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Pharmaceutical Aerosols

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IN MAY OF 1960 a ten-page survey questionnaire was mailed to approximately one-hundred pharmaceutical companies. The purpose of this survey, instituted by a manufacturer of aerosol containers, was to elicit information regarding the needs of the pharmaceutical industry in its projected thinking on the potential of the pharmaceutical aerosol. The results of this survey (227) indicated a greater need for dissemination of more information on the pressure package throughout the pharmaceutical industry than had been realized. This was apparent from the widely divergent views on aerosol components and disagreement on potential aerosol applications. The survey also concluded that only a small number of companies possessed sufficient experience to make considered statements.

The unreliability of questionnaire surveys is well known. Nevertheless, this survey revealed a large void in the scientific and technical knowledge of the principles of aerosols as they pertain to pharmaceuticals. Considering the extent and volume of prognostication in this area (9, 10, 29, 96, 101, 124, 155-157, 159, 163, 171, 173, 185-191, 196, 241), one may speculate as to the reasons why this void has not yet been filled. They may range from traditional conservatism among members of the pharmaceutical industry to the lack of specially trained and experienced research person-

nel to conduct the required experimental studies. In all likelihood, one of the major reasons has been the time required for product development and research personnel to assimilate the new concepts and technologies involved in pressure packaging, and to bring these into play in the design of pressurized dosage forms. Important innovations in medical therapy and dosage forms do not generally spring full grown from idea to practice in short periods of time.

The advantages which are claimed for pharmaceutical aerosols are, for the most part, valid enough to command consideration. Evidence of the unique properties of some of these ideas has already been manifested by several of the products in current use (64, 69, 70, 80, 90).

Lists of pharmaceutical aerosols available in the United States (10, 189) and abroad (4) are beginning to indicate a trend away from products offering only push-button convenience toward those which are truly unique and presumably more effective therapeutically. Advantages of aerosol therapy are being brought to the attention of medical practitioners (136) and this increased familiarity with the properties of aerosol pharmaceuticals is contributing to the upsurge of interest.

Another barometer of the increase in aerosol development is the number of patents issued in this area. Most of these are concerned with valves, containers, and special adapters for use

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with pharmaceuticals. Methods of applying aerosols to the eye (234), for administering medication orally into the lungs (21, 22, 71, 158), pressurized douches (27), and special aerosol formulations for use in veterinary medicine (30, 60, 228) are a few of the many patents which have been issued in recent years.

Most of the advances which have been made in aerosol technologies have been concerned with the development of valves, containers, and propellants. These are the essential components of the pressure system and it is therefore understandable that emphasis should have been placed on their development. It is not the intent of this review to delve into the specifics of these components other than to indicate their role in the problems associated with the development of aerosol pharmaceuticals. The reader is directed to two books (96, 196) which adequately present the basic principles of aerosol technology together with discussions of the factors in formulating and filling aerosols.

PROPELLANTS

One of the most intriguing aspects of aerosol formulation is the dual role played by most of the currently available propellants. These supply the necessary energy required by the self-propelling features of the aerosol, and, in addition, become an integral component of the contents. In many instances the propellant used may be quite satisfactory in supplying pressure, but at the same time introduces serious problems which affect therapeutic efficiency and product stability. The extent to which these problems can be solved will ultimately dictate the range and type of pharmaceutical applications of aerosol systems.

Propellants in current use may be divided into two major categories: liquefied or compressed. The bulk of the liquefied gas propellants are fluorochloro derivatives of methane and ethane. These halogenated propellants are marketed throughout the world under a variety of names, but most of them are also designated by a numbering system which generically indicates the number and identity of atoms in each compound. The newest member of this family of propellants is octafluorocyclobutane (Propellant C-318). This nonchlorinated cyclic compound is considered the most stable of the halocarbon propellants and has been cleared for use with edible products. Its potential in pharmaceutical applications has not yet been fully explored (88). Reed (166) has secured a patent for a mixture of octafluorocyclobutane (Freon C-318) and isobutane which he claims is suitable for pressurized

aqueous products which have either an acid or alkaline pH and are intended for cosmetic or pharmaceutical application.

Among the liquefied halocarbon propellants, trichloromonofluoromethane (Propellant 11) is somewhat more reactive than the others and undergoes hydrolysis in the presence of water and metal catalysts. Solutions containing alcohol and Propellant 11 also become acidic and develop unpleasant odors (233). It has been demonstrated by Sanders (178) that this reaction is not due to hydrolysis but rather to a free radical reaction between Propellant 11 and ethyl alcohol. Experiments with several types of free radical inhibitors showed that nitromethane, a colorless, odorless, nontoxic liquid, was suitable for stabilizing solutions against the reaction (26). Propellant 11 stabilized with nitromethane is now commercially available as "Freon 11" S and seems to offer advantages in the formulation of stable alcohol based solutions.

Hydrocarbon propellant gases, such as propane, isobutane, and *n*-butane have enjoyed limited use in nonpharmaceutical aerosols (2, 36). Their chief disadvantage is their flammability when used alone, but it is claimed that this hazard is minimized when these compounds are mixed with the halocarbon propellants. The possibility of leaks of these flammable propellants from stored containers, however, has become a matter of concern to city fire departments (3, 152).

The nonliquefied or compressed gas propellants such as carbon dioxide, nitrous oxide, or nitrogen (93, 104, 131, 164, 226), and chlorinated propellants such as vinyl chloride (193), methylene chloride, or chloroethene have been used in limited capacities (113).

AEROSOL DOSAGE FORMS

The wide range of pressures and properties offered by the available propellant gases together with the variety of valves (both metering and continuous action) and containers make it theoretically possible to design aerosols which possess advantages not normally encountered in conventional dosage forms. For example, anhydrous suspensions of mucolytic enzymes were developed in this laboratory and were found to retain their enzymatic activity when stored under ambient conditions for extended periods of time. This is not easily possible in any other ready-for-use form. The growth of the aerosol as a dosage form depends, to a large degree, on the ability of the pressurized units to offer similar advantages. Since the attainment of unique features is almost always attended with the necessity of solving

unique problems, a review of the basic types of aerosol dosage forms is in order before considering specific applications.

Solutions

Most of the liquefied propellants used in aerosol formulations exhibit solvent characteristics similar to the nonpolar organic solvents. They are very poor solvents for polar compounds and are immiscible with polar liquids. This rather severe limitation inherent in the properties of the propellants has prevented their use alone in those instances where solutions are desirable or required.

The solvent power of the various propellants for different materials has been investigated only to a limited extent (11, 18, 209). Several methods for describing or evaluating the solvent power of the propellants have been developed (100, 149, 151) and used in solubility studies. A qualitative method of estimating miscibility is the use of kauri-butanol values. These are obtained by titrating 20 Gm. of a standardized solution of kauri gum in butyl alcohol at 77° F. with the liquid under consideration. The end point is reached when turbidity produced due to precipitation of the gum prevents reading 10 point type through the solution in a 250-ml. Erlenmeyer flask. This method is used in the solvent and paint industries and seems to agree with results obtained in solubility studies (126). The kauri-butanol values for halocarbon propellants have been reported (210).

Considering the advantages to be gained, it is surprising to find that very little has been done to circumvent the problems imposed by the poor solvent properties of the propellants for polar compounds. The results of work done in this area may be divided into two types of aerosol systems.

Three-phase Systems.—One method (57) of obtaining sprays containing water-soluble compounds is the use of the three-phase system. This aerosol contains water or an aqueous solution plus the liquefied propellant which forms a separate layer, either below or above the aqueous layer, depending on relative liquid densities. The two immiscible liquid layers and the vapor in the headspace of the sealed container constitute the "three phases" of such systems. When the propellant layer is on the bottom of the container, a dip tube, or standpipe, must be attached to the valve and its length adjusted so that it does not extend into the liquid propellant phase (Fig. 1). In such systems, components which are soluble in, or miscible with, the aqueous layer are maintained as a solution until sprayed.

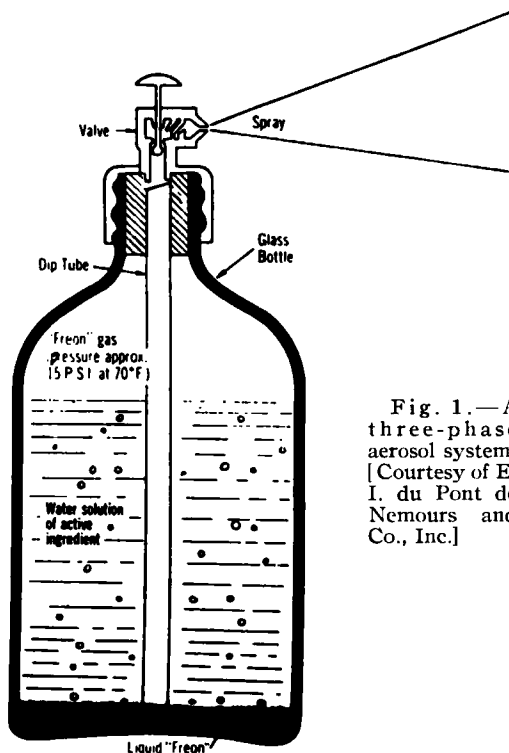


Fig. 1.—A three-phase aerosol system. [Courtesy of E. I. du Pont de Nemours and Co., Inc.]

Actually the propellant phase serves to supply the pressure required to force the aqueous solution up the dip tube and out of the container. It does not materially affect the character of the spray; this becomes the function of the valve components. None of the liquefied propellant is introduced into the aqueous solution while it is being ejected and the atomized spray which results is therefore similar to an aqueous spray produced by conventional squeeze-type atomizers.

Variations of the three-phase type consist of water-based products dispensed by means of the vapor pressure produced by floating small quantities of flammable hydrocarbon gases on top of the aqueous layer. These sprays offer no advantages over those which employ denser halocarbon propellants since the spray characteristics are still limited and pose the additional problem of the possibility of highly flammable liquids being dispensed when the container is nearly empty.

The three-phase system is very similar in operation to the use of compressed gas as the propellant force. A compressed gas (such as nitrogen) occupies the headspace above the liquid solution and simply exerts sufficient pressure on the liquid to force it up the dip tube when the valve is actuated. Here, too, the spray characteristics are limited to the mechanical break-up action of the valve components, and the entire system is sub-

ject to the disadvantages imposed by the use of compressed rather than liquefied gases. Notable among these disadvantages are: (a) a large gas space is required in the container to maintain sufficient pressure to empty the contents, (b) pressure decreases as the contents are discharged giving rise to changes in the nature of the spray, and (c) the possibility of misuse causing an accidental discharge of gas content which produces an inoperable product.

