Factors Affecting Dose Variation in Meter Valves

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Abstract □ Dose variation in commercial meter valves appears to be within acceptable pharmaceutical limits. Changes in delivered dose weights were found to occur during container emptying due to formulation fractionation. A more serious problem results from failure of the meter chamber to fill uniformly when the container is almost empty (~15% remaining). Three valves were found to be superior to others in overcoming this problem. Storage position influenced drainback in meter valves, particularly at later stages of container emptying.

Keyphrases □ Aerosol meter valves—dosage weight variation □ Propellent, formulation effects—aerosol dosage weight □ Fractionation—aerosols □ GLC—analysis

The need for official standards for weight variation of doses obtained from aerosol meter valves has long been recognized. The Chemical Specialties Manufacturers Association is attempting to draw up safe and reasonable specifications. Although much data on meter valves have been generated by the pharmaceutical industry, little has been published. Notable exceptions to this lack of published data are found in articles by Porush *et al.* (1), Young *et al.* (2), Grim *et al.* (3), and Contractor *et al.* (4). These authors have emphasized the importance of uniformity in delivery from meter valves as indispensable in dependable pharmaceutical preparations. Limits of ±15% of the calculated dose have been suggested. However, no articles have addressed themselves to dose variations arising from such critical factors as formulation pressure, container emptying, long standing of containers between actuations, and valve design. Comparison between commercially available meter valves, using identical formulations and evaluation methods, was undertaken with the hope that data would be generated upon which reasonable standards for meter valve performance and dose variation could be based.

EXPERIMENTAL

Valves—Meter valves for use with pharmaceuticals are available in sizes of 200, 100, and 50 μl., the last being the most common. The meter valves employed in this study are listed in Table I. All valves studied, except valve R 50I, contained acetal resin[1] stems with rubber stem seals supported by stainless steel gaskets. The R 50I valve was similar but the stem was made of stainless steel. The resin has replaced stainless steel in many valve stems due to the lower cost and a greater flexibility in design. Valves R 50I-EC and S 50I-EC have an emptying cup to assist in complete product removal from the container. Valve V 50I-DA has such a design that the last traces of product drain into the valve.

Formulations—The same four formulations used in the previous study and listed in Table II, representing various types of products, were employed (4). Since the purpose of the study was to investigate factors affecting dose variation under various conditions, the formulations tested were kept as simple as possible, with no active ingredient in them.

Testing Procedures—Ten replicates of each valve and each formulation were used to provide data in the following areas:

1. Dose-to-dose variation at four levels of container emptying: initial, 10, 50, and 80%.
2. Maximum amount removable before dose became substandard and erratic.
3. Effect of storage position and time on dose.
4. Effect of formulation on dose uniformity.
5. Effect of container emptying on the ratio of formulation components.

The functionality of valves covering dose variation within and between valves has been presented in an earlier paper (4). The testing procedures and parameters measured were the same, except for the quantitative measurement of the ratio of propellent blends before and during container use. Gas chromatography utilizing new sampling procedures was used for the quantitative determination of propellent blends.

The instrument employed was an Aerograph (model A-700 Atuoprep) gas chromatograph with thermal conductivity detection. The column was of stainless steel, 6.09 m. × 0.95 cm. (20 ft. × 0.375 in.), containing 30% SE 30, 60–80-mesh diatomaceous earth.[2] The columns were conditioned at 150° for 24 hr. with a helium flow of 6 ml./min. Analysis was performed isothermally with column temperature at 55°, injector block temperature at 130°, and detector temperature at 190°. The carrier gas, helium, was at an inlet pressure of 50 p.s.i. and a flow rate of 200 ml./min., and the filament current was maintained at 150 ma. A Honeywell recorder (Electronic 15) was employed at a speed of 1.01 cm./min. (0.4 in./min.).

