS

Valves—The delivery of an exact dosage from an aerosol package is largely controlled by the valve design. However, the nature of the formulation and the nature of the propellant must be considered. The number of doses per container and the amount per dose are important standards for inhalation and oral aerosols (95). A comparison between commercially available meter valves using identical formulations and evaluation methods was undertaken (96, 97) to generate data that might result in standards for meter valve performance and dose variation. In addition to the actual dose of medication dispensed, dose-to-dose variation at different levels of container emptying must be considered since the difference between the first dose dispensed and the last dose can be significant.

Fractionation of the propellant blend does occur as the contents are used and could lead to increased variation (Table VII). Formulations I and II contained dichlorodifluoromethane–dichlorotetrafluoroethane (50:50 and 75:25, respectively), while Formulation III contained 50% dichlorodifluoromethane–dichlorotetrafluoroethane (50:50) together with 50% of absolute alcohol. Formulation IV contained only octafluorocyclobutane[4] so no fractionation could occur. From Table VII, it can be readily seen that Formulation IV gave the smallest amount of variation as the container was emptied. This study was completed using formulations that did not contain any active ingredients. Since the formulation will affect not only the dose dispensed but also the dose-to-dose variation, final studies of the valve must include an evaluation of the finished preparation.

While not used in metered valves, the presence of a vapor tap in the valve can result in fractionation occurring not only with propellant blends but also with propellant–concentrate ratios. Flanner and Matera (98) determined the effect of vapor tap valves in the ratio of propellant to concentrate in several cosmetic aerosol formulations. They noted that fractionation of the propellant blend would occur after 75% of the product was consumed. Valves used in this study were of the continuous spray type. Changes were also noted in the ratio of the propellant to the concentrate. As the size of the vapor tap orifice increased, the ratio of propellant to product decreased.

[2] Propellant 114.
[3] Propellant 12.
[4] Propellant C-318.

Table VIII[a]—Fill Tolerances for Propellant 1-Chloro-1,1-difluoroethane–Trichloromonofluoromethane (50:50) Systems

Number of Units Analyzed	Nominal Fill, g	Mean Fill, g	*SD*, g	Experimental Range, g	Tolerance Limits[b], g		Tolerance Limit Spread, g
					Lower	Upper	
50	10	9.517	0.193	1.052	8.914	10.120	1.206
50	20	20.695	0.432	2.026	19.345	22.045	2.700
50	30	30.346	0.407	2.595	29.074	31.618	2.544
50	40	40.671	0.471	2.853	39.199	42.43	2.944
50	60	60.525	0.585	2.989	58.696	62.354	3.658
50	80	80.752	0.358	2.180	79.633	81.871	2.238
50	100	101.152	0.532	3.052	99.489	102.815	3.326
50	115	114.171	0.572	3.006	112.383	115.959	3.576

[a] From Ref. 123. [b] The tolerance limits will be expected to contain 99% of the population with 95% confidence.

Further studies (99) led to the conclusion that fractionation was least where the ratio of valve body orifice to vapor tap was greatest. When alcohol was present in the formulation, its concentration in the total product increased the most with the smallest valve body orifice and the least with the largest valve body orifice.

Applicators and Fitments—A review (100) of various fitments applicable for use with pharmaceutical aerosols indicated a variety of different designs. These are used to dispense oral and topical aerosols. Applicators suitable for use with aerosols designed to be applied to the vagina, ear, nose, and eye were also described.

One problem associated with the use of oral aerosols by asthmatics is their failure to coordinate the release of medication with inspiration. This problem has become rather serious with children and the elderly. A device has been developed that automatically dispenses the medication as the patient inhales, and the operation of this system was described (100, 101). One study (102) reported that this device showed a statistically greater improvement in patients as compared to the standard inhaler. Since the valve operates only when the patient achieves a flow rate of about 40–50 liters/min, one is assured that the medication is released at the proper moment.

Although not used with pressurized systems, a device has been developed for use with dry powder aerosols (103). This inhaler utilizes a powder contained in a gelatin capsule. The capsule is punctured and the powder is then carried into the inspired air during inspiration. Since this unit is used with dry powders, the dosage is not limited except by the size of the capsule used. This inhaler also achieves coordination of inspiratory effort and inhalant administration.

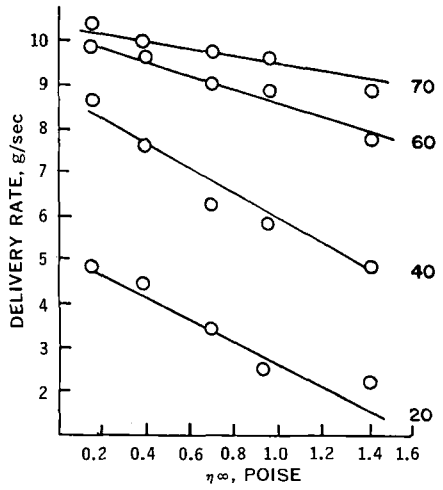

Figure 14—*Plot of* $\eta\infty$ versus *delivery rate for sodium carboxymethylcellulose solution at pressures of 20–70 psig. (From Ref. 93.)*

Containers—A review of the literature concerning developments in aerosol container technology for pharmaceutical aerosols over the past 10–15 years reveals little change. Several reviews appeared (104–108), and additional articles were concerned with various aspects of container corrosion (109–112). Giggard (113) discussed some developments in aerosol can linings. To decrease the danger of attack upon the product by the tin plate or steel of the container, an internal lining is generally applied to the flat tin plate. Following fabrication of the container, an additional coating of organic lining is added over the side seam.

While solder of varying composition has been used to seal the body of a fabricated can, a recent development made available a container electrically welded and not soldered (114). This development may find application for pharmaceutical aerosols where the presence of solder can lead to incompatibility between the container and the product. In addition, the presence of pieces of loose solder in the container can add to the severity of this problem and lead to valve clogging.

Aerosol containers made from aluminum have been used to package many different pharmaceutical aerosols. Since these containers are drawn from a single slug of aluminum, there are no side seams and the container is less prone to leakage. Additionally, aluminum is less subject to attack than tin plate aerosol containers. However, aluminum aerosol containers packaged with ethanol are subject to corrosion under certain conditions. It is known that aluminum will react with anhydrous ethanol to form aluminum alcoholate (115) (Scheme I):

$$2Al + 6C_2H_5OH \longrightarrow 2(C_2H_5O)_3Al + 3H_2$$

Scheme I

Further studies on the relationship between this reaction and the composition of the aluminum used to fabricate the container were carried out by Yamamoto *et al.* (116). Since these workers noted perfora-

Table IX[a]—Fill Tolerances for Dichlorodifluoromethane System

Number of Units Analyzed	Propellant Line, psig	Nominal Fill, g	Mean Fill, g	*SD*, g	Experimental Range, g	Tolerance Limits[b], g		Tolerance Limit Spread, g
						Lower	Upper	
49	500	5	5.556	0.596	2.430	3.691	7.421	3.730
48	500	20	20.078	0.744	3.361	17.743	22.413	4.670
43	500	40	39.931	0.596	3.546	38.038	41.824	3.786
46	500	47	46.690	0.583	2.663	44.847	48.533	3.686
48	500	60	59.020	0.603	3.592	57.127	60.913	3.786
50	500	80	80.289	0.480	2.209	78.789	81.789	3.000
46	900	20	19.313	0.527	2.415	17.647	20.790	3.143
43	900	60	58.469	0.455	2.203	57.024	59.914	2.890
50	900	80	80.312	0.432	0.255	78.962	81.662	2.700

[a] From Ref. 123. [b] The tolerance limits will be expected to contain 99% of the population with 95% confidence.

tions taking place in containers packaged with trichloromonofluoromethane[5] and ethanol and not in the aluminum containers packaged with dichlorodifluoromethane, they concluded that the corrosion taking place was apparently due to the presence of ethanol in combination with trichloromonofluoromethane. They also noted that corrosion was a function of not only the alloy used to prepare the aluminum slug but also of the method used to fabricate the container.

The development of aerosol containers with a pressure relief device was discussed (117, 118). These devices would release the excess pressure if a rapid build-up in pressure in an aerosol container occurred due to a fire or some other cause of heat. One such device, accepted by the Department of Transportation for use with aerosols, consists of a number of scores placed at precisely located points around the top of the aerosol container. Under high internal pressure, the top of the container will buckle upward, opening the scores and allowing the gas to escape slowly.

MANUFACTURING AND PACKAGING OF AEROSOLS

The packaging of pharmaceutical and cosmetic aerosols generally does not involve any special techniques. However, since these products are used topically or orally, special precautions must be taken to ensure that they are manufactured and packaged according to specification and that there is no contamination of the product with either foreign materials or microbial organisms. In regard to the latter, several reports were published as to the need for and the setup of aseptic filling lines for aerosols.

Joyner (119, 120) suggested the addition of ethylene oxide to the container to sterilize the product. He indicated that this method has not been fully accepted by various governmental agencies. The filling of pharmaceutical aerosols under aseptic conditions has been reported (121, 122). Methods useful for sterilizing each component, the equipment, and the final package were indicated. While many will agree upon the importance of aseptic filling, most facilities used to package pharmaceutical aerosols are kept separate from other filling lines and, in many instances, the line is completely glass enclosed.