A patented multi-component three-phase system (36) claims to overcome the cited objections and limitations by employing a mixture of propellants, a hydro-alcoholic phase, and a specially designed valving device. The propellant phase is composed of a mixture of halocarbon and hydrocarbon propellants. Hydrocarbon propellants suggested include propane, isobutane, isopentane, or 2,2-dimethyl propane. The mixture of propellants is adjusted so as to possess a liquid density almost equal to but not exceeding the density of the hydro-alcoholic phase. In this manner the propellant phase floats on top of the other, in the static state, but the two are easily mixed by moderate agitation of the container prior to use. The alcohol (ethyl or isopropyl) content helps in dispersing the propellant liquid throughout the aqueous phase. The water content is said to inhibit flammability, reduce cost, and as a component of the hydro-alcoholic phase, makes possible the use of solutes which are soluble in water and alcohol mixtures.

The admixture of the propellants and hydro-alcoholic solution makes it possible to produce sprays with a variety of desirable characteristics as the dispersed propellants rapidly boil away from the spray. This feature is supposedly assisted by the valving arrangement which is comprised of a mixing chamber to premix the liquid and vapor phases before emission from the valve.

Two-phase Systems.—Aerosol terminology defines the two-phase system as having one vapor and one liquid phase. Any nonvolatile material dissolved in the liquid phase is left suspended in air as a fine dispersion immediately after spraying as the liquefied propellants boil rapidly away. Because of the poor solvent power of the halocarbon propellants for polar compounds, only nonpolar materials are directly dissolved by them. Efforts to increase the solvent power of the liquefied halocarbon propellants have centered mainly on the use of co-solvents. Primary objectives of such studies are the development of water-based aerosol formulations which would

permit the incorporation of ingredients soluble in water, reduce the flammability hazard, and decrease formulation costs. A successfully formulated two-phase aerosol is also the simplest to manufacture. The added solvent becomes an important factor in such systems. It not only diversifies and enhances the solvent action of the propellant, but also exercises a considerable role in determining the characteristics of the spray produced and the applicability of the solution.

Early formulations which appeared employed alcohol as the co-solvent. A patent issued in 1959 (158) describes the use of ethyl alcohol in providing medicaments in aerosol form suitable for inhalation therapy of water-soluble drugs such as isoproterenol hydrochloride, epinephrine hydrochloride, and phenylephrine hydrochloride, or alcohol-soluble materials such as atropine, octyl nitrite, and ephedrine. The liquid phase of the aerosol, according to this patent, consists of the medicament dissolved in ethanol (20–40%) and water (1.5–2.0%), with the remainder of the composition consisting of liquefied halocarbon propellants designed to produce a total vapor pressure of between 20 and 40 pounds per square inch gauge (psig) at 70° F. Antioxidants such as sodium ascorbate, ascorbic acid, or sodium bisulfite are added as stabilizers where required.

A more recent patent (205) utilizes essentially the same procedure for producing aerosol compositions containing isoproterenol hydrochloride for oral inhalation. This patent, however, claims that the use of ascorbyl palmitate as an antioxidant for such solutions is superior to ascorbic acid since the latter agent comes out of alcohol solution in the presence of halocarbon propellants. Isoproterenol hydrochloride is stated to be more suitable than isoproterenol sulfate for the same reason. Apparently, the physical-chemical laws which govern stability of nonpressurized solutions must not be overlooked in formulating pressurized medicaments.

Additional attempts to produce aqueous two-phase systems successfully have utilized a variety of co-solvents. A rather extensive study of co-solvents has been conducted by Geary (72), who first determined the miscibility of the solvents with propellants and then conducted solubility studies of the ternary systems of water, halocarbon propellants, and co-solvents. The ternary plots of these systems are excellent guides in formulating water-based aerosol products with ketones, alcohols, glycols, and other solvents. A similar study (215) has been conducted with glycols, glycol ethers, and polyglycols as the co-solvents.

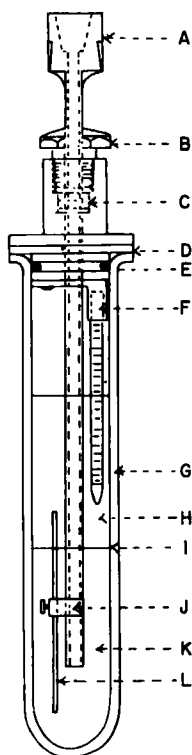


Fig. 2.—A pressure tensiometer for the measurement of surface and interfacial tensions in pressure systems. [From Reference 108 (patent pending).]

On the basis of published data, many of these systems appear to offer improved solvent power for two-phase aerosol formulations together with a wide range of spray characteristics. The major problem associated with their use, however, is the toxicity of many of the solvent materials. Solvents such as acetone, methanol, the "carbitols," and "cellosolves" are almost automatically excluded from pharmaceutical applications in the quantities required. Others, such as 1,3 butylene glycol, dipropylene glycol, and triethylene glycol would require additional toxicity and irritation data before they could be considered for even topical application.

Modification of Interfacial Barrier.—The use of surface-active agents in preparing two-phase aerosol solutions has only recently been considered (106, 108, 110). Surfactants had previously been suggested as a means of forming dispersions with propellants and water. These dispersions were described (32) as being "neither true solutions, nor emulsions, but . . . somewhere in between." These authors proposed the use of nonionic surfactants such as Tweens and Spans, but it was not made clear as to whether water was dispersed in propellants or *vice versa*.

Current concepts and knowledge of the functions of surfactants in solubilizing materials make it obvious that such activity can be successfully

applied to problems in aerosol solutions. The relationships which have been established between the physical-chemical properties of surfactants and their specific activities in nonpressurized systems could conceivably be defined for aerosols as well. A study has been reported which was conducted to initiate the development of procedures to measure the effects of surfactants in aerosols (108). The first requirement in this study was an accurate method of measuring the surface tension of the aerosol propellants and the interfacial tension of the propellants with other immiscible liquids. Of the several methods available for the measurement of surface and interfacial tensions, only the capillary height method was found to be adaptable for use with pressure systems. The capillary height method is generally considered to be the most accurate of all, partly because the theory has been developed with considerable exactitude and partly because the experimental variables can be closely controlled (89).

Figure 2 illustrates the pressure tensiometer which was designed to embody the basic principles of the capillary height method in an instrument capable of controlling the unique variables encountered in working with liquefied gases. The capillary tube (L) was positioned at the surface or interface of the contents of the glass pressure tube (G) by adjusting the height of capillary tube mounting (J) or raising or lowering the inlet tube (A) after loosening the gland nut (B). Escape of pressurized contents was prevented by stainless steel gland washers and a neoprene gland (C) plus "O" ring and washers (E). Liquefied propellants were introduced into the pressure chamber by means of a needle valve inserted in the coupling on top of the Monel inlet tube (A). Water or any other fluid was admitted by means of the same tube but under a positive pressure just exceeding the internal pressure created by the particular propellant in the chamber. A calibrated thermometer inserted into a bracket (F) indicated internal temperature.

The capillary height was measured at constant temperature by means of a micrometer slide cathetometer with a 50-mm. range and an accuracy of 0.005 mm. Surface and interfacial tensions were calculated by

$$\gamma = \frac{1}{2} r h g (d - d') \quad (\text{Eq. 1})$$

where r = radius of the capillary tube, h = height of the meniscus, g = acceleration due to gravity, and $(d - d')$ = difference in density between liquid and vapor phases.

The pressure tensiometer was used to measure surface tensions of selected propellants. The

TABLE I.—SURFACE TENSIONS OF LIQUEFIED HALOCARBON PROPELLANTS

| Propellants | —Dynes/cm. @ 25°C.— | |
|--|---|--|
| | Theoretical Value, ^a Parachor Method | Experimental Value, Pressure Tensiometer |
| Propellant 11 C Cl ₃ F | 19 | 18.86 |
| Propellant 113 C Cl ₂ F—C Cl F ₂ | 19 | 18.40 |
| Propellant 114 C Cl F ₂ —C Cl F ₂ | 13 | 11.66 |
| Propellant 12 C Cl ₁ F ₂ | 9 | 8.41 |

^a Technical Bulletin B-2, E. I. du Pont de Nemours and Co.

TABLE II.—INTERFACIAL PROPERTIES OF WATER PROPELLANT SYSTEMS

| Interface | Interfacial Tension, —Dynes/cm. @ 25°C.— | |
|----------------------|---|------------------------------|
| | Without Surfactant | With Surfactant ^a |
| Water/Propellant 11 | 49.73 | 12.26 |
| Water/Propellant 113 | 49.12 | 6.21 |
| Water/Propellant 12 | 56.70 | 3.52 |
| Water/Propellant 114 | 54.60 | 2.25 |

^a Igepal CO-530, 0.1% w/v, dissolved in propellant phase.

resulting values compared favorably with theoretical values (Table I). Interfacial tensions of propellant-water systems with and without surfactants present were also determined. Table II indicates the effect of one surfactant on these interfacial tensions.

Several interesting and potentially useful preliminary observations were made possible by use of the pressure tensiometer. One was the linear relationship (Fig. 3) between the solvent power of four different halocarbon propellants and the interfacial tension against water with 0.1% of a nonionic surfactant dissolved in the propellants. This introduces the possibility of another param-

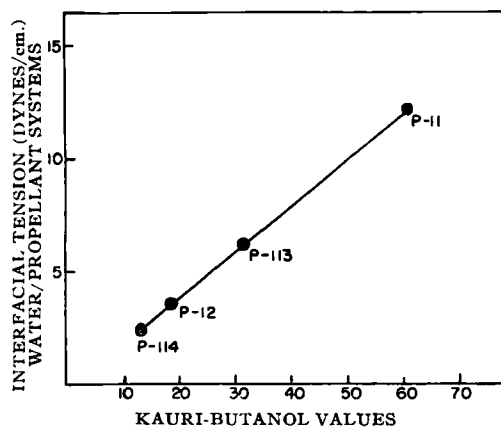


Fig. 3.—Relationship between solvent power of propellants and the interfacial tension against water with 0.1% Igepal CO-530 dissolved in the propellants. [From Reference 108.]

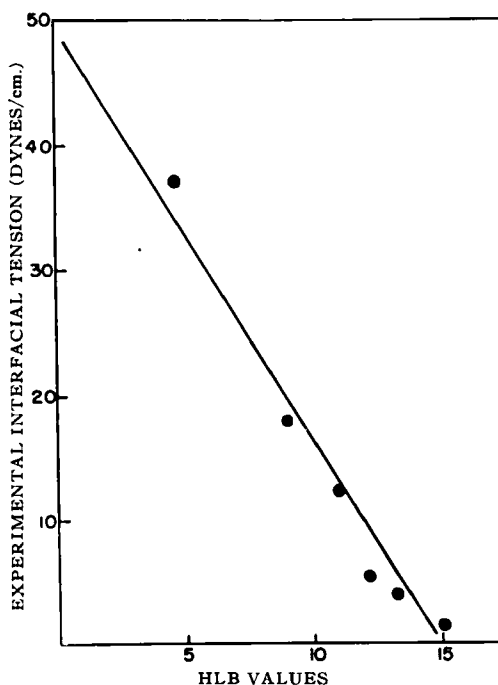


Fig. 4.—Interfacial tension vs. known HLB values. [From Reference 108.]

eter in the ability to predict and control the interfacial barrier. Since the liquefied halocarbon propellants are rarely used alone, but in mixtures, the resulting broad range of solvent power for any given surfactant makes possible a corresponding range of interfacial tensions.

