level. An indication that such a phenomenon occurs has been suggested in this paper when nonsparged vials assayed 16 rather than 21% oxygen. To demonstrate this further, vials of another parenteral product were filled using both the conventional nitrogen-layering technique and also with no attempt to incorporate nitrogen into the vial. The oxygen content of the head space was determined at various time intervals after filling. Because this product was able to react with oxygen, Fig. 4 shows that measurements performed as little as 1–2 hr. after filling gave erroneous results. At the end of 5–6 hours, the data obtained implied that the product was adequately protected. The true oxygen level in the head space was determined by extrapolation to zero time (time of filling). These results further emphasize the need for an awareness of the elapsed time when determining the efficiency of a nitrogen-protecting system.

Antioxidant and Nitrogen—Although an antioxidant could not be considered for inclusion in the system discussed, it may be felt by some that an antioxidant can take the place of an inert atmosphere in other systems. The authors believe that the inert atmosphere should serve to protect a product during its manufacture, filling, and storage prior to use. In this way the integrity of the antioxidant is maintained for the actual use-life of the product. An antioxidant consumed during the filling and manufacture operations may not be available for protection during a product's use-life, unless large amounts are employed. High concentrations of antioxidants should not be used to overcome less than adequate manufacturing techniques, and the maximum amount permitted might not be sufficient to protect the product during both its manufacture and use-life. Although this study has been concerned with a parenteral product, the same approach to filling other dosage forms is obvious. Therefore, in an oral liquid product, where taste is important, it is desirable to use minimum rather than maximum antioxidant concentrations.

Conclusions—As a result of this study, it is felt that anyone using a conventional method for layering nitrogen onto an oxygen-sensitive product should closely scrutinize the technique. A procedure similar to that described in this paper would be useful with any oxygen-sensitive product. Although these studies indicated good nitrogen protection in vials layered by this method, it must be remembered that it represented only a single product in a particular size vial. Therefore, the specific conditions for producing minimum oxygen concentration must be evaluated for each individual product and container.

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Dispensing Efficiency of Nonmetered Topical Spray Aerosols

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Abstract □ In spite of the often-quoted more efficient application advantage of pharmaceutical aerosol dosage form over a cream, an ointment, or a lotion topical preparation, the dispensing or pickup efficiencies of the majority of 10 commercially available nonmetered topical spray aerosols tested were found to be low. The pickup efficiency decreased with increasing target distance, increasing temperature of the aerosol, and tended to increase with increasing nonvolatile content.

Keyphrases □ Aerosols, nonmetered—dispensing efficiency □ Particle size—dispensing efficiency □ Pickup efficiency—nonmetered aerosols □ Temperature effect—pickup efficiency □ Target-aerosol distance—pickup efficiency

Active drugs must usually be dispensed in a formulated dosage form for ease of application. With the advent of pressurized packaging, pharmacists attempted to substitute aerosol dosage forms for the classical dosage forms with less success than anticipated (1). An explanation for the slow growth of the pharmaceutical industry into aerosols has been suggested by some (2) to be due to the poor quality of aerosol-filling services and aerosol components. In the case of drugs used topically, the classical medicated applications consist of creams, lotions, and ointments. Some of the claims (1, 3–7) usually made for topical spray aerosols are: (*a*) no waste or messiness associated with applicator or cotton swab; (*b*) efficient application.

Aerosol products may be broken into three categories (8): (*a*) space sprays; (*b*) surface coating; (*c*) aerated foams.

It is rather obvious that aerosol products intended for topical use can only be made by aerosols of Types *b* and *c*. Space sprays would leave very little deposit of medication on a body surface and thus would tend toward zero dispensing efficiency. At the other extreme, the aerated-foam aerosols would tend toward

Table I—Pickup Efficiency of Spray Aerosol Product *D* as a Function of Spray Time

Valve Actuation Time, sec.	% Pickup Efficiency (Distance 15.24 cm. Operating Temperature 25°C.)
1	34
2	33
3	33
6	33
9	34
12	34

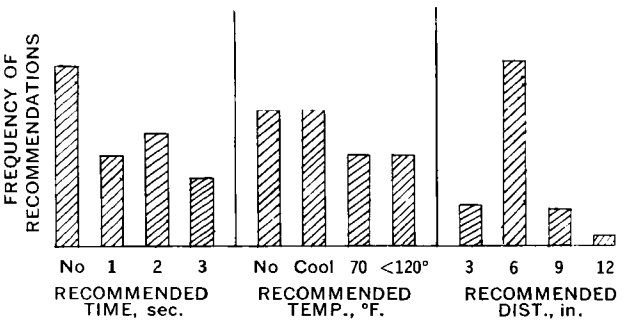

Figure 1—*Frequency of recommended time, temperature, and target distance of 10 topical spray aerosol products.*

100% dispensing efficiency. It is obvious that the surface or residual spray aerosols would tend to have dispensing efficiency between these two limits. Therefore, it is rather surprising that none of the commonly available pharmaceutical aerosol formulation literature (3, 4, 7, 9, 10) make any reference to the concept of pickup (or dispensing) efficiency so adequately described for residual type of aerosols in other industries (11).