In a study designed to determine the fill tolerances and the effect of variables upon the packaging of pharmaceutical and cosmetic aerosols, it was noted that the under-the-cap filler produced satisfactory results (123). Various propellant systems as well as filling pressures were studied. Tables VIII and IX indicate the results obtained using two different propellant systems. Based upon these results, the investigators concluded that only a variation in propellant line pressure from 500 to 900 psig was of practical significance. It was also noted that the fill tolerances of the dichlorodifluoromethane system was greater than the fill tolerance of the 1-chloro-1,1-difluoroethane[6]–trichloromonofluoromethane (50:50) system.

The application of various quality control systems to aerosols was discussed (124–131). The importance of in-process quality controls was stressed since part of the actual manufacture takes place during the packaging operation as the product concentrate and propellant are mixed at this time. Specifications for containers, valves, sampling, acceptable quality levels (AQL), control charts, and other aspects were covered specifically for aerosol products.

TESTING OF AEROSOL PRODUCTS

In addition to general testing procedures used to determine the acceptability of the nonaerosol portion of the pharmaceutical and cosmetic aerosol (concentrate), special test procedures have been developed for the aerosol package as well as the evaluation of the final product. These areas of specialization include particle-size distribution of those products dispensed as sprays, rheological examination of foams and semisolids, and special analytical techniques to obtain a quantitative measure of the stability of the final package.

General Testing—Various test procedures have been developed by the Chemical Specialties Manufacturers Association (132). Several of these methods have been modified for use specifically with pharmaceutical aerosols and appear in NF XIII (133). Delivery rate, leak testing, pressure testing, sampling apparatus, and moisture determination represent those test procedures applied to most aerosols. Additional tests may be indicated for specific aerosols. Table X

[5] Propellant 11.

[6] Propellant 142b.

Table X[a]—Testing of Pharmaceutical Aerosols

Product	Test Procedure			
	Delivery Rate	Leak Testing	Pressure Testing	Other
Dexamethasone aerosol	Yes	Yes	Yes	—
Isoproterenol sulfate aerosol	No	Yes	No	Unit spray content particle size
Povidone-iodine aerosol	No	Yes	Yes	—
Thimerosal aerosol	No	Yes	Yes	—
Triacetin aerosol	No	Yes	Yes	—
Triamcinolone acetonide aerosol	No	Yes	Yes	—

[a] From Ref. 134.

indicates the tests required for some pharmaceutical aerosols included in the NF. Additional test procedures were reviewed (60, 135, 136).

Analytical Procedures—Since the aerosol package is pressurized, the procedures generally used to obtain a sample for analysis cannot be used without modification. A sampling chamber, which can also be used as a titration vessel, was utilized to assay aerosols containing benzocaine, epinephrine bitartrate, ergotamine tartrate, isoproterenol hydrochloride, prednisolone, cyclomethycaine hydrochloride, and pramoxine (137). The results indicated that this chamber could be used to obtain a representative sample of the product; in those cases where a titration was involved, the vessel could also serve for the titration.

A pressure attachment for a rotational rheometer was described (138), and this device made possible the evaluation of pharmaceutical and cosmetic foams. Various soap concentrates were pressurized and the flow characteristics of the foam produced from each emulsion were evaluated using a pressure rheometer. These foams showed pseudoplastic properties which could not always be related to the flow properties of the resultant foams. Sanders (85) described a glass pressure cell which could be used to observe foams under a microscope. He noted that the pressure cell was most satisfactory when used with a stable emulsion system.

Gas chromatography has been used extensively to assay pharmaceutical and cosmetic aerosols. Cohen (139) investigated the accurate sampling and analysis of volatile components of aerosols used in inhalation therapy. By utilizing a pressure syringe, a representative sample of the aerosol was obtained which could then be injected into the gas chromatograph. Air, dichlorodifluoromethane, water, dichlorotetrafluoroethane, ethanol, and ethylene glycol monomethyl ether were separated by this method. When these results were compared to those from other analytical procedures, differences of less than 1% were noted and in most cases these differences were less than 0.5%.

Other investigators applied gas chromatography to the analysis of aerosols containing volatile oils (140) and medicinal amines (141). In both cases, it was noted that these constituents could be easily separated by gas chromatography and gave results comparable to results obtained using other analytical techniques. A method that could be used to separate 18 volatile components common to aerosol formulations was developed (142). By utilizing gas chromatography with thermal conductivity detection, mixtures of alcohols, hydrocarbons, chlorofluorocarbons, and aliphatic halides were separated. The use of vinyl chloride as an internal standard was advantageous because it gave an improvement in the quantitative results.

Methylene chloride in hair sprays was determined using an aerosol transfer button, polyethylene tubing, and a hypodermic needle as a sampling device (143). The sample was introduced into a small serum bottle and transferred to the gas chromatograph with a high pressure liquid sampling syringe. Other studies (144, 145) utilized gas chromatography in conjunction with IR analysis for the detection and analysis of propellants.

Evaluation of Foams—Several methods were developed to evaluate foams, and the various methods used were reviewed (146). Foam density and the effect of propellant substitution and addition of nonpolar constituents upon the foams were determined (147). It was concluded that increasing the concentration of propellant will result in increased foam consistency. Foam consistency increased with an increase in soap concentration. Further studies on foams included foam stability and effect of shear (148). When using a rotational viscometer, it was noted that pressurized foams exhibited a marked decrease in foam consistency with time and that the rate of decrease was independent of formulation. It was concluded that pressurized foams are plastic in nature.

The final study in this series was concerned with changes in propellant concentration as the contents of an emulsion aerosol were discharged (Table XI) (149). This was related to changes in foam consistency. Based upon the results, it can be noted that fractionation of propellant blends will take place along with a change in the ratio of propellant to soap concentrate.

A photographic technique for the analysis of bubble size of foams was studied (150), and foam stiffness was measured (151) using a curd tension meter. The relationship between foam stiffness and density with product discharge was noted. Propellant composition was found to affect both stiffness and foam density.

Particle-Size Analysis—Depending upon the size range of the various particles found in an aerosol spray, several methods can be used for the measurement of particle size. The techniques may be complicated by the properties of the particles as well as the difficulty encountered in sampling the spray to obtain a representative sample. The term particle size generally refers to solid particles, while droplet size refers to liquid particles. In many instances, however, the terms have been used interchangeably.

For medicinal aerosols, the size of both liquid and

Table XI[a]—Computer Data for Emptying of a Pressurized Foam Container Employing a 57:43 (w/w) Mixture of Dichlorodifluoromethane and Dichlorotetrafluoroethane (10% w/w) as Propellant

Dichlorodifluoromethane		Dichlorotetrafluoroethane		Total Emulsion, g	Total Pressure, psia	Amount Removed, g
Parts, g	% (w/w)	Parts, g	% (w/w)			
		Initial Concentrations				
5.700	5.700	4.300	4.300	100.000	0.000	0.0
		Concentrations after Vapor Space Filling				
5.420	5.439	4.229	4.244	99.649	64.550	0.0
		Removing 1 g/Actuation				
5.420	5.439	4.229	4.244	99.649	64.550	0.0
4.701	5.258	3.757	4.202	89.417	64.237	10.0
4.005	5.058	3.288	4.153	79.188	63.885	20.0
3.335	4.837	2.823	4.093	68.961	63.484	30.0
2.694	4.587	2.361	4.020	58.737	63.022	40.0
2.087	4.302	1.904	3.925	48.517	62.482	50.0
1.519	3.968	1.454	3.796	38.302	61.841	60.0
1.000	3.562	1.013	3.607	28.093	61.068	70.0
0.542	3.035	0.589	3.334	18.913	60.228	80.0
0.200	2.594	0.185	2.406	7.721	58.402	90.0
		Removing 5 g/Actuation				
5.420	5.439	4.229	4.244	99.649	64.550	0.0
4.696	5.252	3.757	4.202	89.416	64.358	10.0
3.997	5.047	3.287	4.152	79.187	64.012	20.0
3.322	4.818	2.821	4.091	68.959	63.616	30.0
2.678	4.559	2.359	4.016	58.735	63.159	40.0
2.067	4.261	1.901	3.918	48.514	62.622	50.0
1.497	3.909	1.449	3.784	38.299	61.980	60.0
0.976	3.476	1.006	3.584	28.090	61.196	70.0
0.519	2.903	0.579	3.236	17.891	60.217	80.0
0.149	1.939	0.183	2.380	7.705	58.983	90.0
		Removing 10 g/Actuation				
5.420	5.439	4.229	4.244	99.649	64.550	0.0
4.690	5.245	3.757	4.202	89.415	64.520	10.0
3.985	5.032	3.287	4.151	79.185	64.172	20.0
3.306	4.794	2.819	4.089	68.957	63.786	30.0
2.656	4.523	2.356	4.011	58.732	63.337	40.0
2.041	4.207	1.897	3.910	48.511	62.808	50.0
1.466	3.830	1.443	3.769	38.295	62.179	60.0
0.943	3.358	0.998	3.554	28.086	61.380	70.0
0.485	2.714	0.565	3.163	17.887	60.365	80.0
0.120	1.568	0.159	2.070	7.704	59.003	90.0

[a] From Ref. 149.

solid particles may be involved from the time the particles leave the nozzle of the aerosol package to the time the particles are deposited onto the desired surface of the respiratory tract. In many instances, the active ingredient is a solid such as epinephrine bitartrate, sulfate, or hydrochloride; isoproterenol sulfate or hydrochloride; and ergotamine tartrate; this solid is either dissolved in a solvent such as water and alcohol or suspended directly in the propellant. In any event, the ultimate result is that the solvents and propellant vaporize, leaving behind the solid particles of active ingredient. These solid particles, which must be finely subdivided initially, are generally in the range of from 1 to 10 μm and, in most cases, are from 3 to 4 μm in diameter.