Chun and Martin (35) have demonstrated a linear relationship between interfacial tensions and HLB values of surfactants in toluene-water systems. The pressure tensiometer was employed to establish a similar relationship for surfactants in propellant-water systems. The Igepal CO surfactants were used in Propellant 11-water systems. Interfacial tensions obtained with 0.1% surfactant dissolved in the propellant plotted against HLB values resulted in a linear relationship as shown in Fig. 4. By means of the method of least squares, the equation of this line is given by

$$\gamma = 49.5 - 3.32 (\text{HLB}) \quad (\text{Eq. 2})$$

Utilizing known HLB values for the Igepal CO surfactants, theoretical interfacial tensions in Propellant 11-water systems were calculated by means of Eq. 2. These values and their deviation from experimental values are shown in Table III.* Agreement between calculated and experimental values has encouraged additional studies in this laboratory which currently seek to expand these relationships in the use of surfactants to

* See p. 533 for Table III.

solubilize polar compounds directly in propellant mixtures.

Suspensions

Of all the aerosol dosage forms which have appeared since the time the pressure package became technically feasible, the one offering the greatest challenge in successful formulation is that which consists of a suspension of finely powdered insoluble materials in the liquefied propellants. The ability to dispense a self-propelled dry powder from an hermetically sealed container offers the opportunity for aerosol formulations which are uniquely different from their nonpressurized counterparts.

Attempts to suspend powders in liquefied propellants introduce several problems. Foremost among these is the agglomeration of the suspended particles. This most often occurs immediately after the suspension is prepared, or within a short period thereafter. The rate and extent of agglomeration are apparently modified by the composition of the suspended solids. Agglomeration results in a clogged valve, either initially or after it has been in use for a while. Where uniformity of dosage is imperative, agglomerated particles may cause variation in the amounts of powder delivered even if the valve remains operable. Another problem is the tendency of the suspended powders to become deposited in a cake form on the inner walls of the container, particularly in the area above the liquid level, the headspace. This results in a loss of active ingredients which are not dispensed from the container. Inaccurate dosage also results because the concentration of the ingredients left suspended in the liquid phase progressively decreases.

Early attempts to overcome these problems varied as to method and effectiveness. A patent issued to Beard in 1954 (17) claimed successful formulation of suspensions of powders of terramycin hydrochloride, viral agents used to inoculate chickens against different virus diseases, and sodium bicarbonate. Beard relied on simple suspension of the dry finely powdered materials in various combinations of halocarbon propellants which possessed "a specific gravity such as to inhibit agglomerative sedimentation of the powdered material." No mention was made of optimum particle size or use of additives to stabilize the suspensions.

Several methods have been reported which make use of additives, such as isopropyl myristate (51, 52) or light mineral oil (217), to provide "slippage" between particles, to lubricate the

component parts of the aerosol valve, and to increase adherence of the sprayed particles to skin or other surfaces. Isopropyl myristate was found to be ineffective by Thiel and his co-workers (218) when the suspended powders were dispensed with a metering valve. Bird (23) discovered that he could prepare sprayable antibiotic compositions by converting the crystalline forms of tetracycline hydrochloride and chlor-tetracycline hydrochloride to their amorphous calcium salts. He further specifies that the salt be dry and finely subdivided so that at least 95% of it is less than 15 μ in diameter.

A satisfactory suspension of high solids content without particle agglomeration has been reported by Geary and West (73). This suspension contained bulking agents such as Santocel 54 to fill the void space between suspended particles.

The various factors which are responsible for particulate stability in aerosol suspensions and the relative importance of these factors have been thoroughly elucidated in a patent issued to Thiel, Porush, and Law, assigners to Riker Laboratories, Inc. (219). Their findings have been confirmed by Kanig and Cohn (107) in a parallel study.

Variables Affecting Particulate Stability.—There is general agreement in the literature that the state of subdivision of the solid is critical not only for proper utilization of the aerosol but also as a factor in the stability of the suspension. It is obvious that the particle size of the suspensoids must be at least smaller than the smallest valve orifice and small enough to fulfill the operational objective of the product. However, the more finely subdivided the powder is made, the more free surface energy is generated. Molecules inside a powder particle are acted upon by balanced forces produced by molecules surrounding them. On the surface of each particle, however, the molecules are acted on by inward forces only, and this produces an imbalance of forces at the surface. Decrease in particle size with the attendant increase in surface area results in a surface energies to mass of particles ratio so great that when particles collide they adhere strongly. This is probably one of the primary causes of agglomerate formation in pharmaceutical aerosol suspensions where 95% of the particles are generally under 10 μ in diameter and none are larger than 50 μ .

Another variable is the moisture content of the system. The degree of sensitivity of different suspended materials has been shown to vary directly with the solubility of the solids in water. Observations made on the rate of agglomeration of different suspended materials indicated that

the more soluble the material is in water, the more rapidly it agglomerates in the presence of moisture (107). Since water is immiscible with the propellants, any moisture in the system would tend to be attracted to the more polar solids, and the more water-soluble compounds would undergo physical changes leading to agglomeration. In the presence of a sufficient amount of water, growth of crystalline materials could take place. Crystal growth in this instance is due primarily to the conversion of a less stable configuration to one which has a lower energy state. This has been demonstrated in nonpressurized liquid suspensions of finely divided crystalline materials (99). No significant differences in rate of agglomeration were observed when water was introduced into the system, either by being added to the dried powders before they were suspended in the propellants or to the completed suspension (107).

Relative polarity between suspensoid and suspending medium has an influence on particulate agglomeration. The greater the difference in polarity between the powder and the liquid, the more difficult it is for the liquid to wet the surface of the solids and the greater the tendency for moisture to cause agglomeration.

An additional variable is the relative density of suspended powders and propellants. Where possible, equalization of the densities of the suspension medium and the particulate solids tends to reduce the rate of settling. However, results obtained with suspensions in which the density ratios had been adjusted to unity were inconclusive as to the role of equalized densities in preventing particulate agglomeration (107).

A beneficial result of the adjustment of densities was observed in a decrease in the amount of caking which occurred on the inner walls of the container. Thiel, *et al.* (219), found that the addition of a sufficient quantity of an auxiliary finely divided solid of density greater than that of the liquid phase will prevent the surface spread of lighter powders, thus avoiding "caking out" and its associated drawbacks. The auxiliary powder may be of any chemical type, provided it is compatible with the other ingredients and insoluble in the propellant. It may also serve as a desiccant for the system as when anhydrous sodium sulfate or calcium chloride is used. A formula for the calculation of optimum concentration of the auxiliary powder is provided by these authors.

Control of the Variables.—The use of surface-active agents in overcoming the problems of suspension stability has been recognized in several fields. There is ample evidence in the literature to indicate that surfactants can be

utilized as protectives and stabilizers in the preparation of suspensions (12, 13, 40, 99, 182, 201).

It was found that surface-active agents could be used as dispersing agents in aerosol systems and serve several purposes. By becoming oriented at the solid-liquid interface, a surfactant provides a physical barrier to agglomeration caused by free surface energy, differences in polarity, and the presence of moisture. The ultimate and desired effect is therefore the maintenance, in the suspension, of particles at approximately the original size. Liquid, nonionic, lipophilic surfactants which are readily soluble in the propellants were observed to be the most effective in a range of from 0.25 to 5% by weight of the total composition. Surfactants such as sorbitan trioleate, sorbitan sesquioleate, polyoxyethylene sorbitol tetraoleate, and polyoxyethylene sorbitol pentaoleate have been found satisfactory in providing stable suspensions, provided that no more than 300 p.p.m. of water are present in the total aerosol system. Maximum water content tolerated without particle agglomeration will vary with the solubility of the suspensoid in water, the surfactant employed, and its concentration in the solution.

Additional work is still required in this area since there are some factors inherent in the use of surface-active agents which offer disadvantages. It is conceivable that some surfactants may partially solubilize a suspensoid in the halocarbon propellants. This might lead to changes in crystal configuration and result in growth or agglomeration. Partial solubility and recrystallization may lead to a gradual deposition in the orifices and expansion chambers of the valve and cause a leaking or clogged valve (16). Maximum solids capacities of such systems are somewhat limited. An increase in total solids content requires correspondingly larger quantities of the surfactant. In suspensions containing 25% solids or higher, the films of sprayed powder are oily or greasy in nature. Depending on the intended use of the suspension, this effect may be a nuisance or an advantage.

Emulsions

More fundamental work has been done in the area of emulsions than in any other aerosol form because emulsions have offered the greatest opportunity for new and useful applications of pressurized systems and because the principles which control conventional emulsions are easily applicable to aerosols. In addition, the pressurized emulsion presents features not usually or easily obtained in ordinary emulsions since there

is greater versatility to be found in characteristics of the emulsion spray.

Emulsions which would otherwise be judged as being poorly formulated are vastly improved by the mechanical shearing action of the valve or the flashing off of dissolved propellants. In fact, the mechanical forces brought into play when an aerosol emulsion is propelled from the container may be considered to be the equivalent of *in situ* homogenization. Moreover, the propellant plays a more vital role in aerosol emulsions than in other aerosol forms. Not only does the propellant supply the energy for the self-propelling features of the aerosol, but it also has a decided effect on the spray character by modifying foam density, foam strength, drying time, and other important features (34, 174, 207, 212). These features have accounted for the phenomenal success of aerosol shaving lather which was invented and developed in 1949. The product as described in the original patent (168) consists of an aqueous soap solution and a liquefied propellant in a container with a valve-controlled opening. The propellant is only slightly soluble in the soap solution but is readily emulsified in it to produce what might ordinarily be evaluated as a poor emulsion. When the emulsion is dispensed, however, it develops a lather possessing desirable characteristics as the propellant rapidly expands and flashes off.

Aerosol emulsions do not produce lathers or foams only. Spray characteristics may be varied from a fine mist spray to a stream or a foam, depending on the type of emulsion formulated, the emulsifying agent, the propellant composition and proportion, the presence and nature of additives, and the type of valve and valve actuator used on the container (91, 174, 207, 224). Aerosol emulsions are classified as oil-in-water or water-in-oil types but take on the extra dimension imposed by the propellant. In *o/w* emulsions, the propellant becomes dispersed as fine droplets in the internal phase and has a great effect on the characteristics of the foam. Stiff, dry, resilient foams are obtained with a high vapor pressure propellant and a high concentration of propellant. Conversely, soft, wet, flat foams are produced with lower vapor pressures or lower concentration of propellant in the internal phase (216). These effects are demonstrated by use of either the liquefied halocarbon propellants or the hydrocarbon propellants such as propane, butane, and isobutane. Water-in-oil emulsions produce unstable wet foams since the propellant is in the outer phase and flashes away without creating the voluminous foam which it does when it is dispersed in the internal phase.