The pickup efficiency is defined as the percentage of the low-volatile ingredients discharged that deposit on the target surface. The percentage of the low-volatile ingredients dispensed that do not deposit on the target surface are wasted. A recent series of articles on Quality Control and Aerosol Pharmaceuticals (15) mentions dispensing efficiency as an important consideration for an aerosol product.

Clinically, it matters very little if the pickup efficiency of the topical aerosol product is high or low as long as the amount of active drug deposited is sufficient to be therapeutically active and a reproducible uniform product is manufactured. However, from a practical viewpoint, a significantly less than 100% dispensing efficiency would negate the so-called more efficient dispensing advantage of aerosols. Whether the other advantages of topical aerosol spray formulations [convenience, elimination of irritation which manual applications may produce, therapeutic efficiency (16), *etc.*] can outweigh the loss of dispensing efficiency, can only be judged on the merit of each individual product.

Although the efficiency of residual aerosols depends on particle size, this efficiency can be determined more easily by the percentage of deposit than by the difficult determination of the actual particle size.

Particle size distribution of an aerosol spray is influenced by the following factors (12–14): (*a*) propellant percentage; (*b*) nature of propellant; (*c*) valve; (*d*) button (actuator); (*e*) distance to target area; (*f*) temperature; (*g*) nonvolatile composition; (*h*) viscosity of nonvolatiles; (*i*) head-space pressure.

The type of spray produced by an aerosol product is one of its most important properties. The spray characteristics of aerosol products vary from wet, streamy sprays to very fine sprays. Wet or coarse sprays are desirable for residual products, while sprays with a fine particle size are necessary for space aerosols.

Methods and techniques have been developed for analyzing the spray characteristics of aerosol products (7). The characteristics of the spray which can be measured include pressure, discharge rate, spray pattern, and spray angle. However, an important operational test (determining the pickup efficiency) is usually not performed during the development of an aerosol product.

The only parameters that can be varied by a user of a topical aerosol without a metered valve are (*a*) the length of time the valve is actuated; (*b*) the temperature of the aerosol formulation; and (*c*) the distance the aerosol is held from the target surface.

This study was undertaken to determine the pickup efficiency of nonmetered topical spray aerosols.

EXPERIMENTAL

Samples—Single units of 10 commercially available pharmaceutical nonmetered topical aerosols were used.

Pickup Efficiency—The Chemical Specialties Manufacturers Association (Aerosol Division) (11) procedure was used with Yeomans and Fulton's (17) apparatus. The pickup efficiencies at 15 and 35°C. at a fixed target distance of 15.2 cm. (6 in.) and at 25°C. for target distances of 7.6, 15.2, 22.8, and 30.4 cm. (3, 6, 9, and 12 in.) were determined. The target distance is measured from the aerosol actuator to the target area to be struck.

Table II—Pickup Efficiencies of Nonmetered Topical Spray Aerosols

Spray Aerosol Product	Nonvolatile Content, %	% Pickup Efficiency: Constant Distance (15.24 cm.) Operating Temperatures, °C. 15	25	35	Constant Temp. (25°C.) Operating Distances, in. 3	9	12
A	4.8	81	71	54	88	42	27
B	4.3	70	47	21	75	21	18
C	3.5	51	31	21	54	3	1
D	3.8	52	34	16	40	8	3
E	4.9	82	65	49	90	41	32
F	3.0	50	33	13	69	17	7
G	0.9	33	21	11	33	12	2
H	4.3	93	63	30	79	28	14
I	3.5	94	80	66	94	20	14
J	5.6	79	71	50	86	46	39