Many techniques and instruments have been devised to measure particle size in aerosol systems. Several methods used for aerosols include microscopy, sedimentation, impaction and inertial techniques, and optical methods. Direct methods include the use of microscopes and sieves. Indirect methods are based on the measurement of some property of the particle that is related to its size such as sedimentation velocity, density, viscosity of medium, light-scattering ability, and susceptibility to impaction. Many indirect methods are used to a greater extent than the direct methods since they are more convenient and are less time consuming.

Several review articles covered many of these methods. Licht (152) presented a theoretical treatment of movement of aerosol particles, indicating that the movement was governed primarily by the influence of gravity, drag, inertia, diffusion, and electrostatic charges. It is the combined effect of these forces that determines the path of the particle which, in turn, can be related to the ultimate deposition of the particle. Furthermore, Licht stated that particles less than 50 μm in diameter will be suspended in a free space and that particles greater than 10 μm but less than 50 μm in diameter will have the greatest tendency to deposit upon a surface. This will then take advantage of the inertial effects. Since particles greater than 10 μm will probably not enter the respiratory system, particles should be greater than 10 μm in diameter where inhalation toxicity is a consideration.

Deposition of particles on flat surfaces was also discussed (153). Factors affecting particle-size distribution of aerosol sprays were covered (154). The influence of the valve and propellant upon particle size

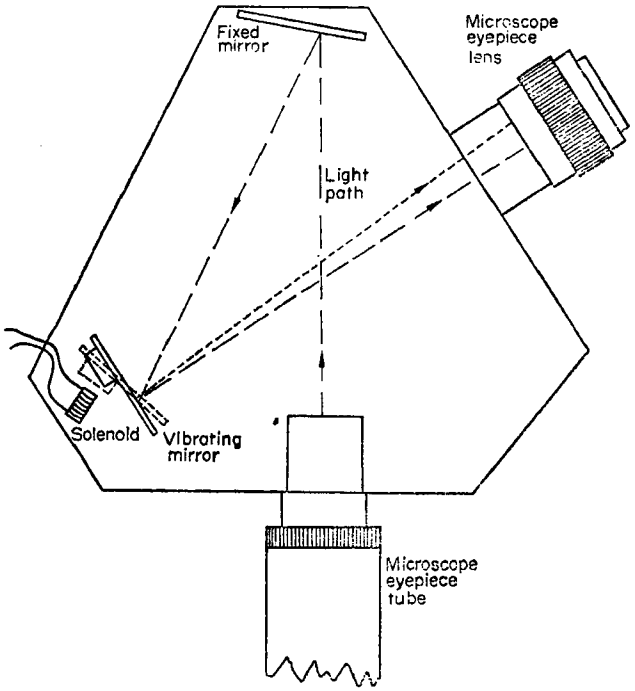

Figure 15—*Cut-away drawing of vibrator unit showing optical system. (From Ref. 159.)*

was determined using high speed electronic photography. Gidwani (155) covered the theoretical aspects of particle-size distribution of powder aerosols. He compared the collection of solid particles on a nest of screens to the collection of particles on the glass slides of a cascade impactor and indicated that the impaction technique was an extension of the sieving technique.

Of these methods, an impaction technique utilizing the cascade impactor has been used to the greatest extent for aerosol products. Polli *et al.* (156) used this technique for determining the influence of drug particle size, drug concentration, surfactant concentration, valve, vapor pressure, and propellant temperature upon the particle-size distribution of inhalation-type aerosols. Based upon the results, it was concluded that the particle size of the spray may be decreased by reducing drug particle size, drug concentration, and orifice of the valve. An increase in vapor pressure and propellant temperature also reduced the particle size. The inclusion of a surfactant in the formulation aided in reducing the particle size.

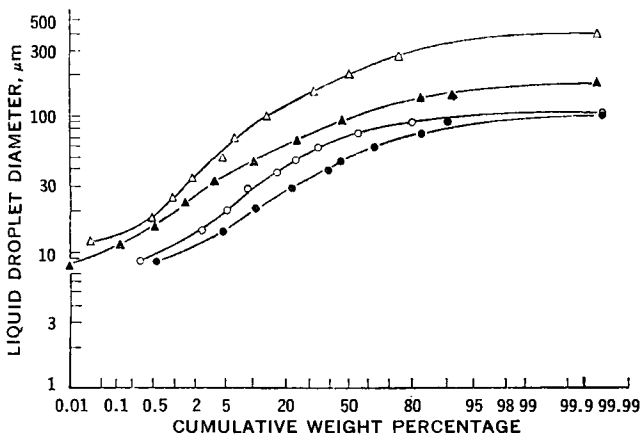

Figure 16—*Particle-size distributions of hair sprays packed at different pressures. Key: △, 145 kNm^{-2}; ▲, 179 kNm^{-2}; ○, 276 kNm^{-2}; and ●, 393 kNm^{-2}. (From Ref. 159.)*

Studies by Sciarra *et al.* (157) utilized the cascade impactor as a screening method for different formulations to select the one producing the least number of particles in the respirable range (less than 10 μm in diameter). The effects of valve orifice and propellant concentration upon the particle-size distribution have been shown. Sciarra and Adelman (158) showed the usefulness of adding a fluorescent tracer to the aerosol prior to the determination of the particle-size distribution of the product. Gussman *et al.* (159) modified the cascade impactor so that samples containing a high volume of airborne particulate matter could be analyzed. With this high volume sampler, these investigators were able to classify aerosol particles between 1 and 20 μm.

Recently, a modification of the microscopic method for measuring the size of particles was utilized to measure the particle-size distribution of a hair spray (160). This method was based upon an extension of the conventional microscopic method using the double-image principle. Particles in the range of from 1 to 250 μm can be classified with an accuracy of ±2%. The system used is shown in Fig. 15, and Fig. 16 illustrates the results obtained using different propellant combinations. The method enables one to count particles on a microscopic slide at the rate of about 2000 particles/hr.

A fairly new development for measuring particle-size distribution of aerosols involves the use of a pulsed ruby laser (wavelength of 0.6943 μm) and a specially designed holographic camera. The laser is fired through the sample to produce the hologram. Particle images then can be reconstructed and viewed on a TV monitor at magnifications up to 1500×. Particles as small as 1.4 μm can be viewed (161).

Particles will deposit in the respiratory tract by inertial impaction. This acts upon particles ranging in diameter from a few microns to over 100 μm. The rate of elimination of particles is a function of their size and mass, as well as the diameter of the air passageways. Particles larger than 5 μm in diameter are prevented from entering the lungs. Particles between 0.5 and 5.0 μm tend to fall against the alveolar walls and mix with the alveolar fluid (162). It is generally agreed that particles larger than 20 μm fail to go beyond the terminal bronchioles, those 6 μm in diameter are removed before they reach the lower alveolar ducts, and almost all particles 2 μm and larger are removed in the lower alveolar ducts (163). There is only a 50% chance for the deposition of particles 1 μm in size. Particles smaller than 1 μm are expired. Idson (162) stated that the particle size for treatment of pulmonary disease should be in the region of 3 μm. For systemic action, particles smaller than 2 μm would be desirable. Dautrebande (164) stated that the depth of penetration increases with decreasing particle size and that the percentage of pulmonary retention increases with increasing particle size. The

relationship between particle size and deposition in the lungs was indicated by many investigators (165–168).

Other Methods—To compare the relative proportion of the doses administered from various aerosol units, Kirk (169, 170) designed a system that could measure the ability of the particles released from an aerosol dosage form to penetrate an artificial system of wet-lined tubes. This system was intended to simulate the upper part of the respiratory tract. Using this system, both solution- and suspension-type aerosols containing isoproterenol were compared as to mean penetrative efficiency using different applicators. In addition, the results were compared with *in vivo* tests conducted on 28 patients. Both clinical and *in vitro* results were comparable, indicating the suitability of the method for the evaluation of the formulations and applicators used with oral aerosols. Kirk also noted that suspension-type formulations were more efficient than those based upon solution in a cosolvent.

A model lung chamber was designed (171) for the evaluation of oral inhalation aerosols. It was shown by evaluating the deposition of materials of known particle size and several commercially available oral aerosols that this lung chamber could be used to determine the efficacy of various aerosol formulations. A vacuum of 30.4 cm (12 in.) of mercury was used based on air flow through the model lung. The deposition of particles in the different compartments was measured as a function of vacuum. Less deviation was noted at this vacuum reading than at 7.6 or 50.8 cm of mercury.