It is only when a compressed gas, such as nitrogen, is used that the emulsion characteristics remain substantially unchanged. Emulsions are merely expelled from the container by the piston-like action of the inert and undissolved gas. This offers no advantages over the conventionally contained emulsion but imposes many shortcomings which are characteristic of the compressed gases.

Nonaqueous emulsions and foams have been developed for use in aerosols. By replacing water with different polyhydric alcohols or with glycol derivatives, Sanders (208) has produced foams which may be varied widely to suit any particular application. Extremely stable foams may be produced because the glycols do not dry rapidly. In some instances, these foams may approach creams in their consistency, or they may be varied to achieve "quick-breaking," unstable foams. The range of foam characteristics together with the nonaqueous feature of these emulsions makes them suitable for pharmaceuticals where water is not desired for reasons of stability, or where it is contraindicated in the condition being treated.

Emulsifying Agents.—The selection of aerosol emulsifying agents is still being made on a rather haphazard and pragmatic basis. Considering the wealth of scientific information available regarding the selection, use, and evaluation of emulsifying agents for nonpressurized systems, it is surprising to observe how little of this has been applied to aerosol emulsions. While it is true that hundreds of surfactants have been evaluated for this purpose, most of the work has been concerned with effects rather than causes. As a result, only generalized rules-of-thumb are available as guides when a new pressurized emulsion is contemplated. Moreover, even these guide lines are inadequate in predicting the behavior of an emulsifying agent in a system other than that in which it was tested (211).

It has been advocated (106) that methods of research and evaluation which have proved reliable for nonpressurized emulsions should be adapted for use in pressurized systems. Proceeding along these lines, effective relationships have been observed between emulsion stability and HLB values of surfactants (Fig. 5) and kauri-butanol values of propellants (Fig. 6). Preliminary evidence exists to indicate that the relative polarity of propellant-surfactant solutions exerts an influence on pressure emulsification (108).

No reports have appeared to indicate that

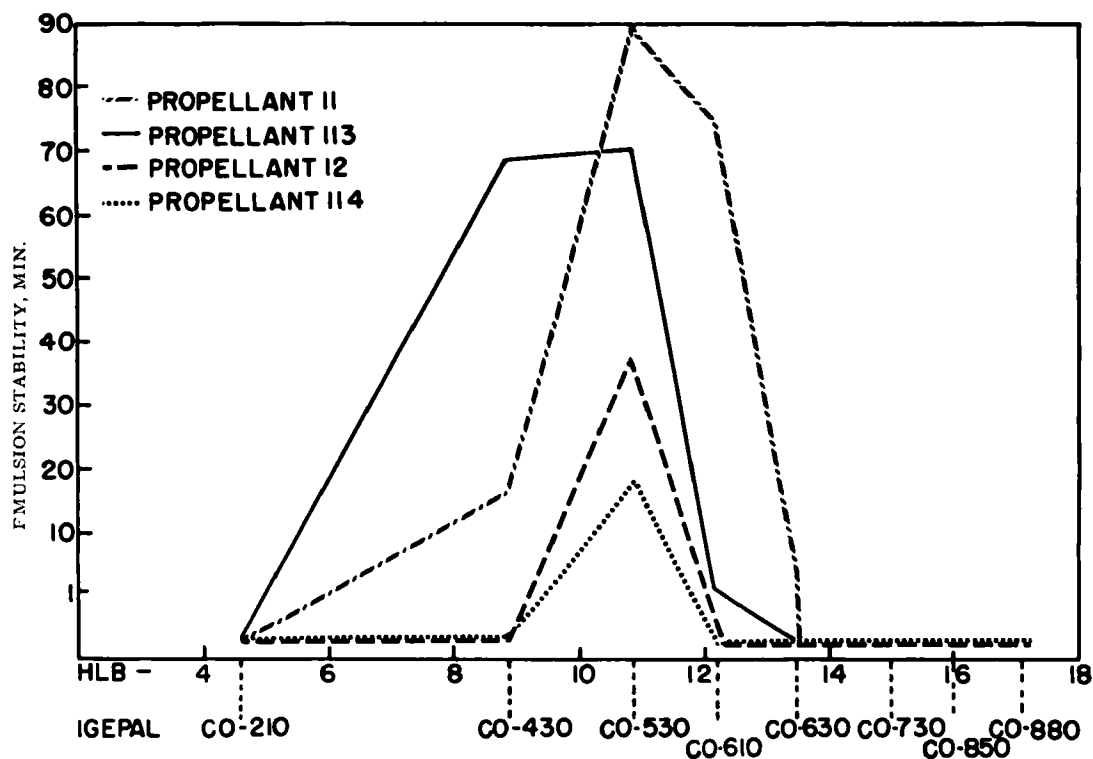


Fig. 5.—Relationship between HLB values of Igepal CO series of surfactants and emulsion stability of propellant-water systems. [From Reference 108.]

studies have been conducted on the use of emulsions in pressure systems as vehicles for insoluble suspended matter. Aerosol emulsion-suspensions offer interesting possibilities for application in topical and related therapeutics.

INHALATION AEROSOLS

Inhalation therapy, it has been said (122, 141, 163, 185), goes back at least as far as written medical history. Fumes of burning herbs or powders, steam inhalations, and nebulized or atomized solutions of a variety of compounds have been in use for the direct therapy of bronchial and pulmonary diseases for many decades (24). Therapeutic aerosols have been produced by various types of equipment (39, 109, 195), and improved devices such as inhalers, atomizers, nebulizers, and insufflators (141) have been a prime factor toward increasing the efficiency and acceptability of inhalation therapy over the years. Long before the introduction of the self-contained pressurized aerosols as pharmaceutical dosage forms, many studies had been conducted on the use of medicaments for local therapy of the respiratory tract or for rapid systemic effects through absorption from the inner surface of the lungs. As newer chemotherapeutic agents of interest in inhalation therapy became available,

they were investigated for a variety of pulmonary conditions (1, 94, 111, 194). These substances include antibiotics (66, 162), antitubercular drugs, sympathomimetic amines (75, 109), anti-spasmodics (160, 161), mucolytics (61, 123, 203, 222, 223), surface-active agents (128–130), certain vitamins (notably Vitamin B₁₂) (137, 138), and corticosteroids (74, 167). This partial accounting of pulmonary therapeutics serves to indicate that the aerosol is not nearly so new an approach as one might assume by reading the recent papers describing the potential of the pressure pack in inhalation therapy. It is only when a comparison is made between the utility, dependability, and reproducibility of the devices employed that the advantages of the new type of unit become apparent.

It has been recognized that the physical state of the particles in therapeutic aerosols exercise a critical effect on the site of deposition and absorption from the respiratory tract (1, 109, 145, 150). Therefore it is claimed that the pressurized aerosol dosage form offers the advantages of accurate delivery of a measured dose of aerosolized drugs, particles of which are within a specified range of effective diameter sizes. Reproducibility of amounts delivered from this dosage form is said to be superior to oral liquid preparations

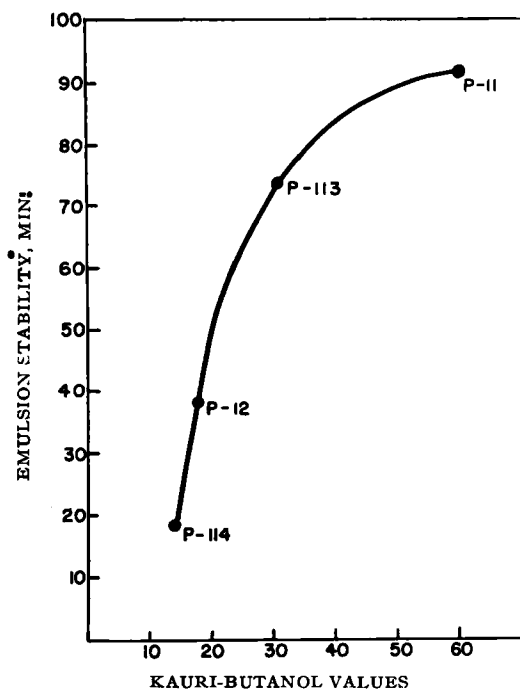


Fig. 6.—Propellant-water emulsion stability related to solvent power of propellants with 0.1% Igepal CO-530. [From Reference 108.]

dispensed by teaspoon or dropper and to compare favorably with weight variations permitted for hard gelatin capsules (159, 241).

Additional unique advantages over other types of vaporizers include: (a) a compact container capable of delivering hundreds of single doses, making it the least clumsy of all devices and perhaps the most economical; (b) application is rapid and convenient and does not require manipulative skill on the part of the patient; and (c) the container is hermetically sealed which makes it tamper-proof and its contents protected against bacterial contamination, moisture, and oxidation or evaporation during periods of disuse. Presumably these factors are sufficient reasons for the reappraisal of the oral inhalation route in therapeutics and for the increased interest in methods for evaluation and control. Enthusiasm for this dosage form has even caused some of its advocates to proclaim that inhaled aerosolized drugs may ultimately replace the parenteral or oral routes of administration in some instances.

This has already been clinically demonstrated in the use of orally inhaled ergotamine tartrate in the treatment of vascular headaches, including migraine and histaminic cephalgia. The efficiency of this route of administration is said to parallel closely that of injection and to be superior in speed and effectiveness to suppositories, sublingual or oral therapy (64, 79, 90, 202).

To appreciate the potential of this route of administration, it is necessary to examine the critical aspects of the physiology of the lungs on the retention and absorption of inhaled particles and to relate these to the ability of the aerosol dosage form to meet these requirements. It is conceivable that some of the negative clinical results obtained by oral inhalation methods were due to poor control over the critical variable of particle sizes.

Deposition in the Lungs.—One square meter of lung surface is required for each kilogram of body weight to sustain the life processes depending on the exchange of oxygen and carbon dioxide. In the normal adult this amounts to the area of a tennis court (37). Such an area is encompassed in the small volume of the thorax by subdivision of the inner lung surface into hundreds of millions of alveoli. Within the walls of the alveoli the blood is spread out in a thin sheet, separated from the air by a membrane about 1μ in thickness. This large area, richly endowed with blood and separated from airborne substances by only a thin membrane, theoretically offers a highly absorptive area for rapid transfer of drugs into the blood stream. Davies has stated "Particles of solid material that deposit on the ciliated lining and the tubes have rapid access to the blood stream. Lung defenses are completely avoided, and immediate toxic action can be exerted, sometimes more effectively than in the case of oral administration. The importance of solubility is demonstrated by the behavior of lead compounds. The dust inhaled by miners of Galena has low solubility and is not dangerous, but the mining and smelting of lead carbonate ore have frequently caused acute lead poisoning by inhalation of the relatively soluble dust" (49).

