Some Aspects of Inhaler Technology

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This communication presents the results of a physical-chemical study of the characteristics of the inhaler dosage form. Such a study has not been reported previously. Analysis of the observations made permit the following generalizations: inhalers may be classified as being either a surface type (provides zero-order release) or a solution type (provides first-order type of release); in inhaler development the rates of volatilization can be controlled or modified; vapor pressure equilibrium concepts play a minor role. These concepts are amplified and discussed with supporting data.

INFORMATION concerning inhaler technology is conspicuous by its absence in readily available sources. The U.S.P. XVI (p. 823), which contains only one inhaler monograph (propylhexedrine inhalant), describes this dosage form as follows: "Inhalants are drugs or combinations of drugs which, by virtue of their high vapor pressure, can be carried by an air current into the nasal passage where they exert their effect. The device making possible the administration of an inhalant is known as an inhaler."

Inhalers, like all pharmaceutical products, should be physically and chemically stable so that satisfactory shelf- and use-life is attained. However, inhalers present somewhat different problems in that the delivered doses are not easily standardized, unlike the cases involving tablets, capsules, or solutions. In fact, the precision with which inhaler doses can be made "uniform" is of a completely different order of magnitude from that attainable with the latter products.

The purpose of this paper is to show that inhaler technology and inhaler problems can be profitably examined by applying the principles of physical chemistry. It is possible by these means to obtain a clearer picture of the behavior, including the limitations, of inhaler dosage forms. Variables such as the shape and size of the inhaler body and pledget, the concentration and state of the pledget charge, and the variation in performance of both individual and groups of inhalers have been studied. No attempt will be made here to discuss all the medical and pharmaceutical aspects or the chemical reactivities which would have to be considered in the formulation of a complete inhaler. Such factors as the physical and chemical stability, solubility, mechanical integrity, or compatibility of the active ingredient with the inhaler body, pledget, solvent, or organoleptic agents will not be discussed.

The paper describes and discusses some of the data obtained during the development of an inhaler whose volatile ingredient was phlorone, 2,5-dimethyl-1,4-benzoquinone. The inhaler was to deliver at least 50 mcg. of phlorone per liter of air passing through it.

EXPERIMENTAL

Apparatus.—Figure 1 pictures the breathing apparatus used in the evaluation of the inhalers. In essence, the system is designed to pull a known amount of air through an inhaler and then through a quantity of liquid in which the active ingredient in the vapor dissolves and which can be analyzed. The device was set so that each cycle took 2 seconds and delivered 200 ml. of air. Because the size of the holes in the glass aerating head affected the quantity of air which would pass per cycle, the apparatus was calibrated with a Collins vitalometer.[1] This was done by inflating the vitalometer, then connecting it in the position at which the inhaler is put during testing, running the breathing apparatus, and noting the decrease in air volume of the vitalometer per breathing cycle.

Procedure.—The manipulations consisted of drawing air serially through the various inhaler formulations and then through 25 ml. of analytical reagent grade isopropanol contained in a 75-ml. test tube. The isopropanol solution was then analyzed on the Beckman DU spectrophotometer. A second tube of isopropanol in series showed that no phlorone was carried out as vapor from the first tube, so only one tube was needed. The pump or breathing apparatus was set so that 200 ml. of air was pumped per complete cycle, each cycle taking 2 seconds (the actual time of air flow then being 1 second, with the machine "exhaling" the other second). To put 1 L. of air through an inhaler then took, of course, five cycles or 10 seconds.

Analytical.—Many standard solutions of phlorone in analytical reagent grade isopropanol were made and run at 250 mμ on the Beckman DU instrument; the response was linear and reproducible to a very

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[1] A. H. Thomas Co., Phila. 5, Pa.; Scientific Apparatus and Reagents Catalog, No. 6433, 1961 Anniversary Edition.

TABLE I.—DOSE OBTAINED FROM SURFACE PHLORONE INHALERS UTILIZING BLOTTER AND COTTON PLEDGETS

Inhaler No.	Pledget[a]	Air, L.	Dose, mcg.	Inhaler No.	Pledget[a]	Air, L.	Dose, mcg.
1	B	1	104	12	B	2	138
2	B	1	106	13	B	1	87
3	B	1	108	14	B	1	73
4	B	1	119	15	B	3	182
5	B	1	117	16	B	3	175
6	B	1	108	17	C	2	95
7	B	1	104	18	C	2	73
8	B	1	110	19	C	1	58
9	B	1	115	20	C	1	58
10	B	1	135	21	C	3	80
11	B	2	152	22	C	3	118

[a] B, paper blotter, folded, 100-lb. white, J. L. N. Smythe Co., Philadelphia, Pa.; C, cotton pledget.