Various workers studied the chilling effect of aerosols upon the skin. Broderick and Flanner (172) and Dunne (173) developed an *in vitro* method for determining the change in temperature upon a surface as it is sprayed with propellant. These methods utilized an aluminum foil-covered surface containing a temperature-recording sensor. Based upon these results, they determined the relative chilling effect of several commonly used propellants alone and in combination with each other as well as with suitable solvents.

A quantitative evaluation of the chilling effect was made (174). The developed method is based on the calculation of the instantaneous cooling rate of a specified thermistor probe exposed to the spray in the test chamber. Cooling curves for the propellants were determined and plotted as probe temperature *versus* time (seconds). A plot of log $(T_t - T_m)$ *versus* time produces a straight line (T_t is the temperature of the probe at time T, and T_m is the minimum probe temperature). Based upon this relationship, the following equation is applicable:

$$\frac{-dT_t}{dt} = K(T_t - T_m) \qquad \text{(Eq. 10)}$$

When integrated between initial probe temperature, T_0, and probe temperature, T_t, at time t, one obtains:

$$\log \frac{T_0 - T_m}{T_t - T_m} = \frac{kt}{2.303} \qquad \text{(Eq. 11)}$$

The constant, k, is the first-order cooling rate constant and is obtained from the plot. From these data, the chill index, I_c, may be computed for each propellant as well as propellant blends and mixtures of propellants with solvents according to the equation:

$$I_c = k(T_n - T_m) = 0.693(T_n - T_m)/t_{0.5^c} \qquad \text{(Eq. 12)}$$

where T_n is the normal body temperature.

Kabasakalian (175) noted the dispensing efficiency of some commercially available nonmetered topical aerosols to be low as compared to ointments, creams, and lotions. This is in contrast to the many reports indicating the efficient application of topical aerosols. In this study, pickup efficiency was used as a criterion for the evaluation of the spray aerosol. A method for determining pickup efficiency has been described in the literature (176) and is commonly used with nonpharmaceutical residual spray-type products. Based upon results obtained using this test method, Kabasakalian noted that time, temperature, and distance from the target area were all important parameters related to pickup efficiency. He also noted a great variation in pickup efficiency at room temperature for some typical pharmaceutical aerosols.

TOXICITY CONSIDERATIONS

The fluorinated hydrocarbons are generally considered to be inert and nontoxic when used as directed. Several complete reviews of this subject were given (177–179). It is on the basis of their nontoxic nature that the fluorinated hydrocarbons have been widely used as refrigerants as well as for aerosol propellants.

DELIBERATE PRODUCT ABUSE

Since 1967 when persons started deliberately to inhale the concentrated vapors of the propellant, attention has been directed toward the toxicity of the propellant. To date, over 100 deaths have been attributed to the deliberate inhalation of aerosols. Death has been attributed to freezing of the larynx, lack of oxygen, and abnormal heart rhythms induced by the simultaneous inhalation of the vapors in high concentration and the secretion of adrenalin in response to excitement, fear, or exertion. Bass (180) collected records of 110 sudden sniffing deaths; he reported that the excessive inhalation of volatile hydrocarbons from aerosols and various chemicals used in glues, paint thinner, gasoline, *etc.*, may be the cause of these sudden deaths (181).

Not only have products containing pure propellant been subjected to abuse (182), but so have products such as hair sprays, deodorants, and antiperspirants (183). There are many other references to this deliberate abuse of propellants either alone or in combination with other ingredients, and the "aerosol industry" has mounted an extensive educational program aimed at the high school population.

Propellant Toxicity—This topic is most contro-

Table XII—Some Physical Properties of Propellants

Propellant	Chemical Structure	Molecular Weight	Boiling Point °F	Boiling Point °C	Vapor Pressure, psia 70°F	Solubility in Water, wt %
Trichloromonofluoromethane	CCl_3F	137.4	74.8	23.8	13.4	0.11[a]
Dichlorodifluoromethane	CCl_2F_2	120.9	−21.6	−29.8	84.9	0.028[a]
Dichlorotetrafluoroethane	$CClF_2—CClF_2$	170.9	38.8	3.8	1.8	0.013[a]
1-Chloro-1,1-difluoroethane	CH_3CClF_2	100.5	15.1	−9.4	43.8	0.14[b]
1,1-Difluoroethane	CH_3CHF_2	66.05	−11.2	−24.0	76.4	0.32[b]

[a] At 1 atm pressure and 22° (77° F). [b] At 1 atm pressure and 21° (70° F).

versial at the present time. Ever since Taylor and Harris (184) reported the cardiotoxicity of aerosol propellants, a flood of reports have indicated either that the propellants were toxic or safe. Taylor and Harris noted that the fluoroalkane gases used to propel aerosols were toxic to the heart of mice, sensitizing them to asphyxia-induced sinus bradycardia, atrioventricular block, and T-wave depression. The propellants were postulated to possess a spectrum of cardiotoxic effects capable of causing bradyarrhythmias, tachyarrhythmias, or myocardial depression. Taylor and Harris concluded that the fluorinated hydrocarbons can no longer be considered inert. Further studies (185–187) reached the same conclusion.

In reply to the Taylor and Harris report, Zapp (188, 189) reported that the lack of oxygen, not cardiac toxicity of the fluorocarbon propellants, was the probable cause of death of the mice. The fluorocarbon propellants have very low order toxicity on the scale of comparative toxicities. The vapors of the fluorocarbon propellants produce narcotic effects if inhaled at a high enough concentration. Deliberate misuse by collecting and inhaling concentrated vapors of propellants in the absence of oxygen probably causes death (181, 189). Azar *et al.* (190) concluded from their study that: "from the practical point of view, it is important to note that the induction of cardiac sensitization or asphyxia requires the deliberate inhalation of high concentrations of propellants—much higher concentrations than those generated when aerosol products, including asthma inhalers, are used as directed." They also noted that there was no evidence of any form of chronic cardiac toxicity. Similar conclusions were reported by others (191–193).

Typical of the many studies following the Taylor and Harris report is one by Flowers and Horan (194).

Table XIII[a]—Blood Concentrations of Trichloromonofluoromethane

Minutes	Blood Concentration, μg/ml: Patient 1 (Three Puffs), Arterial	Patient 2 (Six Puffs), Arterial	Patient 2 (Six Puffs), Venous
0.5	—	0.63	—
1	1.7	0.39	—
2	0.5	0.39	0.20
3	0.35	—	—
4	—	—	0.22

[a] From Ref. 196.

These workers were able to produce cardiac arrhythmias in dogs exposed to aerosols containing fluorinated hydrocarbons as propellants. They indicated that the studies were carried out in an atmosphere containing normal arterial oxygen tension, carbon dioxide tension, and other elements necessary to sustain life. They also showed that trichloromonofluoromethane was readily absorbed into the blood after inhalation. The less volatile propellants are thought to be absorbed to a greater extent than the more volatile compounds such as dichlorodifluoromethane.

Typical of the studies reporting on the absence of sensitization of the myocardium to arrhythmias induced by asphyxia is a report by Egle *et al.* (195). These workers were not able to duplicate the results reported by Taylor and Harris (184). According to Egle *et al.*, their results do not support the contention that inhalation of haloalkane propellants under the conditions employed by Taylor and Harris makes cardiac activity in mice more sensitive to the effects of asphyxia. Further aspects of their study led to the conclusion that the propellants would not sensitize the heart to catecholamines in the generally used concentrations, but that higher concentrations of propellant could result in this effect.

Other studies have been directed toward determination of the concentration of fluorocarbon in the bloodstream following inhalation. A literature search reveals little information as to the presence of a known amount of fluorocarbon in the body. However, the need for this type of information has not been definitely determined.

The detection of fluorocarbons in body fluids is not an easy task. The physical properties of the propellants are such that their detection would be difficult. Their relatively low boiling point, high vapor pressure, and low aqueous solubility tend to minimize their presence in body fluids in sufficient concentration so that they can be detected (Table XII).

As can be seen from Table XII, of the propellants listed, only trichloromonofluoromethane is likely to be found in any reasonable amount in the bloodstream. 1-Chloro-1,1-difluoroethane and 1,1-difluoroethane[7] have higher water solubilities but also lower boiling points and would tend to escape from the bloodstream.

A compound does not have to be in the bloodstream to exert a toxic reaction. Volatile materials such as these gases can act in the lungs and locally

[7] Propellant 152a.