The chance of an inhaled particle reaching the alveolar regions depends on its size, weight, and shape. The defense of the lungs against retention of any particle is provided by the tortuous nature and decreasing size of the channels through which it must pass, thus making impaction with the walls very probable. After impaction, a particle which is slowly soluble in the mucus on the walls is removed upward by ciliary action. This inertial impaction is an important mechanism in the nasal airways and in the upper lung where the air velocity is fairly high (134). Studies on deposition of particles in curved tubes have indicated that the large particles are likely to be removed from the air stream by this mechanism and that the inertial impaction of the particles is directly proportional to the density and to the square of the particle diameter (116, 125).

Large particles which may survive inertial influence in the upper respiratory tract will settle downward in the lungs and become deposited by sedimentation in the areas where air velocity is reduced. Here, too, the sedimentation rate is proportional to density and to the square of the diameter.

Particles small enough to penetrate into the alveolar spaces where air velocity is very low are made to collide with the walls by Brownian motion which increases in activity as the size becomes smaller.

Particle Size and Retention.—Interest in particle retention in the lungs has been sharpened by studies in chemical warfare, aerosol therapy, and the hazards associated with industrial dusts and radioactive fallout (5, 6). Papers published in this area fail to agree on the relationship between particle size and retention in the lungs. Mathematical models have been proposed for theoretic calculations of the extent of retention of particulate matter of various sizes in the lungs of man (7, 20, 48, 59, 65, 92, 221, 232). The classical theoretic treatment of retention was made by Findeisen (65). He computed the average dimensions of the adult

tracheobronchial tree on a functional concept of structure rather than a strictly anatomic description. His calculations were later modified by Landahl (114), who used slightly different dimensions of the tracheobronchial tree and computed retention values for several different flow rates. The schematic representation of the pulmonary tree used by Landahl is shown in Fig. 7. This indicates that particles larger than $20\ \mu$ should fail to go beyond the terminal bronchioles; those $6\ \mu$ in diameter would be removed before they reach the lower alveolar ducts, and almost all particles $2\ \mu$ or larger are removed in the lower alveolar ducts.

Experimental studies in man with heterogeneous aerosols have been reported (5, 15, 31, 42, 43, 47, 48, 55, 115, 116, 120, 121, 127, 139, 180, 236), while others have designed special techniques for generating monodispersed aerosols in which all the particles are nearly the same size. These were used in respiratory retention experiments (8, 117, 118, 231).

Figure 8 indicates the results obtained by Brown (31), using clay dusts having median diameters from $0.24\ \mu$ to more than $5\ \mu$. Employing nasal inhalation techniques, Brown

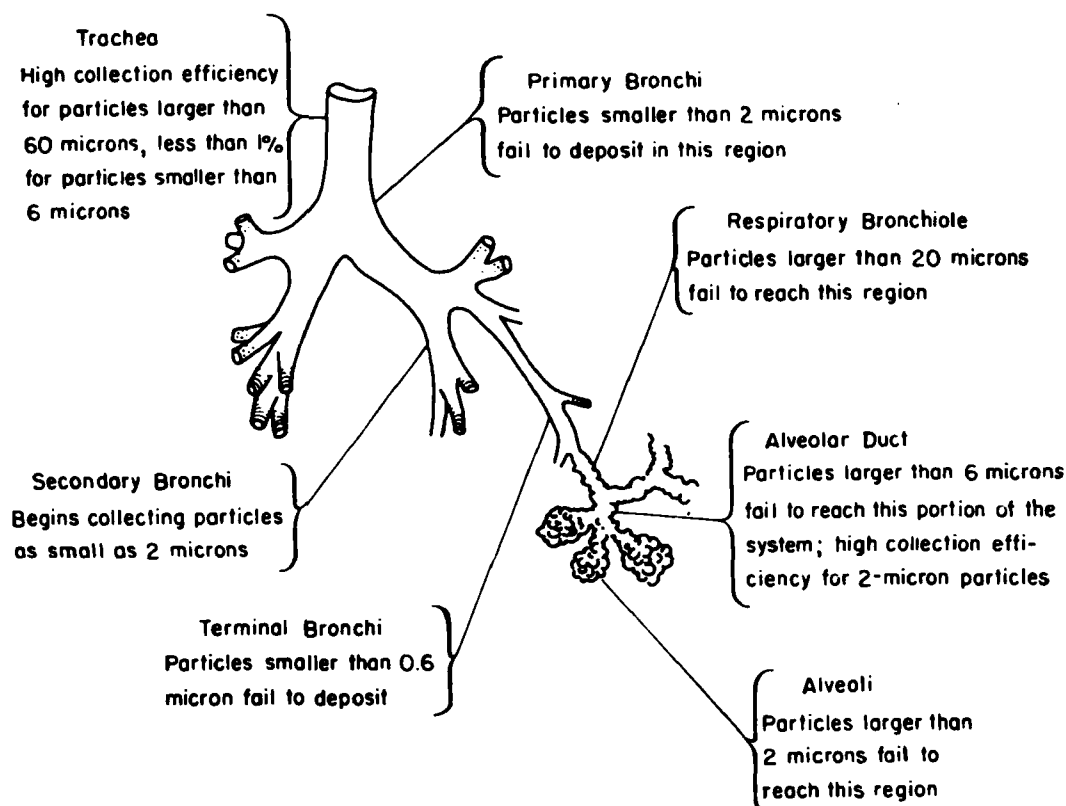


Fig. 7.—Schematic representation of the pulmonary tree showing theoretic retention computed by Landahl. [From Reference 134.]

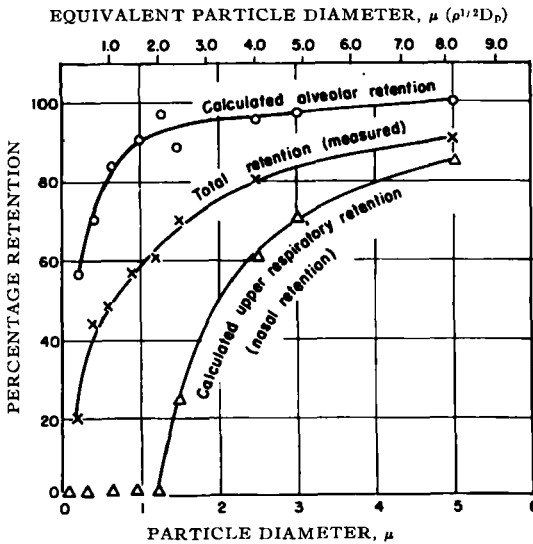


Fig. 8.—Lung retention of clay dusts as a function of particle size. [From Reference 134.]

showed that 85% of the particles of 5 μ in diameter were retained in the upper respiratory tract and that more than 90% of the particles between 1–5 μ in diameter which pass the upper respiratory tract are retained in the alveolar region.

Dautrebande disagrees with such findings and contends "that for ensuring deep penetration into the most efficient part of the lungs of the largest quantity of drugs, the micellar size of the aerosol should be below one micron" (41). He has authored many articles on his studies of methods of generating submicron particles and evaluating their effects and deposition in the lungs (44–46, 50).

The disagreement between these and other workers has not yet been completely resolved. Possible reasons for the conflicting theories and experimental results may be summarized by:

1. Experiments conducted in man or animals may alter normal respiratory mechanics by tracheal catheterization, anesthesia, or use of irritant particles.

2. Differences in the methods of generating aerosolized particles, length of exposure, and methods of detection of expired particles are critical.

3. Either homogeneous or heterogeneous particle size distributions have been used in different studies. Heterogeneous distributions have been criticized because much of the meaning of test results become obscured when an average diameter is used to represent a broad size distribution (134).

4. The possibility exists that materials detected in the lower regions of the pulmonary tree reach

there by the indirect route of systemic absorption and circulation.

5. Depending on the efficiency of the aerosol generating system, agglomeration of the particles may occur after leaving the apparatus. Some particles may also increase in size as they encounter the moist air in the lungs while others generated from aqueous or other volatile solutions may decrease in size. If these dynamic changes are not taken into account, erroneous results may ensue.

6. Some investigators have failed to use uniform breathing rates in experiments with humans. In addition to particle size, the next important variable in the retention of particles is the length of time the particles remain in the lungs. The effect of breathing rate is more pronounced for large particles than for smaller ones (134).

7. Methods of measuring particles vary in accuracy and range. As a result, retention values may vary depending on the validity of the method used in measuring the particles.

The entire picture of inhalation therapy is made more complex by the discovery of the existence of a powerful surface-active agent which coats the alveolar spaces in the lungs (37). The substance is thought to be a phospholipid, particularly dipalmitoyl lecithin. It has been found in the lungs of all mammals tested (mouse, rat, guinea pig, rabbit, cat, dog, cow, and man), but not in amphibians (frog and toad), reptiles (snake and crocodile), or bird (pigeon and chicken). It now appears that the surfactant maintains the elasticity of lung tissue and keeps the lungs from collapsing. The surfactant has the further function of assisting osmotic forces acting across the surface of the lungs, and this keeps the film of moisture present there from drawing fluid into the alveolar spaces.

The presence of this powerful surface-active agent in lung tissue fluids may have a profound effect on particulate retention and absorption. This has not been considered in any of the cited studies.

The fact that a surface-active agent is critical to normal lung function must also be taken into account when oral inhalation dosage forms are designed. Substances which are included in the inhalations as active therapeutic agents or for product stability might have a neutralizing or adverse effect on the physiological surfactant. The ultimate results of continuous or prolonged oral inhalation of a variety of substances are open to investigation.

PARTICLE SIZE MEASUREMENT

Particle technology has become increasingly

important in so many diverse areas (204) that the development of particulate fractionation and measurement techniques have been accelerated by the demands of research into fine particle properties and behavior. Methods have been developed for a variety of industrial, meteorological, and biological purposes. Without such methods the study of the role of particulate matter in production, agriculture, and health and

disease would be seriously hampered. For the most part, however, many of the particle size analysis methods are of limited value in measuring particles which originate from pressurized systems or which fall into the particle size ranges of interest in the therapeutic applications of aerosols.