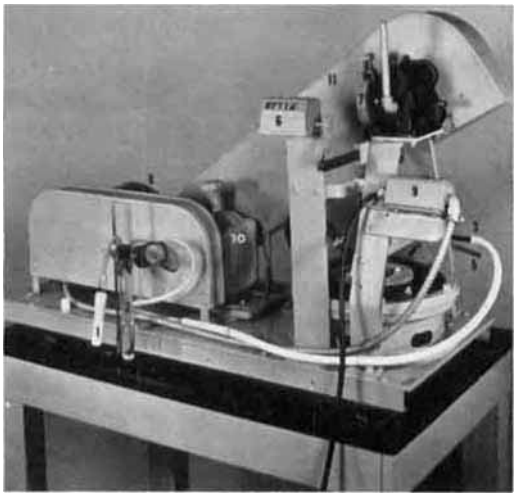

Fig. 1.—Breathing apparatus; *1*, inhaler; *2*, tube, contains aerating head and isopropanol; *3*, air inlet; 4, rubber bellows-diaphragm; *5*, air outlet; *6*, counter; *7*, cam, attached by descending rod to bellows-diaphragm to permit volume adjustment; *8*, motor; *9*, motor switch; *10*, V-belt drive with variable sheave to permit speed adjustment; *11*, belt drive, rotates cam wheel through right-angle transmission.

high degree of precision. Solutions stored in the dark for various periods of time up to 8 days assayed the same as originally. The absorptivity or absorbancy index was found to be 139; $K = 139 =$ absorbance/(Gm./L.). Since 25 ml. was a convenient volume of isopropanol in which to collect phlorone vapors, the relationship became simply: micrograms/25 ml. = absorbance × 180. This assay procedure was found to be very satisfactory. When equal concentrations of camphor, menthol, or eucalyptol were added to the phlorone standard solutions, no interference was noted in the absorbance at 250 mμ.

Materials.—Phlorone or 2,5-dimethyl-1,4-benzoquinone, Eastman Organic Chemicals, Distillation Products Industries, Rochester, N. Y. Benzyl salicylate, Givaudan-Delawanna, Inc., New York, N. Y. Dibutyl phthalate, Matheson, Coleman and Bell, Division of the Matheson Co., Inc., East Rutherford, N. J. Paper-blotter, 100-pound, white, J. L. N. Smythe Co., Philadelphia, Pa. Long and short size inhaler bodies, nose-pieces, caps, and cotton pledgets as shown in Fig. 2. Isopropyl alcohol, analytical reagent, Mallinckrodt Chemical Works, St. Louis, Mo. Eucalyptol U.S.P., Dodge and Olcott, Inc., New York, N. Y. Camphor U.S.P., S. B. Penick and Co., New York, N. Y. Menthol U.S.P., racemic, Givaudan-Delawanna, Inc., New York, N. Y.

RESULTS AND DISCUSSION

Initial Studies.—The first inhalers were made by dissolving the phlorone in ether, placing the appropriate number of pledgets in the solution, and then evaporating the ether. The ether evaporating process is unwieldy and results in uneven distribution of the phlorone on the surface of either the cotton or folded blotter pledgets. Table I presents some of the data taken on inhalers which contained 50 mg. of phlorone and 4 mg. of menthol made by this process. The long plastic body was used. The greater available surface area of the blotter provided somewhat higher doses than the cotton pledget.

To replace the ether evaporation procedure, phlorone was added to the pledgets in solution form. Two solvents of very low volatility were chosen for study: dibutyl phthalate and benzyl salicylate. A solubility study was done to determine the limits of concentration that could be used. The limits determined were: 50 mg./ml. in dibutyl phthalate and 85 mg./ml. in benzyl salicylate. The solutions made with the latter formed more easily.

A group of inhalers was made by putting 1 ml. of a 50 mg./ml. solution of phlorone in dibutyl phthalate on cotton and blotter pledgets encased in the long plastic body. Doses obtained from this group are given in Table II. Again it is seen that the greater exposed surface area of the blotter pledget provides the higher doses.

TABLE II.—DOSE OBTAINED FROM SOLUTION PHLORONE INHALERS UTILIZING BLOTTER AND COTTON PLEDGETS

Inhaler No.	Pledget	Dose, mcg./2 L. Air	Inhaler No.	Pledget	Dose, mcg./2 L. Air
1	Cotton	98	7	Blotter	150
2	Cotton	77	8	Blotter	135
3	Cotton	76	9	Blotter	135
4	Cotton	80	10	Blotter	135
5	Cotton	80	11	Blotter	119
6	Cotton	80	12	Blotter	133

TABLE III.—COMPARISON OF DOSES OBTAINED FROM NINE DIFFERENT GROUPS OF INHALERS

Inhaler No.	Inhaler Group	Dose, mcg./L. of Air	Inhaler No.	Inhaler Group	Dose, mcg./L. of Air	Inhaler No.	Inhaler Group	Dose, mcg./L. of Air
1	A	76	13	D	89	25	G	110
2	A	78	14	D	90	26	G	66
3	A	76	15	D	88	27	G	71
4	A	82	16	D	93	28	G	67
5	B	83	17	E	57	29	H	57
6	B	65	18	E	62	30	H	44
7	B	81	19	E	72	31	H	41
8	B	102	20	E	62	32	H	50
9	C	93	21	F	92	33	I	94
10	C	101	22	F	90	34	I	81
11	C	131	23	F	91	35	I	84
12	C	91	24	F	101	36	I	87

TABLE IV.—AVERAGE DOSES FROM INHALER GROUPS OF TABLE III

Inhaler Group	Dose, mcg./L. of Air	Inhaler Group	Dose, mcg./L. of Air	Inhaler Group	Dose, mcg./L. of Air
A	78	B	83	C	95[a]
D	90	E	63	F	93
G	68[b]	H	48	I	86

[a] Neglecting reading of 131 as being somewhat out of line for purposes of obtaining these initial impressions. [b] Neglecting reading of 110, same reason.