Table XIV[a]—Peak Blood Levels of Fluorocarbons in Dogs after Aerosol Administration[b]

Fluorocarbon	Peak Level, μg/ml		Peak Arterial Level as Percent of Administered Dose[c]	
	10 Actuations	5 Actuations	10 Actuations	5 Actuations
Trichloromonofluoromethane				
Arterial	22.3 ± 1.0	13.2 ± 1.4	15.9	8.89
Venous	6.22 ± 2.6	2.45 ± 0.29		
Dichlorodifluoromethane				
Arterial	6.17 ± 0.38	3.16 ± 0.06	4.41	4.51
Venous	1.54 ± 0.84	0.56 ± 0.04		
Trichlorotrifluoroethane				
Arterial	11.56 ± 1.78	6.43 ± 0.61	8.26	9.19
Venous	2.96 ± 1.40	0.79 ± 0.06		
Dichlorotetrafluoroethane				
Arterial	3.80 ± 0.52	2.32 ± 0.12	2.71	3.31
Venous	0.87 ± 0.41	0.26 ± 0[d]		

[a] From Ref. 197. [b] Five or 10 actuations of an aerosol mixture containing 25% (w/w) of trichloromonofluoromethane, dichlorodifluoromethane, trichlorotrifluoroethane, and dichlorotetrafluoroethane were administered to three or four dogs, respectively. One actuation delivered 16.8 mg of each fluorocarbon. The results are expressed as the mean ± *SE* of the peak fluorocarbon blood level determined for three or four dogs. [c] Calculated for a 15-kg dog with 8% of body weight as blood volume. [d] Mean ± *SE* from two dogs.

upon the respiratory system. However, for systemic toxicity to occur, the material must be present in the bloodstream and from there be carried to the site of action. The recent reports in which it was noted that propellants were found in the bloodstream of patients and dogs gave rise to additional investigations.

Since the amount of propellant that may be present in the bloodstream is very small, analytical techniques capable of detecting fairly low levels of fluorocarbons were investigated. Gas chromatography was useful for this purpose. Dollery *et al.* (196) used gas chromatography with a nickel-63 electron-capture detector; Shargel and Koss (197) also used an electron-capture detector, but the source of the electrons was from tritium. Under these conditions, both groups were able to detect fluorocarbons in the bloodstream in the quantities noted in Tables XIII and XIV. An examination of these two tables indicates that generally trichloromonofluoromethane is detected in a greater concentration than the other propellants.

Product Toxicity—For many years, aerosols containing epinephrine or isoproterenol have been the center of controversy. Restrictions were placed on the labeling of aerosol preparations containing isoproterenol in 1968 (198–202) when several reports of death through alleged overuse of isoproterenol aerosols came to light. The Federal Register of June 18, 1968 indicated that all inhalation preparations containing isoproterenol must bear the following statement:

> *Occasional patients have been reported to develop severe paradoxical airway resistance with repeated, excessive use of isoproterenol inhalation preparations. The cause of this refractory state is unknown. It is advisable that in such instances the use of this preparation be discontinued immediately and alternative therapy instituted, since in the reported cases the patients did not respond to other forms of therapy until the drug was withdrawn.*
>
> *Deaths have been reported following excessive use of isoproterenol inhalation preparations, and the exact cause is unknown. Cardiac arrest was noted in several instances.*

Since 1968, reports continued to appear in the medical literature as to adverse reaction (30, 203–206). Recently, in addition to isoproterenol preparations, epinephrine aerosols were said to cause similar reactions when overused. As a result, the Federal Register of April 15, 1972, published that similar warning statements would now be required for epinephrine inhalation preparations.

The reports showed that severe paradoxical bronchoconstriction episodes, but no deaths, occurred as a result of excessive and repeated use of epinephrine inhalation preparations. Thus, only the first warning statement as indicated for isoproterenol inhalation preparations must be included and not the statement concerned with deaths following excessive use.

Since the time when the first aerosol product was used commercially in the late 1940's, reports have appeared as to the possible hazard of inhaling the particles. Today, many reports have been issued as to the potential hazard of using these products. Many of these reports have been issued by various consumer groups, and these findings were recently summarized (207). Cambridge (208) reviewed the toxicity noted with hair sprays in the early 1950's as well as some recent studies. Different household aerosol products were studied by Marier *et al.* (209). With an exposure to fluorocarbons of about 10 times greater than normal, these workers were not able to detect any measurable fluorocarbon blood levels nor any indication of toxicity.

Other aerosols have become suspect in various toxic manifestations. Feminine hygiene sprays, medicated vaporizer sprays, and adhesive sprays have been subjected to scrutiny by various consumer and governmental agencies. Their status, as well as the status of other aerosols, is currently under attack due to suspected toxicity. A massive research program is underway at present, and hopefully the results of these reports will shed light on this highly controversial subject.

CONCLUSION

The aerosol dosage form has been accepted by both

the medical and pharmaceutical professions as another means for the administration of drugs orally, topically, or into one of the body cavities. As noted by the number of original research articles appearing in various publications, there is a great deal of interest in furthering the use of this dosage form. However, there is need for additional research and development before it can fully realize its potential.

The administration of many drugs for inhalation therapy by means of a pressured system represents a rather large area in need of development. With the exception of drugs intended to relieve the symptoms of asthma, this dosage form has not been applied to many other drugs. Encouraging, however, is the fact that the literature does give reports on the use of insulin (210) and other drugs (211–215) by inhalation therapy. These drugs represent a potential for further application. The use of antibiotic aerosols, with or without a plastic dressing, following surgery has also been indicated (216–218). Additional applications include contraceptives (219), topical anesthetics (220–221), and antimycotics (222–223). These represent only a few of many other applications which have been studied but may not have been fully developed.

New techniques for the formulation need to be developed. Codispensing systems and barrier packs have not been used to any great extent. Microencapsulation techniques, while widely used in the pharmaceutical industry, recently have been applied to aerosol systems (224, 225). As these and other systems are developed, many advantages of the aerosol dosage form can be fully realized.

At the present time, the toxicity potential of aerosols and the hazards, if any, that they may cause are important problems. The Food and Drug Administration and other governmental and private agencies are concerned with these problems. Further studies are indicated to determine the toxicity of these products. Particle-size distribution and inhalation and the effect that they have upon the human body must be determined. Current studies are directed toward this end.

Publications by the Food and Drug Administration (Federal Register of March 7, 1973) indicated the "proposal regarding warning statements" to be included on the label of all food, drug, and cosmetic aerosol products containing "halocarbons" and, to a lesser extent, hydrocarbons.

The proposed regulations mandate the inclusion on the label of these products the following statements:

Warning—Do not inhale directly; deliberate inhalation of contents can cause death.

or:

Warning—Use only as directed; intentional misuse by deliberately concentrating and inhaling the contents can be harmful or fatal.

In addition, pharmaceutical aerosols must contain the following:

Warning—Avoid inhaling. Keep away from eyes or other mucous membranes.

The statement "avoid inhaling" is not necessary for preparations specifically designed for use by inhalation, and the phrase "or other mucous membranes" is not necessary for preparations specifically designed for use in mucous membranes. These exemptions have been included for oral inhalants such as the antiasthmatics.

These statements are to be included along with the previously required statements as to contents under pressure, keep out of reach of children, do not incinerate or puncture container, *etc.*

Pharmaceutical aerosols represent only a small segment of all dosage forms available. However, the application of all areas of research is required to develop and manufacture the finished product. While most manufacturing and packaging of these aerosols are left to outside contract facilities, the need for the marketer to develop suitable quality control procedures and packaging specifications is apparent. These procedures have been available and are widely used, although there is need for greater sophistication of the methods and specifications. Metered valves along with delivery of dosage, uniformity of dosage, valve leakage, *etc.*, are all factors that must be satisfactorily considered before the product can be introduced into the marketplace.

REFERENCES

(1) "Aerosol and Pressurized Products Survey—1972," Chemical Specialties Manufacturers Ass., New York, N.Y., May 1974.

(2) J. M. Borland, *Soap Cosmet. Chem. Spec.*, **48** (8), 53(1972).

(3) A. Herzka and J. Pickthall, "Pressurized Packaging (Aerosols)," Academic, New York, N.Y., 1958.

(4) *Ibid.*, 1961.

(5) "Aerosols: Science and Technology," H. R. Shepherd, Ed., Interscience, New York, N.Y., 1961.

(6) A. Herzka, in "International Encyclopaedia of Pressurized Packaging (Aerosols)," Pergamon Press, London, England, 1966.

(7) D. R. Devesa, "Tecnologia de los Aerosoles," Dario Rodriguez Devesa, Avda. Generalisimo, 118 Madrid, Spain, 1965.

(8) D. R. Devesa, "Formulacion de los Aerosoles," Dario Rodriguez Devesa, Avda. Generalisimo, 118 Madrid, Spain, 1971.

(9) P. A. Sanders, "Principles of Aerosol Technology," Van Nostrand Reinhold, New York, N.Y., 1970.

(10) M. A. Johnsen, W. E. Dorland, and E. K. Dorland, "The Aerosol Handbook," Wayne E. Dorland Co., Caldwell, N.J., 1972.

(11) J. J. Sciarra and L. Stoller, "The Science and Technology of Aerosol Packaging," Wiley–Interscience, New York, N.Y., 1974.

(12) F. A. Mina, in "Chemistry and Manufacture of Cosmetics," vol. 1, 2nd ed., Van Nostrand, New York, N.Y., 1962, p. 1.

(13) M. J. Root, in "Cosmetics: Science and Technology," vol. 2, 2nd ed., M. S. Balsom and E. Sagarin, Eds., Wiley–Interscience, New York, N.Y., 1972, p. 417.