Particle size measurement is rarely an absolute procedure. Inherent in almost every method are limitations which are imposed by the physical

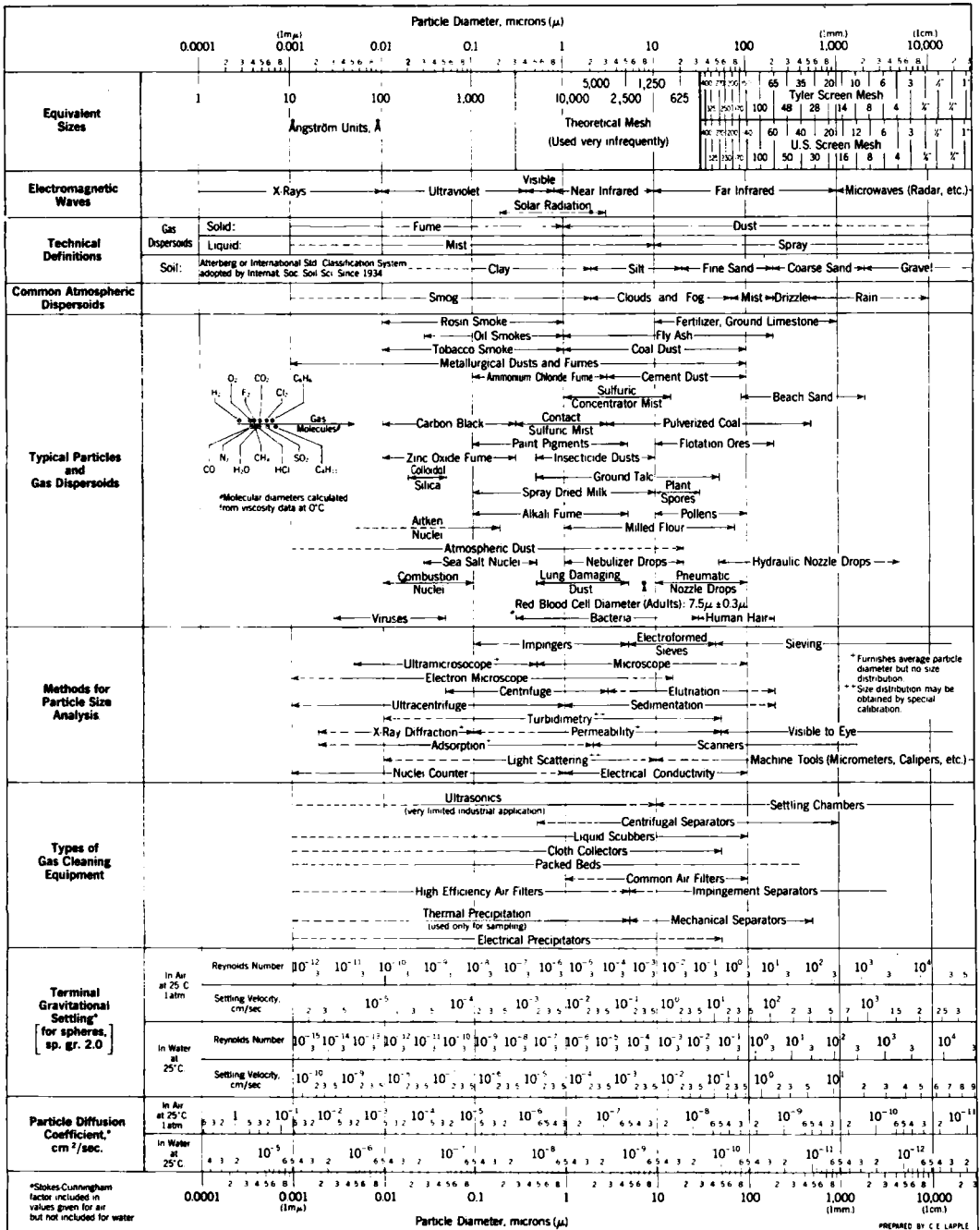


Fig. 9.—Characteristics of particles and particle dispersoids. [From Reference 204.]

principles which are employed. These limitations affect not only the accuracy of the method but also dictate the types of particles which may be measured and their sources. Many of them furnish only average particle diameters but no size distribution, while the size distribution obtained from others may be accomplished only by means of special calibration. The scope of characteristics of particles and an indication of the complexities which exist in the area of particle technology may be ascertained from Fig. 9.

It must also be remembered that almost every technique which has been employed in particle size measurement presupposes an accurate conveyance of a valid and representative sample to the instrument. Particles sampled from a pressurized container must be prevented from agglomerating before they are measured; this aspect of the procedure imposes serious limitations on the types of techniques which may be employed. When little attention is placed on the sampling of particles and the effect it can have on the accuracy of the method, the results obtained are only approximate answers (81).

As a consequence of these limitations, relatively few methods may be considered as being capable of accurately measuring the size range of particles within the framework of aerosol dosage forms and under the restrictions of the unique variables imposed by the generating mechanisms.

The nature of the particle delimits the size analysis method as well. Suspensions of particulate solids in aerosol propellants produce particles essentially unchanged if agglomeration can be avoided as the propellants boil away. Solution-type aerosols offer additional complications in that the droplets are constantly changing size after being sprayed. A reduction in size with time results when the propellants or co-solvents evaporate within seconds and precipitate or crystallize the dissolved solids. Particle size growth may occur when the particles suspended in air are hygroscopic and begin to absorb moisture (77), or when they are liquids under ambient conditions and coalesce upon impact.

Any measurement of aerosol particles must therefore take into account the changes which occur in these dynamic systems after spraying and the possible effects these may have on the accuracy of sampling and size analysis.

Methods of Particle Size Measurement

Microscopic Measurement.—Microscopic techniques have been classified as being among the most accurate of the *direct* methods (*i.e.*, methods in which the actual dimensions of par-

ticles are directly measured as contrasted with *indirect* methods which are based on measuring some other property of the particles which is related to their size) (67, 98).

The unique feature of microscopic measurement is that particles are sized directly and individually rather than being grouped statistically by some process of classification. Disadvantages to the method lie in the tediousness associated with the necessity of measuring a sufficiently large number of particles to provide adequate representation.

Limitations in the use of the optical microscope are due to the fundamental laws fixing maximum resolution which set the lower limits of particle size measurement using visible light. This limit of resolution has been reduced by use of ultraviolet light or monochromatic sodium light. Electron microscopy has further reduced the lower limit of resolution to 0.001μ . However, the upper limit of size is not greater than 10μ and problems associated with sample preparation reduce the utility of the electron microscope. Ultra-microscopy has been employed to count and measure particles suspended in a gaseous medium but has been supplanted, for the most part, by light-scattering techniques.

Sedimentation Techniques.—Speed of fall under controlled or predictable conditions has become one of the more widely used techniques among the indirect methods of measurement. Application of Stoke's law to free falling particles in liquid or air media is the basis for several instrumental methods of measuring. The physical methods involved in the actual determination of particle size generally conform to the same fundamental principle. If the particles are initially distributed uniformly in a column of fluid at rest, there will be, after a lapse of time, a density gradient in concentration of particles along the height of the column. Determination of this density gradient enables the proportion by weight of the various sizes of particles to be calculated. Any property of the suspension which is a function of the density or particle concentration may thus be used to determine the size distribution. A discussion of the methods of determining variation in particle concentration has been published by Work and his associates (184, 235). Additional theoretical concepts advanced by Heywood (97) and Egolf and McCabe (58) are useful in this area.

A sedimentation balance, described by Oden (142), provides a method of directly weighing particles at selected time intervals as they fall in a liquid system. For continuous observations, an automatic recording-type balance is available.

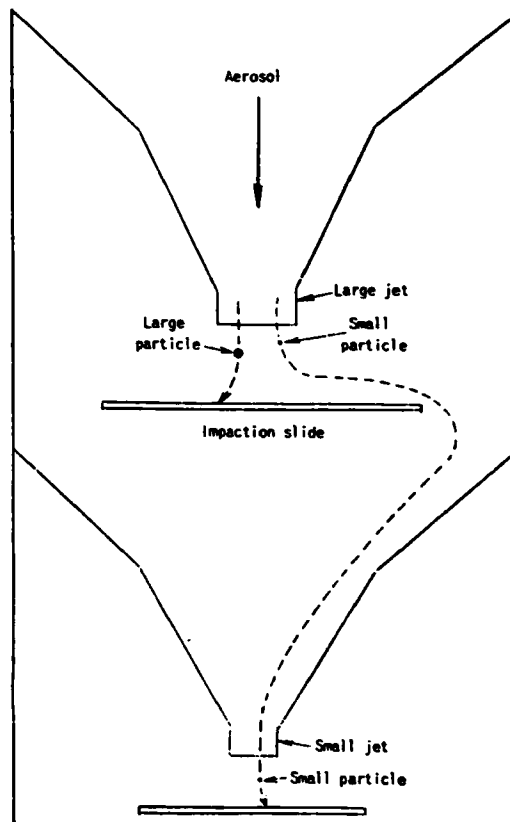


Fig. 10.—Schematic diagram showing principle of the cascade impactor. [From Reference 154.]

Additional refinements of the sedimentation method have been reported. The pipet method, advocated by Schweyer (183), involves the withdrawal of samples of the dispersion at predetermined depths. Evaporation of the solvent then yields concentration data from which particle size may be derived.

A hydrometer bulb method, advanced by Bauer (14), measures changes in density induced by variations in concentration. This is an advantage over the pipet method in that it does not permanently withdraw a portion of the suspension under study. A disadvantage of this method is that the introduction of the hydrometer bulb tends to disturb the settling particles. The Diver method (102) overcomes this disadvantage by utilizing small vessels of varying known density which assume equilibrium positions in the suspension system according to the density gradient that forms as the particles settle.

An innovation in the area of gravitational sedimentation is the Carey and Stairmand photo-sedimentometer (33) which photographs the tracks of particles as they fall in a dispersion system. The size determination is derived from the length of the photographic track, which is an

indication of the distance traveled by the particles, and the time of exposure of the photograph.

The lower limit of size to which gravitational sedimentation methods can be applied is controlled by temperature variations causing circulatory currents in the suspension, by flocculation of particles during the progress of sedimentation, and by diffusion or Brownian movement of the very small particles. All these factors, plus the extreme length of time required by these methods, make it advisable to shorten the sedimentation process as much as possible. This may be accomplished by substituting centrifugal force for gravitational acceleration. The principles of sedimentation are unaffected, except that the factor g in Stoke's equation becomes a variable according to the speed and radius of rotation of the particle within the centrifuge. For example, using gravitational sedimentation, it would require 1057 minutes for a $1\text{-}\mu$ diam. particle to fall 5 cm. but would only require 3.3 minutes to traverse the same distance when using a centrifugal speed of 2000 r.p.m. Instruments embodying the centrifugal principle have been described by Schachman (181) and Kamack (105).

Another process which considers the velocity of motion relative to a fluid for the determination of particle size is that of elutriation. Elutriation differs from sedimentation techniques in that the particles are held stationary in space through the attainment of balance between the gravitational

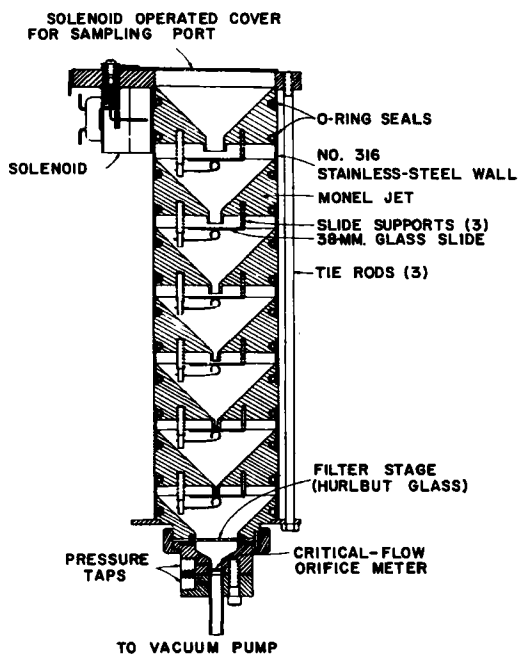


Fig. 11.—Multi-stage cascade impactor. [From Reference 154.]

forces acting on the particles and the viscous forces between the particles and an upward moving column of fluid or gas (78, 170).