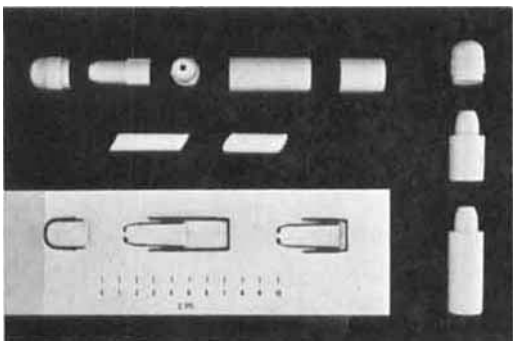

Fig. 2.—External and cut-away views of inhaler components.

On the basis of these data (Tables I and II) more inhaler groups were made in an attempt to decide which type of pledget and which inhaler type (surface or solution) would give better results. The following nine groups, all in long bodies, were then made: Surface: (*A*) evaporated ether method, 50 mg. charge, blotter pledget; (*B*) same method, long cotton pledget; (*C*) same method, short cotton pledget. Solution: (*D*) method: 1 ml. of warm 100 mg./ml. solution of phlorone in benzyl salicylate per pledget, blotter pledget; (*E*) method same, long cotton pledget; (*F*) method same, short cotton pledget; (*G*) method: 1 ml. of 50 mg./ml. solution of phlorone in dibutyl phthalate per pledget, blotter pledget; (*H*) same method, long cotton pledget; (*I*) same method, short cotton pledget.

The data obtained from these nine groups are given in Tables III and IV.

Taking an overview of the data of Table III, we may look at the averages as presented in Table IV.

Besides these data, trial runs with other Group A and B inhalers were made. Fifteen analyses (three inhalers breathed five times each at half-hour intervals) from each group showed that Group A gave an average dose of 78 mcg./L. of air; Group B gave 72 mcg./L. of air.

The data indicate that, all things considered (dose level, ease of making, solubility, etc.), the short cotton pledget charged with phlorone in benzyl salicylate appears to produce the best inhaler. We recognize that the "package" is an inherent part of the formula in an inhaler dosage form because the internal size and shape may govern the amount of drug put into the formula and the dosage obtained per "whiff."

Although inhalers made by the "evaporated ether" process were of less interest, some limited usage tests were made using inhalers of this type. The same four inhalers of Group A used to obtain the data of Table III were also used here. The time of breathing is also shown along with the dose data in Table V.

The data of Table V provide an insight into how well and with what variation some of the original inhalers perform.

Because of the possibility that more efficient utilization of the drug might result from its application closer to the nasal openings so that more of the inner nasal surfaces would be bathed with the vapors, some larger, aluminum inhaler bodies (identical to those of the obsolete Benzedrine inhaler) were tested. These bodies are somewhat thicker, and the nose-piece is of such size that it does not easily penetrate the nose as far as the nozzles shown in Fig. 2. It was found that the airflow characteristics of this inhaler body are such that the pledgets supply a dose lower than they do when encased in the plastic bodies. Even when four extra holes were drilled (No. 50 drill) in the sides of the air-inlet end in an attempt to permit more air to pass through, no increase in dosage was obtained. This indicates that resistance to air flow can be a rate-limiting factor. Table VI presents the data obtained.

Final Studies.—On the basis of the data collected on the preliminary inhalers, further work was done only on solution-type inhalers. Tables VII–IX present some of the data taken on inhalers containing 85 mg. of phlorone and 10, 20, or 30 mg. of camphor dissolved in 1 ml. of benzyl salicylate. The short size body and pledget was used. The camphor odor persisted throughout the trials. The data indicated also that the phlorone dosage is not affected by the presence of various amounts of camphor.

TABLE V.—LIMITED USAGE TEST OF SURFACE INHALERS OF TABLE III, GROUP A

Inhaler No.	Time of Day	Breathing Interval, hr.	Dose, mcg./L. of Air	Inhaler No.	Time of Day	Breathing Interval, hr.	Dose, mcg./L. of Air	Inhaler No.	Time of Day	Breathing Interval, hr.	Dose, mcg./L. of Air
1	1	..	45	1	2	1	123	1	3	1	61
2	1	..	54	2	2	1	73	2	3	1	62
3	1	..	72	3	2	1	73	3	3	1	66
4	1	..	71	4	2	1	45	4	3	1	71
1	1	1	95	1	2	1	63	1	3	1	60
2	1	1	101	2	2	1	58	2	3	1	58
3	1	1	89	3	2	1	68	3	3	1	68
4	1	1	72	4	2	1	65	4	3	1	71
1	1	1	138	1	2	1	99	1	3	2	57
2	1	1	84	2	2	1	65	2	3	2	56
3	1	1	85	3	2	1	69	3	3	2	69
4	1	1	78	4	2	1	65	4	3	2	72
1	1	1	105	1	2	1	53	1	3	1.5	56
2	1	1	70	2	2	1	53	2	3	1.5	57
3	1	1	86	3	2	1	53	3	3	1.5	67
4	1	1	75	4	2	1	58	4	3	1.5	68
1	1	1	67	1	2	1	56	1	3	1	54
2	1	1	66	2	2	1	59	2	3	1	55
3	1	1	79	3	2	1	62	3	3	1	70
4	1	1	58	4	2	1	61	4	3	1	66
1	1	1	129	1	2	1	112	1	4	..	58
2	1	1	87	2	2	1	60	2	4	..	64
3	1	1	91	3	2	1	55	3	4	..	77
4	1	1	78	4	2	1	58	4	4	..	65
1	1	1	114	1	2	1	52	1	4	1	56
2	1	1	79	2	2	1	52	2	4	1	58
3	1	1	75	3	2	1	52	3	4	1	67
4	1	1	65	4	2	1	62	4	4	1	68
1	1	1	120	1	3	..	62	1	4	3	57
2	1	1	66	2	3	..	62	2	4	3	61
3	1	1	78	3	3	..	53	3	4	3	..
4	1	1	72	4	3	..	60	4	4	3	72
1	2	..	86	1	3	1	58	1	4	2	58
2	2	..	59	2	3	1	65	2	4	2	58
3	2	..	63	3	3	1	69	3	4	2	68
4	2	..	65	4	3	1	68	4	4	2	78