Sampling Technique—A 3.81-cm. (1.5-in.) 25G regular point hypodermic needle[3] was attached to the top of the stem of a 50-μl. valve, using a piece of polyethylene tubing as packing. The needle was carefully introduced into the injector block, and the valve was actuated by pressing the container against the injector block. A sample of about 50 μl. was thus injected through the needle. The pressurized container acted as a pressure syringe and delivered about a 50-μl. sample every time the valve was actuated. By comparing the ratio of the peak heights, proportions of components were calculated, because the volumes of samples were about and not exactly 50 μl. Initial sample composition served as a standard control for comparing subsequent sample compositions at various levels of container emptying.

RESULTS AND DISCUSSION

The mean dose delivered from each valve for each formulation at various levels of container emptying can be seen in Tables III and IV. Since the doses were measured in milligrams, there is a significant difference in dose between formulations due to the differences in densities of the various propellent and propellent–alcohol blends. Although the differences between the same size valves of different types and manufacturers were considerable, these differences are not of importance in determining the precision of

[1] Delrin, E. I. du Pont de Nemours, Wilmington, Del.

[2] Gas-Chrom P, Applied Science Laboratories, State College, Pa.

[3] Becton, Dickinson and Co., Rutherford, N. J.

Table I—Meter Valve Specifications[a]

Experimental Identification Number	Chamber Size, μl.	Actuation Position	Type of Stem	Container	Manufacturer
E 100U	100	Upright	Acetal resin	Glass vial[b]	Emson Res., Inc., Bridgeport, Conn.
E 50U	50	Upright	Acetal resin	Glass vial	Emson Res., Inc., Bridgeport, Conn.
E 50I	50	Inverted	Acetal resin	Glass vial	Emson Res., Inc., Bridgeport, Conn.
V 100U	100	Upright	Acetal resin	Glass vial	Valve Corp. of Am., Bridgeport, Conn.
V 50U	50	Upright	Acetal resin	Glass vial	Valve Corp. of Am., Bridgeport, Conn.
V 50I	50	Inverted	Acetal resin	Glass vial	Valve Corp. of Am., Bridgeport, Conn.
V 50I-DA	50	Inverted	Acetal resin	Glass vial	Valve Corp. of Am., Bridgeport, Conn.
R 50I	50	Inverted	Stainless stl.	Aluminum tb.[c]	Riker Labs., Northridge, Calif.
R 50I-EC	50	Inverted	Stainless stl.	Glass vial	Riker Labs., Northridge, Calif.
S 50I-EC	50	Inverted	Acetal resin	Glass vial	(Experimental Valve, English)

[a] Actuator buttons: Emson S-1, orifice 0.020 in Gasket: Buna rubber. [b] Plastic-coated round glass vial, model S-1409F1 (20 ml.), Wheaton Plasticote Corp., Mays Landing, N. J. [c] Aluminum tube, 2.2 × 5.79 cm. ($^7/_8$ × $2^9/_{32}$ in.), Emson Research, Inc., Bridgeport, Conn.

Table II—Composition of Test Formulations

Ingredients	% w/w I	II	III	IV
Ethanol (absolute)	0	0	50	0
Propellent 12[a]	50	75	25	0
Propellent 114[b]	50	25	25	0
Propellent C-318[c]	0	0	0	100
~ Pressure at 25° (77°F.), p.s.i.g.	53	67	13	29

[a] Dichlorodifluoromethane. [b] Dichlorotetrafluoroethane. [c] Octafluorocyclobutane.

each type of valve. They are, however, of great importance in terms of product development departments, because each formulation must be tailored to each specific valve, even though the valves are labeled to contain equal volumes (*i.e.*, 50 or 100 μl.).

The precision of meter valves is extremely good and would certainly compare favorably to other dosage forms when limited to a single formulation and a single level of container emptying. The precision exhibited by inverted valves is generally better than that of the upright valves.