Impaction and Inertial Techniques.—Methods in this category for the sampling and estimation of particles in the sub-sieve range are based on laws governing the trajectories of particles in fluid streams. These inertial principles, which are a function of size, have permitted the development of a wide variety of instruments. Included are techniques embodying cyclone deposition, impactor sampling, inertia separation, and electrostatic and thermal precipitation. In a number of these methods it is possible only to effect a separation of a sample into a series of size fractions. The exact particle size of each fraction must subsequently be determined by additional means. In other instances, a size analysis can be obtained directly by theoretical treatment or prior calibration of the instrument.

Impaction devices utilize the deposition characteristics of fine particles in a moving air stream when directed past obstacles of defined geometric form, or in being forced from a jet device onto a plane surface. The cascade impactor has received considerable attention for use with aerosol particles. This device, described by Pilcher and his co-workers (154), forces particle-laden air at very high speed and fixed rate through a series of jets (each smaller than the preceding one) onto glass slides; impaction takes place in a series of stages. The velocity of the air stream and particles suspended in it are increased as they advance through the impactor. As a result, the particles are classified by impaction on the different slides, with the larger particles on the top slides and the smaller particles on the downstream slides. Figure 10 illustrates the basic principles in operation. Modifications in the cascade impactor method have been made to increase the sharpness of classification and to extend the range of particle sizes (135) (Fig. 11). Additional impaction devices employing similar principles have been described by Owens (148), Gurney (84), and Sawyer and Walton (179). Extensive theoretical treatment has been reported by Ranz and Wong (165), Gillespie and Johnstone (76, 103), and Wilcox (229, 230). A small light compact portable cascade impactor for industrial use has been designed and studied by Brink (28). An instrument which operates on similar inertial principles to those of the cascade impactor has been described by Tillotson (220). This variation may be adapted for automatic readout of size distribution by means of light scattering techniques and

electronic counters. The method is claimed to be able to produce a complete particle size distribution in a few minutes.

The most serious deficiency of the cascade impactor is the relatively large sample required for analysis. Porush, *et al.* (159), have indicated that this makes determinations of particles emanating from single doses of most aerosols impossible by ordinary analytical methods.

Thermal Precipitation.—The movement of fine particles in a thermal gradient has been described by Watson (225). The underlying principle depends on the introduction of the particles into a region between two bodies of differing temperatures. The particles will move toward the colder body and be deposited on it since the particles are affected by a force directly proportional to the temperature gradient and inversely proportional to the absolute temperature (197). Watson's instrument (225) was capable of measuring particles of 5μ or smaller, but size distribution was possible only by resorting to microscopic methods of measurement.

Electrostatic Precipitation.—Determination of particle size by the estimation of the magnitude of charges on individual particles has been studied. The charges are either naturally present or are induced on the particles. The magnitude of the charge is directly related to the size of the particle (56, 112, 119). This method has been criticized by Orr and Dalla Valle (147) as being capable of producing erroneous size distribution due to the chance of precipitating more than one size particle at a given point. Instruments which have been developed in attempts to overcome this shortcoming are described by Yoshikawa (240) and Guyton (85). A more advanced and accurate method described by Berg (19) suspends the particles in a conductive liquid which flows through an aperture with a simultaneous flow of electrical pulses (each pulse being proportional in size to the volume of the particle originating it). The pulses are amplified, scaled, and counted to provide data for plotting cumulative particle frequency against particle size. The size range claimed for the instrument is 0.5 to 200 μ diameter at a counting rate of 6000 particles per second.

An excellent review of the theoretical consideration involved in the determination of aerosol particle size distribution by precipitation of charged particles is offered by Drozin and La Mer (56). These authors also describe a method utilizing this principle which takes about 20 minutes, including the necessary calculations, and is carried out with relatively inexpensive equip-

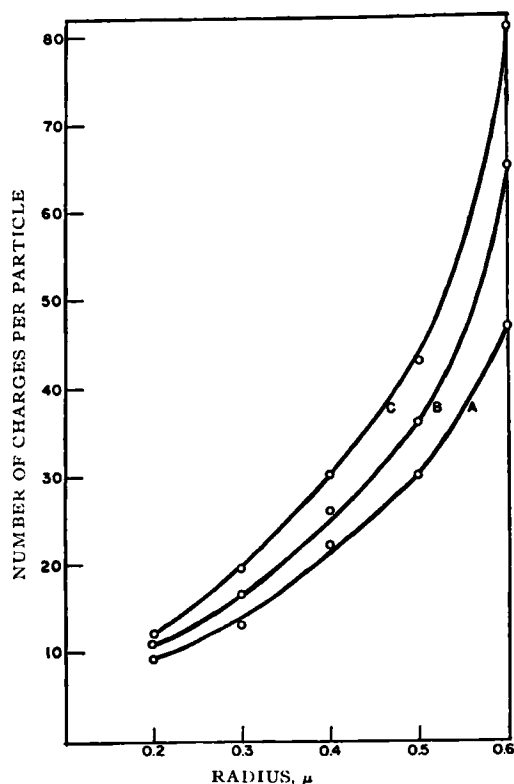


Fig. 12.—Number of charges per particle vs. particle radius. Stearic acid aerosol particles charged with current of 40 μ a. (A); 80 μ a. (B); and 120 μ a. (C). [From Reference 56.]

ment on particles in the submicron range above 0.2- μ radius. Figure 12 illustrates some of the results of their study.

Optical Methods.—The characteristic optical behavior of small suspended particles forms the basis of several indirect methods for assessing particle size. Observations of suspended particles transversed by a beam of light disclose the ability of the particles to scatter, absorb, or reflect the incident radiation to a specific degree. These phenomena have been investigated, and it has been found that the degree is dependent upon the size of the particles, among other variables.

Theoretical treatment of these properties has led to the formulation of equations based upon light scattering and light transmission which permit the evaluation of particle size and cloud concentration (146, 198).

Light transmission or extinction methods are based on the Beer-Lambert law (25) and an instrument utilizing this principle is described by Sinclair (198). The instrument measures the extent to which a beam of light of known intensity is diminished as it emerges from a suspension of particles in gaseous media.

The principles of light scattering formulated by Mie and Rayleigh have been used more extensively in fine particle measurement by Sinclair and La Mer (200). Rayleigh's equations state that the intensity of light scattered from a particle varies as the sixth power of the particle radius for particles which are very much smaller than the wavelength of light, approximately 0.5 μ . The upper limit of size applicable to these equations is about 0.03 μ radius, therefore, these equations have a restricted value for the study of general particulate systems. In the case of larger particles equal to or greater than the wavelength of light, the equations of Mie apply. Here the angular distribution of scattering intensity varies as a function of the scattering angle, and the complexity of the mathematical calculation of size increases markedly with increasing particle size. Consequently, since the computations are massive and difficult and the equations for these larger particles are applicable to spherical monodisperse systems only, these theoretical methods do not lend themselves easily to universal application for particle size measurement. The value of light scattering, however, is apparent as a method of detection of changes in cloud concentration. For this application, light scattering techniques are more than sufficiently sensitive and have been found to be of great value (82, 83, 199).

Dimmick, *et al.* (53), have described an instrument employing light scattering techniques for measurement of small particles. The method is rapid, accurate, and reproducible and depends on an analysis of the change in intensity of a light beam projected through an aerosol cloud under turbulent conditions.

The settling rate of a monodisperse aerosol in a closed chamber under turbulent conditions (stirred sedimentation) is an exponential function of concentration defined as

$$\frac{N}{N_0} = e^{-Vt/H} \quad (\text{Eq. 3})$$

where N = concentration at time t in minutes, N_0 = concentration at time zero, V = Stoke's velocity of fall in cm./min. for a given particle and density expressed in Gm./cm.³, and H = the effective height of the chamber.

Being exponential in nature, the log of the concentration plotted against time results in a straight line. The same slope is obtained whether the concentration is expressed in terms of number, geometric area, or volume (related to mass).

The slope is then defined in terms of the half-life ($L_{1/2}$) and the authors provide a nomograph which relates particle size and density to half-life for a chamber height of 100 cm. This instrument was employed in measuring particle size of iso-

proterenol and epinephrine aerosol suspensions and the distribution of particles was reported by giving the mass median diameter (159).

A similar approach has been developed by Mintzer (133) and has been used in a study on stability of aerosol suspensions (107). The instrument consisted of a separate sedimentation chamber in which the aerosol cloud was mechanically stirred. Air-tight connections continuously carried particles from the sedimentation chamber to the cell of an extremely sensitive light-scattering photometer. The cell was modified so that the particles could pass out of the instrument after being measured. Readout of phototube signals was accomplished by means of a wide-strip recorder (Fig. 13).

A portion of the recorder chart for a typical determination (Fig. 14) indicates the response to samples of particles withdrawn from the sedimentation chamber. Figure 15 is a plot of the slopes from which particle diameters were calculated using Dimmick's equations.

O'Konski and Doyle (144) have also measured aerosol particles by using light scattering coupled with an electronic particle counter in a single instrument. Fisher, *et al.* (67, 68), have described an instrument which they call an "aerosoloscope." The procedure involves the massive dilution of the airborne particles so that flow rate is con-

trolled and each particle passes through an illuminated region where it produces a pulse of scattered light. The light scattered by each particle is received on a photomultiplier which gives rise to an electrical pulse, the amplitude of which is related to the size of the particle. The counts are sorted and registered separately on a bank of 12 electromechanical counters. Aerosol particles ranging from 1-64 μ in diameter can be measured at a maximum rate of 2000 per minute.

Patents have been issued to O'Konski (143) and Mumma (140) in which electrical impulses are used to measure particles illuminated by an incident light source.

Another aerosol particle analyzer employing right-angle light scattering was recently reported (242). This instrument is said not only to measure particle size distribution but also count them.