Although the data are given in quite a detailed manner, attempts to summarize the information result in too great a loss of clarity and completeness in the total picture.

Because rate processes should control inhaler function, it is interesting to note the effect of temperature on the rate of volatilization of phlorone. Several inhalers from the groups used to obtain the data of Tables VIII and IX were heated to 37°, then breathed. It can be seen that this increase in temperature increases the dose about 80% over that obtained at room temperature. Table X presents the data.

The data shown in Table XI resulted from study of the following solution-type inhaler formula: phlorone, 85.0 mg.; eucalyptol U.S.P., 0.03 ml.; and benzyl salicylate *q.s. ad.* 1.0 ml.

The phlorone and eucalyptol are dissolved in the benzyl salicylate, then 1 ml. of the solution is dropped onto the small cotton pledget which is then encased in the body of the inhaler. Some less extensive data on similar formulas (same except having 0.01 or 0.02 ml. of eucalpytol) were also collected but are not given here because they essentially duplicate the data following. The eucalyptol odor persisted throughout the trials.

The data of Table XI corroborate the concept that rate processes exert more weight than equilibrium does. For example, one of the continuous breathing series, dose numbers 122–150, shows that recovery times are essentially nonexistent.

In addition to the data already presented, this table also permits one (by examining the vertical columns) to see the variation in the performance of individual inhalers. Even though the ranges are fairly wide, the inhalers do perform quite consistently on the average. The following are the average doses given by the Table XI inhalers: No. 1, 85; No. 2, 90; No. 3, 83; No. 4, 91; No. 5, 84.

To check the effect of the state of the total charge the following was done: two groups of inhalers were made, each inhaler containing 42.5 mg. of phlorone and 0.015 ml. of eucalyptol. However, one group had the ingredients dissolved in 0.5 ml. of benzyl salicylate, the other in 1.0 ml. Each of the ten inhalers (short body, cotton pledget) was breathed six times with the following results: the "0.5-ml. group" averaged 64 mcg./L. of air, whereas the "1.0 ml. group" averaged 37. The conclusion is that in a solution type inhaler the concentration of drug is of much greater importance than the surface area over which it is spread. Again, this concentration dependence indicates that rate rather than equilibrium factors predominate.

We further investigated the effect of charge concentration on delivered dose. Phlorone-eucalyptol-benzyl salicylate inhalers were made having phlorone concentrations of 80, 70, 60, 50, and 40 mg./ml. in benzyl salicylate. Each short cotton inhaler pledget was charged with 1 ml. of solution. Figure 3 illustrates the results. It can be seen that

TABLE VI.—DOSE OBTAINED FROM SHORT COTTON PLEDGETS ENCASED IN THE BENZEDRINE INHALER ALUMINUM BODY, SOLUTION TYPE INHALER, BENZYL SALICYLATE SOLVENT[a]

Inhaler No.	Dose, mcg./L. of Air	Inhaler No.	Dose, mcg./L. of Air	Inhaler No.	Dose, mcg./L. of Air
1	61	7	56	13	54
2	60	8	52	14	64
3	57	9	61	11	49
4	53	10	55	12	53
5	56	7	75	13	55
6	50	8	56	14	55
7	64	9	64	11	49
8	53	10	52	12	54
9	62	11	58	13	62
10	54	12	69	14	69
7	46	13	67	11	48
8	53	14	68	12	52
9	60	11	56	13	56
10	52	12	55	14	65
7	50	13	63	11	46
8	61	14	53	12	48
9	58	11	52	13	51
10	54	12	57	14	60
7	51	13	60	15	53
8	52	14	64	16	51
9	56	11	51	17	55
10	53	12	52	18	55
7	44	13	52	15	46
8	44	14	57	16	45
9	62	11	57	17	51
10	50	12	58	18	54
7	50	13	49	15	46
8	50	14	65	16	48
9	64	11	68	17	51
10	59	12	63	18	56

[a] Inhalers had doses taken from them at half-hour intervals; inhalers No. 15–18 were modified by drilling four holes (No. 50 drill) into side of inlet end.

the inhaler life and dosage level are predictable when such data are available.

The following was done to check the behavior of a surface type inhaler. Inhalers (blotter pledget, long body) were made by the evaporated ether method containing 10, 20, 30, 40, 50, 60, and 70 mg. of phlorone. Figure 4 illustrates the results. It can be seen that in this case the dosage does not fall off as quickly as with the solution type inhaler.

As a comparison to the above and to fortify still further the conclusions drawn from the data of Fig. 3, more inhalers were made containing 40, 50, 60, 70, and 80 mg. of phlorone dissolved in 1 ml. of benzyl salicylate. This time blotter pledgets in the large inhaler body were used. Figure 5 presents the data obtained. Again, just as in Fig. 3, the line goes through the origin.