(14) "Remington's Practice of Pharmacy," 12th ed., Mack Publishing Co., Easton, Pa., 1961, p. 512.

(15) H. Mintzer, in "Dispensing of Medication," 7th ed., E. W. Martin, Ed., Mack Publishing Co., Easton, Pa., 1971, p. 928.

(16) I. Porush, in "Aerosols: Science and Technology," H. R. Shepherd, Ed., Interscience, New York, N.Y., 1961, p. 387.

(17) C. O. Ward, in "The Science and Technology of Aerosol Packaging," J. J. Sciarra and L. Stoller, Eds., Wiley–Interscience, New York, N.Y., 1974, p. 617.

(18) J. J. Sciarra, in "International Encyclopaedia of Pressurized Packaging (Aerosols)," Pergamon Press, London, England, 1966, p. 571.

(19) J. J. Sciarra, in "Remington's Pharmaceutical Sciences," 14th ed., Mack Publishing Co., Easton, Pa., 1970, p. 1729.
(20) J. J. Sciarra, in "Prescription Pharmacy," 2nd ed., J. B. Sprowls, Jr., Ed., J. B. Lippincott, Philadelphia, Pa., 1970, p. 280.
(21) J. J. Sciarra, in "The Theory and Practice of Industrial Pharmacy," L. Lachman, H. A. Lieberman, and J. L. Kanig, Eds., Lea & Febiger, Philadelphia, Pa., 1970, p. 605.
(22) "The United States Pharmacopeia," 18th rev., Mack Publishing Co., Easton, Pa., 1970, p. 807.
(23) "The National Formulary," 13th ed., Mack Publishing Co., Easton, Pa., 1970, p. 825.
(24) *Ibid.*, p. 721.
(25) *Ibid.*, p. 224.
(26) *Ibid.*, p. 225.
(27) *Aerosol Age*, **15** (1), 47(1970).
(28) P. D. Stolley, *Amer. Rev. Resp. Dis.*, **105**, 883(1972).
(29) T. E. Van Metre, Jr., *J. Allergy*, **43**, 101(1969).
(30) D. Lehr, *N. Engl. J. Med.*, **287**, 988(1972).
(31) J. J. Sciarra, *Drug Cosmet. Ind.*, **105** (2), 46(1969).
(32) J. J. Fabijanic, *ibid.*, **109** (6), 40(1971); *ibid.*, **110** (1), 38(1972); *ibid.*, **110** (2), 48(1972).
(33) A. J. Parisse, *Proc. Chem. Spec. Mfg. Ass.*, 55th midyear meeting, May 1969, p. 38.
(34) P. G. Pick, *ibid.*, p. 44.
(35) J. Yakubik, *Drug Cosmet. Ind.*, **95** (1), 36(1964).
(36) A. J. Parisse, *Amer. Perfum. Cosmet.*, **83** (9), 45(1968).
(37) R. Marsden, *Pharm. J.*, **193**, 396(1964).
(38) H. Kubler, *Int. Pharm. Abstr.*, **9**, 4217(1972).
(39) J. J. Sciarra, *Aerosol Age*, **14** (1), 43(1969).
(40) *Ibid.*, **14** (2), 58(1969).
(41) *Ibid.*, **18** (5), 70(1973); *ibid.*, **18** (6), 30(1973).
(42) D. A. Davis, *Drug Cosmet. Ind.*, **106** (2), 38(1970).
(43) R. S. Schultz, *Soap Chem. Spec.*, **38** (3), 127(1962).
(44) L. F. Irland and J. W. Kinnary, *Drug Cosmet. Ind.*, **101** (2), 42(1967).
(45) *Aerosol Age*, **19** (1), 14(1974).
(46) J. Pedersen, *ibid.*, **18** (3), 36(1973).
(47) J. J. Sciarra, *ibid.*, **18** (3), 30(1973).
(48) H. Boden, *ibid.*, **13** (3), 19(1968).
(49) "Freon Aerosol Report A-74," E. I. duPont de Nemours, Wilmington, Del., 1968.
(50) G. Hostier, *Aerosol Rep.*, **10**, 474(1971).
(51) G. Holzner, *ibid.*, **8**, 557(1969).
(52) H. Hsu and D. Campbell, *Aerosol Age*, **10** (12), 34(1964).
(53) J. J. Sciarra and R. N. Gidwani, *J. Soc. Cosmet. Chem.*, **21**, 667(1970).
(54) J. J. Sciarra and R. N. Gidwani, *J. Pharm. Sci.*, **61**, 754(1972).
(55) J. J. Sciarra and S. P. Patel, *J. Soc. Cosmet. Chem.*, **23**, 605(1972).
(56) L. Lachman and A. Drubulis, *J. Pharm. Sci.*, **53**, 639(1964).
(57) W. Eckardt, *J. Soc. Cosmet. Chem.*, **21**, 281(1970).
(58) R. W. Rance, *ibid.*, **24**, 501(1973).
(59) I. Porush, C. Thiel, and J. Young, *J. Amer. Pharm. Ass., Sci. Ed.*, **49**, 70(1960).
(60) J. Young, I. Porush, C. Thiel, S. Cohen, and C. Stimmel, *ibid.*, **49**, 72(1960).
(61) J. J. Sciarra, J. M. Patel, and A. L. Kapoor, *J. Pharm. Sci.*, **61**, 219(1972).
(62) H. Salem and T. Ellison, *Ann. Ophthalmol.*, **5**, 417(1973).
(63) H. Kubler, *Aerosol Age*, **14**, 36(1969).
(64) A. Herzka, *J. Soc. Cosmet. Chem.*, **21**, 553(1970).
(65) S. C. Elvin, *Aerosol Age*, **16**, 26(1971).
(66) J. M. Crotty, R. L. Raymond, and B. Siegal, *J. Soc. Cosmet. Chem.*, **22**, 153(1971).
(67) R. F. Van de Heide, *Mfg. Chem. Aerosol News*, **43** (3), 25(1972).
(68) *Soap Perfum. Cosmet.*, **44**, 229(1971).
(69) P. Peter, *Aerosol Rep.*, **10**, 283(1971).
(70) *Soap Perfum. Cosmet.*, **42**, 723(1969).
(71) P. E. G. Kenmore and D. R. Rink, U.S. pat. 3,081,223 (1963).
(72) *Aerosol Age*, **13** (9), 24(1968).
(73) T. Kunzmann, *Seifen-Oele-Fette-Wachse*, **97**, 425(1971).
(74) M. Harry and C. Carrion, *J. Soc. Cosmet. Chem.*, **20**, 511(1969).
(75) C. McBride, *Aerosol Rep.*, **8**, 606(1969); *Aerosol Age*, **14** (10), 36(1969).
(76) B. Foss and H. Schaeffer, *Chem. Technol.*, **2**, 398(1972).
(77) P. A. Sanders, *Aerosol Age*, **14** (9), 34(1969).
(78) H. Kubler, *Fette, Seifen, Anstrichm.*, **72**, 396(1970).
(79) P. A. Sanders, *J. Soc. Cosmet. Chem.*, **21**, 377(1970).
(80) S. Friberg, L. Rydhag, and G. Jederström, *J. Pharm. Sci.*, **60**, 1883(1971).
(81) G. Jederström, L. Rydhag, and S. Friberg, *ibid.*, **62**, 1979(1973).
(82) S. Friberg, L. Mandell, and M. Larsson, *J. Colloid Interface Sci.*, **29**, 155(1969).
(83) S. Friberg and L. Mandell, *J. Pharm. Sci.*, **59**, 1001(1970).
(84) P. A. Sanders, *J. Soc. Cosmet. Chem.*, **20**, 577(1969).
(85) *Ibid.*, **24**, 87(1973).
(86) *Ibid.*, **24**, 623(1973).
(87) P. A. Sanders, *Amer. Perfum. Cosmet.*, **84**, 111(1969).
(88) G. K. Cooper, *Aerosol Age*, **12** (4), 32(1967); *ibid.*, **12** (5), 71(1967).
(89) P. A. Sanders, *Drug Cosmet. Ind.*, **99** (2), 56(1966); *ibid.*, **99** (3), 57(1966).
(90) R. Lemlich, *J. Soc. Cosmet. Chem.*, **23**, 299(1972).
(91) D. D. Schiefer and W. M. Henderson, *Amer. J. Hosp. Pharm.*, **26**, 114(1969).
(92) J. T. Fisher and B. B. Sheth, *Aerosol Age*, **18** (2), 28(1973).
(93) *Ibid.*, **18** (3), 22(1973).
(94) J. A. Monson, U.S. pat. 3,541,581 (1970).
(95) R. J. Davies, M. F. D'Souza, and S. P. Simmonds, *Brit. Med. J.*, **1**, 177(1972).
(96) A. M. Contractor, M. D. Richmond, and R. F. Shangraw, *J. Pharm. Sci.*, **59**, 1488(1970).
(97) A. M. Contractor, R. F. Shangraw, and M. D. Richmond, *Aerosol Age*, **14** (7), 19(1969).
(98) L. T. Flanner and T. J. Matera, *J. Soc. Cosmet. Chem.*, **20**, 365(1969).
(99) L. T. Flanner, *ibid.*, **21**, 661(1970).
(100) D. N. Parker, *Amer. Perfum. Cosmet.*, **86**, 105(1971).
(101) J. C. Armstrong, *Aerosol Age*, **17** (3), 19(1972).
(102) F. J. McIlreath and B. M. Cohen, *J. Med. Exp. Clin.*, **1**, 229(1970).
(103) J. H. Bell, P. S. Hartley, and J. S. G. Cox, *J. Pharm. Sci.*, **60**, 1559(1971).
(104) B. Benjamin, *Aerosol Rep.*, **11**, 331(1972).
(105) R. Eck, *Seifen-Oele-Fette-Waschse*, **97**, 241(1971).
(106) T. Kunzmann, *ibid.*, **96**, 105(1970).
(107) M. A. Johnsen, *Aerosol Age*, **7** (6), 20(1962); *ibid.*, **7** (7), 29(1962); *ibid*, **7** (8), 39(1962); *ibid.*, **7** (9), 39(1962).
(108) *Ibid.*, **15** (8), 20(1970); *ibid.*, **15** (9), 26(1970).
(109) D. M. Howard, *J. Soc. Cosmet. Chem.*, **20**, 17(1969).
(110) A. S. Glessner, *Soap Perfum. Cosmet.*, **45**, 87(1972).
(111) M. J. Layzell and A. Kleniewski, *Mfg. Chem. Aerosol News*, **40** (10), 30(1969).
(112) T. P. Murphy and J. F. Walpole, *Aerosol Rep.*, **11**, 525(1972).
(113) E. D. Giggard, *Aerosol Age*, **13** (7), 16(1968).
(114) *Aerosol Age*, **17** (8), 38(1972).
(115) S. T. Craige, in "The Science and Technology of Aerosol Packaging," J. J. Sciarra and L. Stoller, Eds., Wiley–Interscience, New York, N.Y., 1974, pp. 209–222.
(116) H. Yamamoto, M. Tsurumaru, and T. Kurihara, *Amer. Perfum. Cosmet.*, **86** (11), 41(1971).
(117) W. V. Toffey, *Prod. Manag.*, **No. 6**, 46(1973).
(118) *Aerosol Age*, **18** (1), 36(1973).
(119) B. D. Joyner, *Mfg. Chem.*, **40** (8), 63(1969).
(120) B. D. Joyner, *Labo-Pharma.*, **17** (9), 71(1969).
(121) R. P. Harris, *Aerosol Age*, **13** (7), 25(1968).
(122) J. J. Sciarra, *ibid.*, **12** (2), 65(1967); *ibid.*, **12** (3), 45(1967); *ibid.*, **12** (4), 65(1967).
(123) R. T. Boegeli, J. B. Ward, and H. H. Hutchins, *J. Soc. Cosmet. Chem.*, **20**, 373(1969).
(124) J. J. Sciarra, in "Quality Control in the Pharmaceutical Industry," vol. 2, M. S. Cooper, Ed., Academic, New York, N.Y., 1973, pp. 1–54.
(125) K. Morrissey, *Aerosol Age*, **14** (2), 16(1969).