It would appear from Tables III and IV that the precision was influenced by formulation. Formulation IV gave an unusually high level of precision, while Formulation III generally exhibited low precision. These results indicate possible container-emptying effects due to fractionation. Formulation IV, containing only propellent C 318, could not fractionate. On the other hand, Formulation III, containing propellents and alcohol with significantly different densities and vapor pressures, would be most prone to show fractionation effect. The result of this fractionation is proportionally higher vaporization of component with higher vapor pressure, thereby leaving the liquid phase gradually more and more concentrated in the component with lower vapor pressure as the level of container emptying increases. To confirm this container-emptying effect due to fractionation, Formulations I, II, and III were subjected to quantitative analysis, using gas chromatography. Figures 1 and 2 are the plots of data obtained by quantitative analysis of the liquid phase at various levels of container emptying. These figures confirm the fractionation effect.

Although container-emptying effects are not large, they are real and should not be ignored. Formulations that minimize these effects would appear to be preferable. Fractionation effects in themselves are not critical in regard to dose of active ingredient as the formulation is measured by volume in the metering chamber. Vaporization of the propellent into the headspace would tend to concentrate any active ingredient during container use. However, persons evaluating aerosols should be aware that weights will change in most formulations with container emptying. Even when

Table III—Mean Dose[a] Delivered, mg., from Meter Valves at Various Levels of Container Emptying

Level of Emptying	Type of Meter Valve E 100U	V 100U	V 50U	E 50U	E 50I	V 50I	R 50I	V 50I-DA	R 50I-EC	S 50I-EC
Formulation I										
Initial	165.4	134.0	69.5	74.5	68.0	69.0	71.0	73.0	68.3	87.6
10%	163.5	130.2	68.7	74.6	68.1	69.2	71.7	75.2	68.7	88.7
50%	163.0	130.2	68.9	73.2	68.5	69.7	72.5	76.2	69.6	91.3
80%	159.2	131.0	68.3	72.6	68.9	69.8	72.2	77.4	70.5	92.9
Total mean	162.8	131.3	68.9	73.3	68.3	69.4	71.8	76.1	69.3	90.1
Coeff. of variation, %	4.24	5.18	3.63	6.21	2.08	4.90	3.39	5.73	2.22	3.80
Formulation II										
Initial	168.6	123.1	65.9	75.5	65.4	65.8	70.9	75.4	69.7	89.4
10%	161.9	123.0	64.9	75.1	66.0	65.6	72.2	76.2	70.6	90.8
50%	156.0	122.1	64.2	74.0	68.0	67.4	73.0	77.3	71.6	92.9
80%	146.2	121.8	64.2	72.0	68.5	67.2	73.4	78.3	72.3	94.6
Total mean	158.2	122.5	64.8	74.2	66.9	66.5	71.6	76.7	71.0	91.9
Coeff. of variation, %	7.96	3.43	2.64	4.31	2.48	5.26	3.38	1.51	2.43	2.87
Formulation III										
Initial	89.1	74.4	39.8	38.2	38.4	41.0	46.4	43.4	40.1	43.3
10%	88.7	71.7	38.5	37.8	37.4	38.7	44.4	43.0	39.3	47.8
50%	79.1	67.7	37.8	35.9	37.3	37.9	43.9	41.8	37.8	46.9
80%	70.5	67.6	36.0	33.7	36.8	36.9	42.8	40.0	36.8	45.5
Total mean	81.8	70.4	38.0	36.4	37.5	38.9	44.1	42.0	38.5	47.1
Coeff. of variation, %	12.35	4.69	5.26	6.87	5.01	3.78	2.15	3.33	3.94	5.41

[a] Average of 40 values.