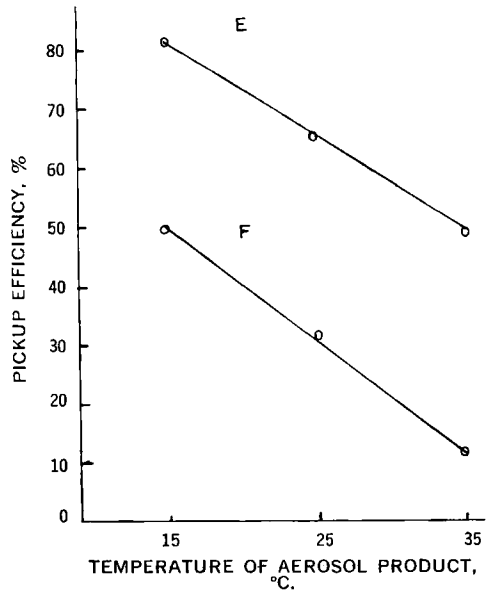

Figure 2—*Pickup efficiencies of spray aerosol products* E *and* F *as a function of temperature (target distance 6 in.).*

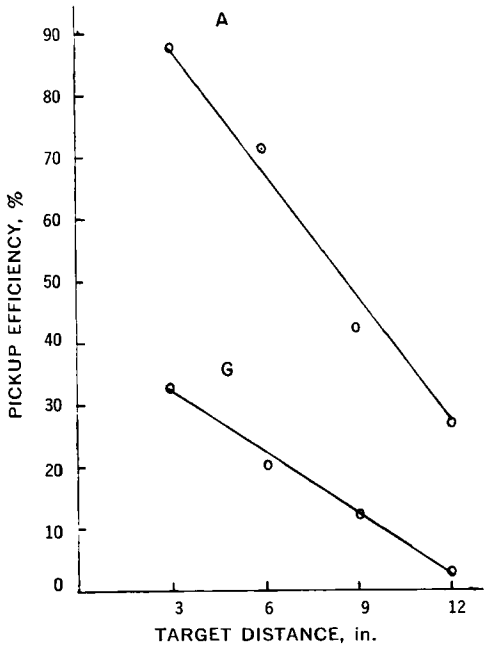

Figure 3—*Pickup efficiencies of spray aerosol products* A *and* G *as a function of target distance (temperature 25°C.).*

DISCUSSION

The results of the study of the length of time of actuation of the valve in aerosol Product *D* on the pickup efficiency are shown in Table I. Pickup efficiency is essentially independent of time of valve actuation. Four of the products studied did not have a recommended length of time for actuating the valve. Recommendations of times from 1 to 3 sec. were almost equally divided (Fig. 1) among the remaining six products. The average time recommended was 2 sec.

The results of the study of the temperature parameter and pickup efficiency are shown in Table II. The effect of temperature of the aerosol product on the pickup efficiency is shown in Fig. 2 for Products *E* and *F*. In all cases the pickup efficiency drops substantially with increasing temperature. This is obviously due to two factors, increase of propellant pressure and decrease in nonvolatile viscosity. Decrease in aerosol particle diameter with temperature has been previously reported by Lefebvre and Tregan (12). The labels of three of the products did not have any comments with regard to storage temperature of the product (Fig. 1). Two of the products recommended a temperature (less than 120°F.) with only safety of the aerosol product in mind. Two of the remaining products recommended 70°F. and the last three recommended "store in a cool place."

The results of the study of target distance and pickup efficiency are also tabulated in Table II. The effect of target distance on the pickup efficiency for Products *A* and *G* are shown in Fig. 3. In general, the pickup efficiency decreases substantially with increasing distance from the target. In recognition of this fact that the spray package functions most effectively when held at some fixed distance from the surface in question, all the 10 commercial topical aerosol products had recommended target distances as shown in Fig. 1. Six inches (15.24 cm.) was the generally recommended distance.

It will be noticed that the pickup efficiency *versus* temperature of the aerosol product or target distance (Figs. 2 and 3) is a function of the product and is displaced toward higher pickup efficiency as the nonvolatile content of the aerosol product increases for Products *A*, *G*, *E*, and *F*. Although there is a general trend of increasing pickup efficiencies with increasing percentage of nonvolatiles, this relationship is not unequivocal since other factors, (*i.e.*, viscosity) which also have an influence on dispensing efficiency are confounded with the nonvolatile content factor.

SUMMARY AND CONCLUSIONS

The effects of the three parameters, time, temperature, and distance (which a user of a nonmetered topical aerosol product could vary), on the dispensing efficiency of 10 topical spray aerosols were studied. The results indicated that pickup efficiency was very sensitive to the temperature of the aerosol product and target distance. At normal operating temperature (25°C.) there is a great variation in the pickup efficiency among the 10 products tested.

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