The data of Figs. 3–5, beside contributing to the general picture, enable one to make a calculation of the useful life of the inhaler. It can be seen that the formula would deliver more than 400 doses of at least 50 mcg./L.

CONCLUSIONS AND COMMENTS

In general, it appears that inhalers may be classified as being one of two types. One kind may be called a "surface" type, i.e., the volatile material, *per se*, resides on the surfaces of the

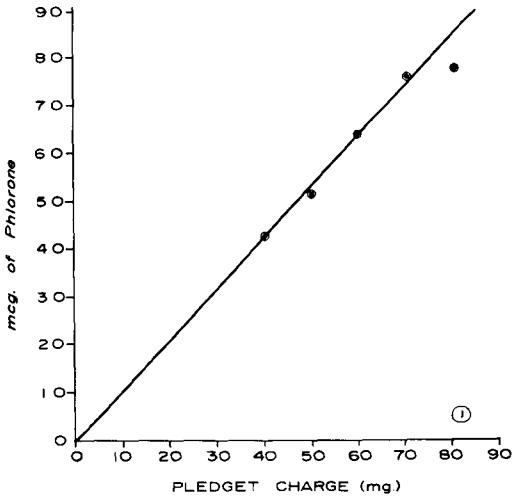

Fig. 3.—Effect of concentration of charge on pledget on dosage delivered when 1 L. of air travels through inhaler (solution type—short cotton pledget).

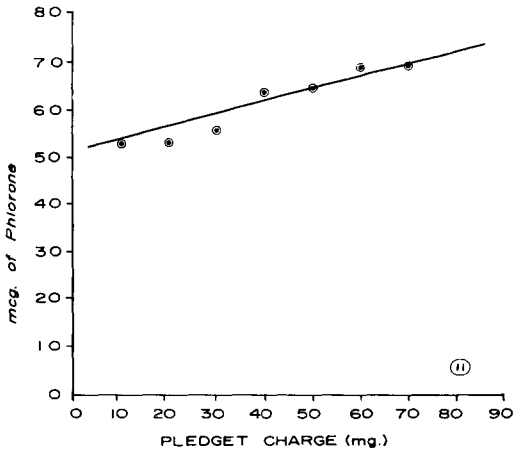

Fig. 4.—Effect of amount of charge on pledget on dosage delivered when 1 L. of air passes through inhaler (surface type—long blotter pledget).

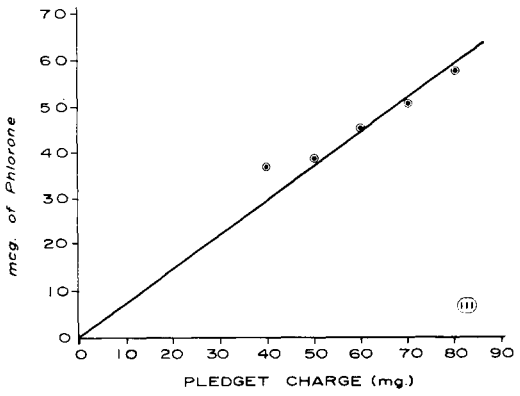

Fig. 5.—Effect of charge concentration on dosage delivered when 1 L. of air passes through inhaler (solution type—long blotter pledget).

TABLE VII.—DOSE OBTAINED FROM PHLORONE (85 MG.)–CAMPHOR (10 MG.)–BENZYL SALICYLATE INHALERS

Inhaler No.	Time of Day	Breathing Interval, hr.	Dose, mcg./L. of Air	Inhaler No.	Time of Day	Breathing Interval, hr.	Dose, mcg./L. of Air	Inhaler No.	Time of Day	Breathing Interval, hr.	Dose, mcg./L. of Air
1	1	...	87	1	2	0.75	X[a]	1	5	1	X
2	1	...	86	2	2	0.75	84	2	5	1	X
3	1	...	90	3	2	0.75	X	3	5	1	98
4	1	...	90	4	2	0.75	84	4	5	1	X
5	1	...	83	5	2	0.75	X	5	5	1	X
1	1	1	86	1	2	0.75	84	1	6	...	82
2	1	1	85	2	2	0.75	X	2	6	...	X
3	1	1	81	3	2	0.75	80	3	6	...	86
4	1	1	87	4	2	0.75	X	4	6	...	98
5	1	1	87	5	2	0.75	88	5	6	...	93
1	1	3	84	1	2	0.75	X	1	9	...	X
2	1	3	81	2	2	0.75	75	2	9	...	86
3	1	3	75	3	2	0.75	X	3	9	...	83
4	1	3	89	4	2	0.75	83	4	9	...	94
5	1	3	88	5	2	0.75	X	5	9	...	97
1	1	1	83	1	5	...	86	1	9	0.75	X
2	1	1	76	2	5	...	X	2	9	0.75	90
3	1	1	78	3	5	...	X	3	9	0.75	X
4	1	1	82	4	5	...	88	4	9	0.75	93
5	1	1	90	5	5	...	X	5	9	0.75	X
1	2	...	75	1	5	1	X	1	9	1.5	X
2	2	...	80	2	5	1	81	2	9	1.5	X
3	2	...	76	3	5	1	X	3	9	1.5	86
4	2	...	83	4	5	1	X	4	9	1.5	X
5	2	...	86	5	5	1	95	5	9	1.5	85
1	2	1	86	1	5	1	X	1	12	...	X
2	2	1	X	2	5	1	X	2	12	...	91
3	2	1	81	3	5	1	82	3	12	...	X
4	2	1	X	4	5	1	X	4	12	...	96
5	2	1	95	5	5	1	X	5	12	...	X
1	2	1	X	1	5	1	94	1	12	7.5	X
2	2	1	81	2	5	1	X	2	12	7.5	X
3	2	1	X	3	5	1	X	3	12	7.5	87
4	2	1	87	4	5	1	87	4	12	7.5	X
5	2	1	X	5	5	1	X	5	12	7.5	108
1	2	2.75	82	1	5	1	X	1	12	0.5	X
2	2	2.75	X	2	5	1	114	2	12	0.5	100
3	2	2.75	78	3	5	1	X	3	12	0.5	X
4	2	2.75	X	4	5	1	X	4	12	0.5	101
5	2	2.75	91	5	5	1	103	5	12	0.5	X