(126) L. Flanner, *ibid.*, **15** (5), 28(1970).
(127) L. Flanner, *Amer. Perfum. Cosmet.*, **86,** 116(1971).
(128) R. J. Scheffler, *Aerosol Age,* **14** (1), 27(1969).
(129) R. Bernhardt, *ibid.*, **17** (9), 23(1972).
(130) J. E. Kilsheimer, *Package Eng.*, **10** (6), 79(1965).
(131) M. A. Johnsen, W. E. Dorland, and E. K. Dorland, "The Aerosol Handbook," Wayne E. Dorland Co., Caldwell, N.J., 1972, pp. 333–376.
(132) "Aerosol Guide," 6th ed., Chemical Specialties Manufacturers Ass., New York, N.Y., Mar. 1971.
(133) "The National Formulary," 13th ed., Mack Publishing Co., Easton, Pa., 1970, pp. 770–772.
(134) J. J. Sciarra, *Aerosol Age,* **15** (7), 61(1970).
(135) M. A. Johnsen, W. E. Dorland, and E. K. Dorland, "The Aerosol Handbook," Wayne E. Dorland Co., Caldwell, N.J., 1972, pp. 377–400.
(136) J. J. Sciarra, in "The Science and Technology of Aerosol Packaging," J. J. Sciarra and L. Stoller, Eds., Wiley–Interscience, New York, N.Y., 1974, pp. 301–346.
(137) S. P. Tuesley, J. J. Sciarra, and A. J. Monte-Bovi, *J. Pharm. Sci.*, **57,** 488(1968).
(138) K. R. M. Vora, L. L. Augsburger, and R. F. Shangraw, *ibid.*, **59,** 1012(1970).
(139) S. Cohen, *ibid.*, **57,** 966(1968).
(140) C. B. Rifino, A. J. Monte-Bovi, and J. J. Sciarra, *ibid.*, **54,** 413(1965).
(141) G. B. Lawless, J. J. Sciarra, and A. J. Monte-Bovi, *ibid.*, **54,** 273(1965).
(142) R. D. Cannizzaro and D. A. Lewis, *J. Soc. Cosmet. Chem.*, **20,** 353(1969).
(143) R. Schubert and L. Ketel, *ibid.*, **23,** 115(1972).
(144) P. Silverman, J. Marcis, and C. N. Schmidt, *Soap Chem. Spec.*, **43** (2), 78(1967).
(145) L. T. Flanner, *Proc. Chem. Spec. Mfg. Ass.*, 53rd midyear meeting, Chicago, Ill., May 1967, pp. 53, 54.
(146) M. D. Richman and R. F. Shangraw, *Aerosol Age,* **11** (5), 36(1966); *ibid.*, **11** (6), 30(1966).
(147) *Ibid.*, **11** (7), 28(1966); *ibid.*, **11** (8), 39(1966).
(148) *Ibid.*, **11** (9), 45(1966).
(149) *Ibid.*, **11** (10), 32(1966); *ibid.*, **11** (11), 28(1966).
(150) L. L. Augsburger and R. F. Shangraw, *J. Pharm. Sci.*, **57,** 624(1968).
(151) P. Sanders, *Aerosol Age,* **8** (7), 33(1963).
(152) W. Licht, *J. Soc. Cosmet. Chem.*, **23,** 657(1972).
(153) J. Rosinski and B. Langer, *Powder Technol.*, **1** (10), 167(1967).
(154) M. Lefebvre and R. Tregan, *Aerosol Age,* **10** (7), 31(1965); *ibid.*, **10** (8), 32(1965).
(155) R. Gidwani, *ibid.*, **16** (2), 22(1971).
(156) G. P. Polli, W. M. Grim, F. A. Bacher, and M. H. Yunker, *J. Pharm. Sci.*, **58,** 484(1969).
(157) J. J. Sciarra, P. Mc Ginley, and L. Izzo, *J. Soc. Cosmet. Chem.*, **20,** 385(1969).
(158) J. J. Sciarra and D. Adelman, *ibid.*, **22,** 867(1971).
(159) R. A. Gussman, A. M. Sacco, and N. M. Mc Mahon, *J. Air Pollut. Contr. Ass.*, **23,** 778(1973).
(160) R. W. Rance, *J. Soc. Cosmet. Chem.*, **23,** 197(1972).
(161) G. Seger, *Aerosol Rep.*, **8,** 119(1969).
(162) B. Idson, *Drug Cosmet. Ind.*, **107** (1), 46(1970).
(163) J. L. Kanig, *J. Pharm. Sci.*, **52,** 513(1963).
(164) L. Dautrebande, *Physiol. Rev.*, **32,** 214(1952).
(165) S. Blaug, *Aerosol Age,* **13** (12), 48(1968).
(166) E. Robillard, C. Lepine, and L. Dautrebande, *Can. Med. Ass. J.*, **86,** 362(1962).
(167) T. T. Mercer, *Arch. Intern. Med.*, **131,** 39(1973).
(168) B. O. Stuart, *ibid.*, **131,** 60(1973).
(169) W. F. Kirk, *J. Pharm. Sci.*, **61,** 262(1972).
(170) W. F. Kirk, *Cesk. Farm.*, **18,** 142(1969); through *Int. Pharm. Abstr.*, **7,** 4421(1970).
(171) A. W. Karig, G. E. Peck, and G. J. Sperandio, *J. Pharm. Sci.*, **62,** 811(1973).
(172) G. F. Broderick and L. T. Flanner, *Proc. Chem. Spec. Mfg. Ass.*, midyear meeting, 34(1965).
(173) T. F. Dunne, *Aerosol Age,* **4,** 36(1959).
(174) B. Kulkarni, P. J. Carrigan, J. B. Ward, and H. H. Hutchins, *J. Pharm. Sci.*, **58,** 481(1969).
(175) P. Kabasakalian, *ibid.*, **58,** 245(1969).
(176) "Aerosol Guide," 5th ed., Chemical Specialties Manufacturers Ass., New York, N.Y., 1971, p. 113.
(177) J. W. Clayton, Jr., in "Principles of Aerosol Technology," P. A. Sanders, Ed., Van Nostrand Reinhold, New York, N.Y., 1970, pp. 373–390.
(178) C. O. Ward, in "The Science and Technology of Aerosol Packaging," J. J. Sciarra and L. Stoller, Eds., Wiley–Interscience, New York, N.Y., 1974, pp. 617–640.
(179) F. T. Reed, *Amer. Perfum.*, **75** (10), 40(1960).
(180) M. Bass, *J. Amer. Med. Ass.*, **212,** 2075(1970).
(181) C. F. Reinhardt, A. Azar, M. E. Maxfield, P. E. Smith, Jr., and L. S. Mullin, *Arch. Environ. Health,* **22,** 265(1971).
(182) J. J. Sciarra, *Aerosol Age,* **18** (9), 51(1973); *ibid.*, **18** (10), 47(1973).
(183) R. A. Kramer and P. Pierpaoli, *Pediatrics,* **48,** 322(1971).
(184) G. J. Taylor and W. S. Harris, *J. Amer. Med. Ass.*, **214,** 81(1970).
(185) W. S. Harris, *Arch. Intern. Med.*, **131,** 162(1973).
(186) W. S. Harris, *J. Amer. Med. Ass.*, **223,** 1508(1973).
(187) S. M. Kilen and W. S. Harris, *J. Pharmacol. Exp. Ther.*, **183,** 245(1973).
(188) J. Zapp, *Aerosol Age,* **16** (1), 23(1971).
(189) J. Zapp, *Soap Chem. Spec.*, **47** (1), 92(1971).
(190) A. Azar, J. A. Zapp, C. F. Reinhardt, and G. J. Stopps, *J. Amer. Med. Ass.*, **215,** 1501(1971).
(191) A. Silverglade, *ibid.*, **222,** 827(1972).
(192) D. W. Reddy, *Aerosol Age,* **18** (4), 20(1973).
(193) F. A. Bower, *ibid.*, **17** (12), 28(1972).
(194) N. C. Flowers and L. G. Horan, *J. Amer. Med. Ass.*, **219,** 33(1972).
(195) J. L. Egle, Jr., J. W. Putney, and J. F. Borzelleca, *ibid.*, **222,** 786(1972).
(196) C. T. Dollery, G. H. Draffan, D. S. Davies, F. M. Williams, and M. E. Conolly, *Lancet,* **2,** 1164(1970).
(197) L. Shargel and R. Koss, *J. Pharm. Sci.*, **61,** 1445(1972).
(198) F. E. Speizer, R. Doll, and P. Heaf, *Brit. Med. J.*, **1,** 335(1968).
(199) F. E. Speizer, R. Doll, P. Heaf, and L. B. Strang, *ibid.*, **1,** 339(1958).
(200) F. E. Speizer and R. Doll, *ibid.*, **2,** 245(1968).
(201) W. H. W. Inman and A. M. Adelstein, *Lancet,* **2,** 279(1969).
(202) B. Gandevia, *Med. J. Aust.*, **1,** 747(1968); *ibid.*, **1,** 884(1968).
(203) A. Silverglade, *Aerosol Age,* **17** (11), 24(1972).
(204) W. D. Riding, S. S. Chatterjee, A. Bernstein, and P. Dinda, *Amer. Rev. Resp. Dis.*, **104,** 688(1971).
(205) R. N. Pierson, Jr., and M. H. Grieco, *ibid.*, **100,** 533(1969).
(206) W. S. Eisenstadt and S. S. Nicholas, *Ann. Allergy,* **27,** 283(1969).
(207) *Med. World News,* **Nov. 16, 1973,** 49–56.
(208) G. W. Cambridge, *Aerosol Age,* **18** (5), 32(1973).
(209) G. Marier, H. Mac Farland, and P. Dussault, *ibid.*, **18** (12), 30(1973).
(210) F. W. Wigley, J. H. Landono, S. H. Wood, J. C. Shipp, and R. H. Waldman, *Diabetes,* **20,** 552(1971); through *Biol. Abstr.*, **53** (6), 33204(1971).
(211) G. Hanbleton and E. A. Shinebourve, *Arch. Dis. Child.*, **45** 766(1969); through *Biol. Abstr.*, **52** (23), 132695(1970).
(212) T. Smelzer and T. B. Barnett, *J. Amer. Med. Ass.*, **223,** 884(1973).
(213) T. J. H. Clark, *Lancet,* **1,** 1361(1971); through *Biol. Abstr.*, **54** (10), 56927(1972).
(214) H. K. Tweel, *Ann. Allergy,* **29,** 142(1971); through *Int. Pharm. Abstr.*, **8,** 4192(1971).
(215) H. M. Brown, G. Storey, and W. H. S. George, *Brit. Med. J.*, **1,** 585(1972); through *Int. Pharm. Abstr.*, **9,** 2989(1972).
(216) T. W. Slattery and W. M. Henderson, *Amer. J. Hosp. Pharm.*, **26,** 43(1969).
(217) S. B. Purssey, *Med. J. Aust.*, **57-1,** 989(1970); through *Biol. Abstr.*, **52** (7), 35898(1970).
(218) J. D. Beasley, S. N. Bhaskar, A. Gross, and D. E. Cutright, *Mil. Med.*, **136,** 566(1971); through *Int. Pharm. Abstr.*, **8,** 4022(1971).
(219) G. S. Bernstein, *Contraception,* **3,** 37(1970); through *Biol.*