Size Analysis of Droplets.—Size analysis of water aerosols or droplets of completely volatile components is difficult because the droplets evaporate quickly in room air. "For this reason," state Reif and Mitchell (169), "most methods of size analysis are indirect, in the sense that water droplets are allowed to hit a suitably prepared surface where they leave a permanent imprint. However, evaporation may occur before the droplets reach the sam-

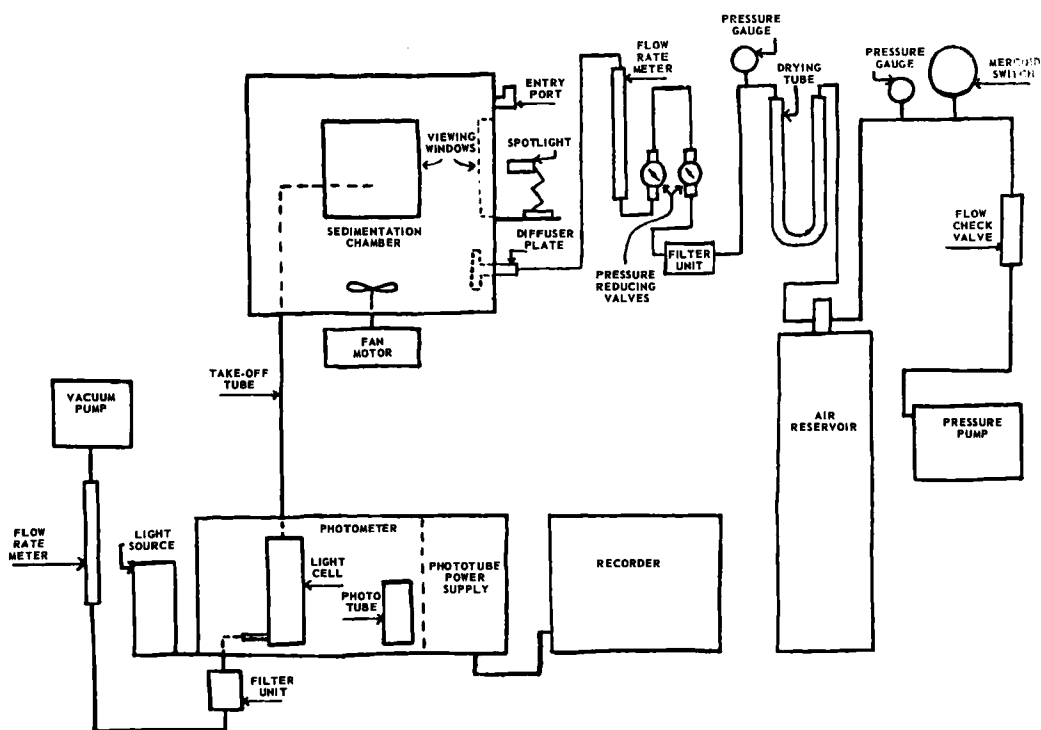


Fig. 13.—Schematic diagram of apparatus employing stirred sedimentation and light-scattering photometer for measurement of particle size. [From Reference 133.]

pling surface and only the largest droplets may carry sufficient momentum to penetrate it. Moreover, a round droplet is smaller than the flat imprint that it leaves on the sampling surface. Therefore, a calibration factor must be determined to convert the measured diameter of the flat imprint into the diameter of the round droplet that originally made the imprint." In recognition of this problem, these authors report an original study involving a vertical sedimentation chamber and the measurement of the effluent aerosol by means of a spectrophotometer. Unfortunately, their method is found to be applicable only to nonvolatile aerosol liquids. However, their report offers an excellent review and laboratory comparisons between six different methods which have been advocated for aerosol droplets. These methods are: (a) photographic film coated with polyvinyl alcohol which retains imprints of water droplets that hit it (62, 63); (b) a microscope slide covered with an even deposit of amorphous methylene blue powder which is dissolved by water droplets at point of impact and push it to the periphery of a circle (125); (c) a film of magnesium oxide which will leave pits proportional to the size of the droplets that hit it (125); (d) water droplets are "fixed" by allowing them to impinge on a viscous liquid such as oils or jellies (153, 199, 237); and (e) a lens method whereby aerosol droplets are permitted to impact on a scrupulously clean slide and form plano-convex "lens." The diameter of the equivalent spherical droplet can be calculated from three

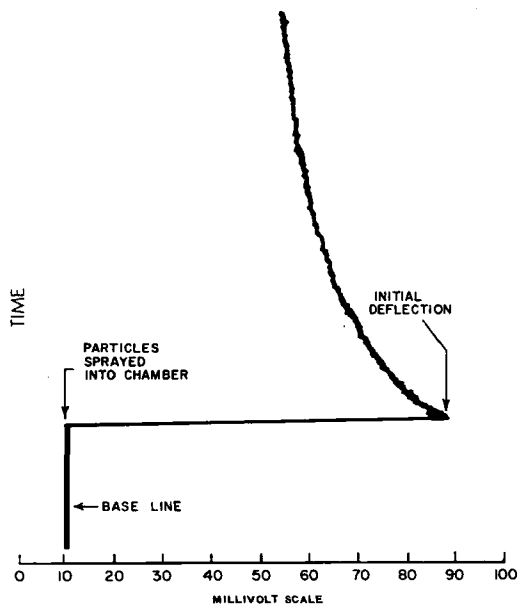


Fig. 14.—Section of strip recorder chart indicating phototube responses to initial stages of particle cloud settling. [From Reference 133.]

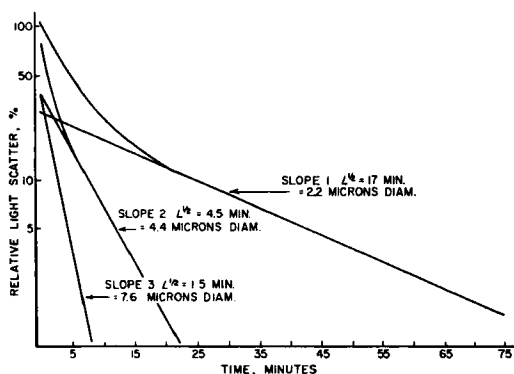


Fig. 15.—Light scattering curves for the determination of mean particle diameter. [From Reference 133.]

parameters. the diameter of the liquid lens, the focal length of the liquid lens, and the refractive index of the liquid (125). Owing to rapid evaporation, this latter method was also found to be suitable for nonvolatile liquids only. The authors conclude that the photographic film-polyvinyl alcohol method is satisfactory and presents factors required to convert the measured imprint to the original droplet diameter.

Standardized Particles.—Since many of the indirect methods of measurement require standardization of the instrument employed, the ready availability of a variety of fine particles of different chemical and physical properties is often welcomed. The Stanford Research Institute at Menlo Park, California, maintains a Particle Bank for both deposits of quantities of surplus particles and withdrawal of samples by research organizations.

EVALUATIVE PROCEDURES

Spray Patterns.—The thermodynamics of spray formation has been discussed by York (239), who analyzed the production of aerosol particulate matter and the energy relationships which exist under the influence of variables encountered in pressurized containers. In order to evaluate the effect of the variables on spray patterns, specialized techniques were developed. These techniques and the apparatus involved have been reviewed by Yeomans and Fulton (238), Dixon (54), Herzka (95), and Root (172). In general, the techniques utilize methods for visualizing and recording spray patterns under standardized conditions. Duplication of results is often poor and, if quantitative values are required, improved methods must be instituted.

Rheological Characterization.—Flow rates and rheological behavior of pressurized materials are important factors in the choice of valve, propellant, and specific formulation components. Consequently, a study of rheo-

logical behavior is of unusual importance when formulations possessing relatively high viscosities are pressurized. The rheological study of an aerosol product is a difficult problem because of different shear rates which are encountered in the various parts of the system. Cohen and his associates have divided the contents of a pressurized product into three rheological zones; within the container, in the narrow orifices within the valve, and at the point of delivery. This comprehensive report (38) analyzes the different shear rates within these zones and describes the use of an extrusion rheometer in measuring the types of flow of several pressure-packed formulations of high viscosities. The relationships between pressure and viscosity have been studied in the dispensing of liquid aerosols of high viscosities and their effect on delivery rates reported by Mina (132). This study also offers a suggested procedure for estimating delivery rates under various pressures.

Analysis of Volatile Constituents.—Gas chromatographic techniques have been shown to effectively circumvent the manifold problems associated with volatile constituents. Root and Maury (175–177) describe their methods of adapting gas chromatography for the analysis of a variety of volatile components under pressure.

Propellant Composition.—Since the vapor pressure exerted by the blend of propellants is critical to the performance of an aerosol, it becomes equally critical to determine accurately the exact composition of the blend. A simple and inexpensive pressure pycnometer has been developed which quickly relates halocarbon propellant composition to density of the blend (214). Tables of vapor pressures and densities as functions of composition at given temperatures are available (213). A similar approach has been reported for the determination of hydrocarbon gases in blends of these gases with liquefied halocarbon propellants (192)

Other Evaluative Procedures.—The Aerosol Division of Chemical Specialties Manufacturers Association publishes a loose-leaf Aerosol Guide which contains descriptions of procedures for a large number of tests developed by the Scientific Committee of the division. Many of these are still classified as "tentative methods" but this compilation is valuable as a reference source to the most reliable methods currently available. The Aerosol Guide also contains a premarketing product check list and information on federal and local acts pertaining to pressure packs.

STERILIZATION OF AEROSOLS

The temperature-pressure gradients of most propellants and the nature of the contents often preclude the use of terminal heat sterilization of the sealed units. The use of ethylene oxide together with liquefied halocarbon propellants has been shown to sterilize effectively the contents of aerosol systems (86, 87). One method (206) consists of presterilizing the containers in hot air ovens, the product and valves with ethylene oxide and ultraviolet light, and the propellant mixture through Seitz bacterial filters. Filling and assembling the antibiotic aerosol is then conducted under aseptic conditions in specially designed filling lines. Sterilization of aerosol products apparently does not pose any serious problems.

SUMMARY

While the development of pharmaceutical aerosols has not been as rapid or widespread as predicted, there is evidence in support of the contention that the aerosol may be counted among useful innovations in dosage forms.

Advances which have been made in evaluating the physical and therapeutic performances of drugs dispensed from pressurized units have made it possible to compare favorably the aerosolized drugs with other methods of administration. The possibility that orally inhaled medicinals may one day become a routine dosage route has been explored but it is clear that a large number of unknown factors must be investigated to insure predictable and controllable results. Other applications of aerosols in treatment of disease must meet the challenge of being compared with currently available medicinals. Unless they offer advantages not now possible with existing dosage forms, pressurized drugs will not be sustained on the basis of consumer convenience alone.

TABLE III.—INTERFACIAL TENSIONS vs. HLB VALUES^a

| Surfactant | HLB Values | Interfacial Tension, Dynes/cm. @ 25°C. Deviation | | |
|---------------|------------|--|--------|-------------|
| | | Exptl. | Calcd. | (dynes/cm.) |
| Igepal CO-210 | 4.6 | 37.2 | 34.2 | 3.0 |
| Igepal CO-430 | 8.9 | 18.0 | 20.0 | 2.0 |
| Igepal CO-530 | 10.9 | 12.3 | 13.3 | 1.0 |
| Igepal CO-610 | 12.2 | 5.5 | 8.9 | 3.4 |
| Igepal CO-710 | 13.5 | 4.0 | 4.7 | 0.7 |
| Igepal CO-730 | 15.0 | 1.5 | 0.3 | 1.2 |

^a Igepal CO surfactants, 0.1%, in Propellant 11-Water.

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