[a] X indicates that the inhaler was breathed but not assayed.

pledget. This represents a conventional adsorption situation; it is easy to appreciate the fact that the more surface area the pledget has the greater the surface area of the material exposed to the airflow and the greater the opportunity for volatilization. Thus a larger or more loosely packed pledget will cause a larger dose to emanate from an inhaler than a smaller or tightly packed pledget. It is convenient to make this type of inhaler if the volatile material itself is a liquid. It should also be pointed out that the doses produced from a surface type inhaler stay relatively high while the pledget charge is being depleted according to a zero-order scheme. This is reasonable when one visualizes that the volatile material has formed a multimolecular (as distinguished from a monomolecular) layer on the pledget surfaces; thus, even though molecules are stripped off, the surface area and hence the dose remain essentially unchanged. However, as some areas of the pledget are denuded, the total exposed surface area of the volatile material decreases, and so does the dose.

The second inhaler type may be termed a "solution" type, i.e., the volatile material is dissolved in a suitable nonvolatile solvent, and this solution is placed on the pledget. The situation may be taken as an example of the operation of Raoult's and Henry's laws, i.e., the vapor pressure of the components are proportional in some way to their concentrations expressed as mole fractions. To keep the vapor pressure contribution of the solvent low in order to enhance the vapor pressure of the solute, a solvent of very low vapor pressure is used as the vehicle. In this inhaler type the exposed surface area of the material does not change as the inhaler is used; what does change is the concentration of the volatile material in the solvent. Thus the dose gradually decreases according to a first-order scheme as the drug concentration decreases. Of course, the nature of the pledget and the inhaler body

TABLE VIII.—DOSE OBTAINED FROM PHLORONE (85 MG.)–CAMPHOR (20 MG.)–BENZYL SALICYLATE INHALERS

Inhaler No.	Time of Day	Breathing Interval, hr.	Dose, mcg./L. of Air	Inhaler No.	Time of Day	Breathing Interval, hr.	Dose, mcg./L. of Air	Inhaler No.	Time of Day	Breathing Interval, hr.	Dose, mcg./L. of Air
1	1	...	97	1	2	0.75	95	1	5	1	102
2	1	...	95	2	2	0.75	X[a]	2	5	1	X
3	1	...	91	3	2	0.75	91	3	5	1	X
4	1	...	90	4	2	0.75	X	4	5	1	98
5	1	...	85	5	2	0.75	96	5	5	1	X
1	1	1	93	1	2	0.75	X	1	6	...	98
2	1	1	86	2	2	0.75	80	2	6	...	100
3	1	1	82	3	2	0.75	X	3	6	...	93
4	1	1	91	4	2	0.75	82	4	6	...	95
5	1	1	88	5	2	0.75	X	5	6	...	90
1	1	3	87	1	2	0.75	87	1	9	...	99
2	1	3	85	2	2	0.75	X	2	9	...	94
3	1	3	83	3	2	0.75	85	3	9	...	89
4	1	3	87	4	2	0.75	X	4	9	...	95
5	1	3	89	5	2	0.75	86	5	9	...	91
1	1	1	93	1	5	...	X	1	9	0.75	103
2	1	1	83	2	5	...	86	2	9	0.75	X
3	1	1	91	3	5	...	X	3	9	0.75	94
4	1	1	84	4	5	...	X	4	9	0.75	X
5	1	1	83	5	5	...	87	5	9	0.75	99
1	2	...	80	1	5	1	X	1	9	1.5	X
2	2	...	80	2	5	1	X	2	9	1.5	85
3	2	...	74	3	5	1	100	3	9	1.5	X
4	2	...	81	4	5	1	X	4	9	1.5	95
5	2	...	83	5	5	1	X	5	9	1.5	X
1	2	1	X	1	5	1	91	1	12	...	100
2	2	1	91	2	5	1	X	2	12	...	X
3	2	1	X	3	5	1	X	3	12	...	99
4	2	1	90	4	5	1	93	4	12	...	X
5	2	1	X	5	5	1	X	5	12	...	94
1	2	1	99	1	5	1	X	1	12	7.5	X
2	2	1	X	2	5	1	86	2	12	7.5	93
3	2	1	86	3	5	1	X	3	12	7.5	X
4	2	1	X	4	5	1	X	4	12	7.5	95
5	2	1	95	5	5	1	89	5	12	7.5	X
1	2	2.75	X	1	5	1	X	1	12	0.5	104
2	2	2.75	88	2	5	1	X	2	12	0.5	X
3	2	2.75	X	3	5	1	100	3	12	0.5	95
4	2	2.75	89	4	5	1	X	4	12	0.5	X
5	2	2.75	X	5	5	1	X	5	12	0.5	100