Abstr., **52** (14), 80172(1970).
(220) T. H. Johnsen, Jr., *Arch. Otolaryngol.*, **92**, 511(1969); through *Biol. Abstr.*, **52** (10), 56762(1970).
(221) D. A. Pelton, M. Daly, P. D. Cooper, and A. W. Conn, *Can. Anaesthesiol. Soc. J.*, **17**, 250(1970); through *Biol. Abstr.*, **52** (7), 39247(1970).
(222) W. Rupollo, M. P. Fillio, O. A. Da Silverra, L. C. Pereira, and A. Elias, *Hospital*, **77**, 346(1970); through *Biol. Abstr.*, **52** (9), 106264(1970).
(223) A. A. Cunha and A. Colin, *ibid.*, **77**, 209(1970); through *Biol. Abstr.*, **52** (24), 135257(1970).
(224) R. Charle, G. Kaloplassis, and C. Zviak, U.S. pat. 3,679,109 (1972).
(225) W. Feinstein, dissertation, St. John's University, Jamaica, N.Y., 1973.

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RESEARCH ARTICLES

Spectrofluorodensitometric Determination of Flurazepam and Its Major Metabolites in Blood

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Abstract □ The spectrofluorodensitometric assay for the determination of flurazepam and its major metabolites in blood involves selective extraction of flurazepam and its major metabolites into ether and hydrolysis in acid to their respective benzophenones, which are cyclized in dimethylformamide–potassium carbonate to their respective 9-acridanone derivatives and separated by TLC. The fluorescence of the 9-acridanones is measured directly on the chromatoplate, using a scanning TLC analyzer in the reflectance mode. The limits of detection of the assay are 0.5–1.0 ng of each compound/ml of blood using a 4-ml specimen/analysis.

Keyphrases □ Flurazepam and major metabolites—fluorometric TLC analysis in blood □ TLC, spectrofluorodensitometry—analysis, flurazepam and metabolites in blood □ Spectrofluorodensitometry—analysis, flurazepam and metabolites

The quantitation of organic compounds separated by TLC has usually been done after elution of the component into a suitable solvent, followed by the use of an appropriate physicochemical assay procedure (1). These methods impart a high degree of flexibility and specificity for quantitation. However, the precision of the assay requires minimal physical loss of the silica gel during its transfer from the chromatoplate and maximal elution recovery of the compound.

Direct quantitation of compounds on a chromatoplate using scanning chromatogram analyzers has the distinct advantages of greater precision, sensitivity, and time saving (2–5). The advantages and disadvantages of quantitative measurements made in the transmission *versus* the reflectance modes of operation for spectrophotodensitometry and spectrofluorodensitometry have been extensively discussed (6–13). The use of these direct scanning techniques for the quantitation of drugs has also been well documented (11–16).

A spectrofluorometric assay for the determination of flurazepam[1] (I) and its major metabolites in blood and urine, the hydroxyethyl (II) and *N*-desalkyl (III) analogs, was reported (17), which uses the fluorescence of their respective 9-acridanone derivatives (18, 19) for quantitation after TLC separation. The chemical structures and reactions of flurazepam (I) and its major metabolites are shown in Scheme I.

The use of a direct scanning chromatogram analyzer enabled the simultaneous quantitation of the 9-acridanones with greater precision and sensitivity because the component to be quantitated is concentrated over a small surface area. The three compounds are completely resolved from each other and from interfering biological contaminants and migrate as distinct fluorescent spots (Fig. 1). They are quantitated by scanning the chromatoplate at a fixed excitation wavelength (383 nm) and measuring the fluorescence emitted (at 457 nm) at a 45° angle of reflectance (20).

[1] Flurazepam, 7-chloro-1-[2-(diethylamino)ethyl]-5-(*o*-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one dihydrochloride, is the active drug in the pharmaceutical formulation Dalmane, Hoffmann-La Roche Inc., Nutley, N.J.