[a] X indicates that the inhaler was breathed but not assayed.

exert some effect here also, because if the airflow through the inhaler and the pledget type do not permit volatilization of the material, insignificant, low doses will result. The phlorone inhaler was of the solution type because the volatile drug is a solid, and solids do not lend themselves to easy pledget charging procedures. The inhaler was designed to deliver in excess of 50 mcg./L. of air passing through. The original doses (when the charge is a full 85 mg.) were about 90 mcg./L. of air; after the equivalent of over 400 doses are delivered and the amount of phlorone drops to 50 mg., the doses were about 52 mcg./L. of air.

If an inhaler were part solution and part surface in nature, one would expect the dosage drop-off line to be steeper than the type exemplified in Fig. 4, yet not as steep as those of Figs. 3 or 5.

Further amplification and clarification of the "surface" and "solution" type classification concept of inhalers might be achieved by considering the existing analogy to chromatographic systems. The surface-type inhaler corresponds to adsorption chromatography wherein the material is initially adsorbed on a carrier, then desorbed by a passing stream of liquid or gas, as the case may be. The solution-type inhaler corresponds to partition chromatography in which material in a solvent is supported by some medium and then partitioned between its original solvent and a passing stream of gas or liquid and thus removed.

Another conclusion which is implicit in the data but somewhat submerged concerns the relationship of the volatile active ingredient to the solvent. An increase in dose should result when the active ingredient is dissolved in solvents which cause it to deviate more positively from Raoult's law. Thus, the less the solute-solvent interaction and the greater the solute-solute interaction, the more pronounced will be the tendency toward volatilization of the solute. Using

TABLE IX.—DOSE OBTAINED FROM PHLORONE (85 MG.)–CAMPHOR (30 MG.)–BENZYL SALICYLATE INHALERS

Inhaler No.	Time of Day	Breathing Interval, hr.	Dose, mcg./L. of Air	Inhaler No.	Time of Day	Breathing Interval, hr.	Dose, mcg./L. of Air	Inhaler No.	Time of Day	Breathing Interval, hr.	Dose, mcg./L. of Air
1	1	...	93	1	2	0.75	X[a]	1	5	1	X
2	1	...	90	2	2	0.75	89	2	5	1	105
3	1	...	88	3	2	0.75	X	3	5	1	X
4	1	...	83	4	2	0.75	88	4	5	1	X
5	1	...	79	5	2	0.75	X	5	5	1	107
1	1	1	95	1	2	0.75	86	1	6	...	95
2	1	1	88	2	2	0.75	X	2	6	...	91
3	1	1	87	3	2	0.75	85	3	6	...	92
4	1	1	83	4	2	0.75	X	4	6	...	89
5	1	1	77	5	2	0.75	85	5	6	...	94
1	1	3	89	1	2	0.75	X	1	9	...	90
2	1	3	90	2	2	0.75	86	2	9	...	101
3	1	3	86	3	2	0.75	X	3	9	...	89
4	1	3	84	4	2	0.75	83	4	9	...	95
5	1	3	80	5	2	0.75	X	5	9	...	98
1	1	1	88	1	5	...	X	1	9	0.75	X
2	1	1	90	2	5	...	X	2	9	0.75	102
3	1	1	90	3	5	...	90	3	9	0.75	X
4	1	1	84	4	5	...	X	4	9	0.75	101
5	1	1	79	5	5	...	X	5	9	0.75	X
1	2	...	86	1	5	1	91	1	9	1.5	93
2	2	...	80	2	5	1	X	2	9	1.5	X
3	2	...	82	3	5	1	X	3	9	1.5	95
4	2	...	80	4	5	1	95	4	9	1.5	X
5	2	...	81	5	5	1	X	5	9	1.5	91
1	2	1	94	1	5	1	X	1	12	...	X
2	2	1	X	2	5	1	93	2	12	...	98
3	2	1	91	3	5	1	X	3	12	...	X
4	2	1	X	4	5	1	X	4	12	...	94
5	2	1	93	5	5	1	94	5	12	...	X
1	2	1	X	1	5	1	X	1	12	7.5	96
2	2	1	84	2	5	1	X	2	12	7.5	X
3	2	1	X	3	5	1	91	3	12	7.5	104
4	2	1	91	4	5	1	X	4	12	7.5	X
5	2	1	X	5	5	1	X	5	12	7.5	100
1	2	2.75	92	1	5	1	105	1	12	0.5	X
2	2	2.75	X	2	5	1	X	2	12	0.5	98
3	2	2.75	92	3	5	1	X	3	12	0.5	X
4	2	2.75	X	4	5	1	96	4	12	0.5	94
5	2	2.75	92	5	5	1	X	5	12	0.5	X

[a] X indicates that the inhaler was breathed but not assayed.

TABLE X.—EFFECT OF TEMPERATURE ON LEVEL OF PHLORONE DOSAGE OF INHALERS FROM TABLES VIII AND IX[a]

Inhaler No.	Dose, mcg./L. of Air 25°C.	37°C.	Inhaler No.	Dose, mcg./L. of Air 25°C.	37°C.
VIII-1	95	165	IX-2	92	170
VIII-2	88	194	IX-3	90	159
VIII-3	90	170	IX-4	89	145
VIII-4	90	175	IX-5	89	165
VIII-5	90	152	IX-6	..	150
VIII-6	..	154	IX-7	..	153
VIII-1	95	147	IX-1	92	163
VIII-2	88	152	IX-2	92	165
VIII-3	90	141	IX-3	90	164
VIII-4	90	131	IX-4	89	170
VIII-5	90	138	IX-5	89	162
VIII-6	..	132	IX-6	..	156
IX-1	92	175	IX-7	..	143

[a] Breathing temperature = 25 and 37°. Data are averages of the appropriate figures from Tables VIII and IX.

relative solubility as a gauge of such interaction, one would expect greater doses of phlorone from dibutyl phthalate (in which it is less soluble) than from benzyl salicylate, at the same concentrations. This appears to be the case as comparable inhalers containing phlorone in dibutyl phthalate (50 mg./ml.) give doses of 86 mcg./L. (Table IV, group I), and in benzyl salicylate, 52 mcg./L. (Fig. 3).

Some comments on vapor pressure may be appropriate here. Although it might seem that the vapor pressure of the drug and additives would assume a position of primary importance, this does not appear to be the case. Vapor pressure values represent an equilibrium situation, whereas what is involved in the inhaler cases is a process controlled by factors affecting rates of volatilization. Now it is true of course that volatile materials usually have appreciable vapor pressures. However, it is not generally true that a compound with a vapor pressure value of, e.g., twice that of another compound will volatilize just twice as fast. Besides this fact, inhaler recovery times may be essentially zero, no equilibration time may be needed. Also, no dosage drops would be noted with the surface

TABLE XI.—DOSE OBTAINED FROM PHLORONE INHALERS

Dose No.	Time of Breathing Interval, Day	min.	Dose, mcg./L. of Air Inhaler No. 1	2	3	4	5	Dose No.	Time of Breathing Interval, Day	min.	Dose, mcg./L. of Air Inhaler No. 1	3	5
1	1	...	101	101	101	116	98	60	39	...	78	77	87
2	2	...	94	96	98	93	100	61	39	2	84	97	89
3	2	30	110	109	110	110	102	62	39	1	90	96	88
4	3	...	96	95	X[a]	X	104	63–76	39	2	X	X	X
5	3	40	X	X	102	90	X	77	39	1	91	79	81
6	3	45	103	X	96	X	103	78–97	39	2	X	X	X
7	3	120	X	105	X	98	X	98	39	18	63	63	69
8	4	...	99	102	100	100	95	99–116	39	2	X	X	X
9	4	40	X	X	99	X	X	117	39	1	72	69	69
10	4	30	101	X	X	97	X	118	39	5	75	61	70
11	4	30	X	103	X	X	101	119	39	5	77	65	67
12	24	...	84	79	87	93	90	120	39	98	60	53	57
13	24	5	88	84	90	95	92	121	39	4	57	59	64
14	25	...	75	75	85	85	89	122	51	...	X	X	X
15–23	25	3	X	X	X	X	X	123	51	2	87	98	89
24	25	13	82	81	81	75	81	124	51	2	89	95	91
25–33	25	3	X	X	X	X	X	125–131	51	1.5	X	X	X
34	25	3	75	77	74	70	69	132	51	2	94	81	82
35	28	...	73	76	77	89	77	133	51	2	82	87	87
36–38	28	3	X	X	X	X	X	134–140	51	1	X	X	X
39	28	6	94	98	97	96	91	141	51	29	98	77	74
40–51	28	3	X	X	X	X	X	142	51	2	81	79	84
52	28	24	79	80	79	80	81	143–148	51	1	X	X	X
53–58	28	3	X	X	X	X	X	149	51	27	96	65	64
59	28	1	87	79	77	72	83	150	51	2	75	81	76

[a] X indicates that the inhaler was breathed but not assayed.

type inhaler and no regular (i.e., linear with concentration) dosage drops would be noted with the "solution" type inhaler if the vapor pressure were the controlling factor.

Unfortunately (from the standpoint of not having a more straightforward system to analyze), equilibrium and rate concepts are inextricably intertwined in the present situation. This easily leads to the basically incorrect tendency to try to predict kinetic data from thermodynamic values. However, because vaporization is relatively unencumbered with exotic entropy and orientation factors, rates of volatilization are often qualitatively proportional to the equilibrium properties of the materials involved. For example, equimolar quantities of the following compounds, allowed to evaporate at room temperature under the same conditions, will complete the evaporation process in this order: ether, acetone, chloroform, carbon tetrachloride, ethyl acetate, water. This order corresponds to both the materials' vapor pressures and boiling points. To further becloud the cause-and-effect relationship, the very magnitude of the numbers is such that the partial vapor pressure of the phlorone increases proportionately with the mole fraction. The concentration of benzyl salicylate is 5.15 moles/L. in the solutions, whereas the phlorone concentrations are 0.08–0.63 moles/L. Thus, the situation takes the form of plotting X and Y when the relationship is $Y = X/K + X$; when K is much larger than X, X and Y are essentially proportional to each other, i.e., if one doubles, so does the other; when K is much smaller than X, Y may be virtually a constant through a whole range of X values.

Hence, while vapor pressure concepts should not be neglected entirely in inhaler development, it is the rates of volatilization which must be controlled or modified.