Table IV—Mean Dose[a] Delivered, mg., from Meter Valves at Various Levels of Container Emptying

Level of Emptying	Type of Meter Valve: E 50I	V 50I	V 50I-DA	R 50I-EC	S 50I-EC
	Formulation IV				
Initial	64.2	71.1	79.6	72.7	96.7
10%	64.1	70.7	79.2	73.0	97.7
50%	64.0	70.2	79.0	72.8	97.1
80%	63.9	70.1	79.4	72.8	97.6
Total mean	64.1	70.5	79.3	72.8	97.0
Coeff. of variation, %	1.5	1.73	1.28	1.61	1.42

[a] Average of 40 values.

Table V—Percent Remaining in Package after Dose Fell below Acceptable Limits[a]

Formulation	Type of Valve: E 100V	V 100U	E 50U	V 50U	E 50I	V 50I	R 50I	V 50I-DA	R 50I-EC	S 50I-EC
I	18	14	19	16	11	15	16	0.9	2.3	3.7
II	16	13	12	11	12	12	15	0.6	1.8	3.2
III	7	10	8	9	7	8	11	0.2	1.1	1.3
IV					8	11		0.7	2.3	3.9
Average	13.7	12.3	13.0	12.0	9.5	11.5	14.0	0.6	1.9	3.0

[a] Sudden decrease (>10%) in the weight of individual doses for two successive actuations.

Table VI—Comparison of Initial Dose after 16-hr. Storage with Doses Obtained at 45-min. Intervals[a]

Formulation	Valve Type: E 100U	V 100U	E 50U	V 40U
I Initial	164[b]/165[c]	129/134	75.4/74.5	70.1/69.5
80% *CE*	164/159	126/131	70.1/74.6	68.3/68.3
II Initial	173/169	125/123	79.4/75.5	66.3/65.9
80% *CE*	157/146	123/122	73.0/72.0	64.6/64.2
III Initial	91.0/89.1	74.1/74.4	42.9/38.2	40.3/39.8
80% *CE*	72.2/70.5	68.4/67.6	34.2/33.7	35.2/36.0

[a] Upright valves stored in upright position. [b] Initial dose after 16-hr. storage (average of 10 values). [c] Doses obtained at 45-min. intervals between actuations (average of 40 values).

Table VII—Comparison of Initial Dose after 16-hr. Storage with Doses Obtained at 45-min. Intervals (Inverted Valves)

Formulation	Valve Type: E 50I (Stored Upright)	V 50I (Stored Upright)	R 50I (Stored Inverted)	V 50I-DA (Stored Inverted)	R 50I-EC Upright	R 50I-EC Inverted	S 50I-EC Upright	S 50I-EC Inverted
I Initial	58.9[a]/68.0[b]	68.3/69.8	73.0/72.0	75.6/73.9	67.0/68.3	68.1/68.3	85.7/87.6	88.0/87.6
80% *CE*	27.8/68.7	34.7/69.0	73.3/71.2	78.3/79.4	69.9/70.5	70.5/70.5	70.0/92.9	91.3/92.9
II Initial	35.7/65.4	53.9/65.8	72.2/70.9	76.9/75.4	66.4/69.7	69.9/69.7	88.7/89.4	89.8/89.4
80% *CE*	18.0/68.5	19.1/67.2	72.8/70.4	79.9/78.2	70.9/72.3	72.6/72.3	89.3/94.6	94.1/94.6
III Initial	37.8/37.5	40.5/41.0	46.9/46.4	44.4/43.4	38.6/40.1	39.9/40.1	46.1/48.3	48.7/48.3
80% *CE*	35.7/36.8	35.1/36.9	43.3/41.8	40.9/40.0	35.2/36.8	38.0/36.8	42.0/45.5	45.1/45.5

[a] Initial dose after 16-hr. storage (average of 10 values). [b] Doses obtained at 45-min. intervals (average of 40 values).

Table VIII—Comparison of Initial Dose after 16-hr. Storage with Doses Obtained at 45-min. Intervals (Inverted Valves), Formulation IV

	Valve Type: E 50I		V 50I		V 50I-DA		R 50I-EC		S 50I-EC	
	Inverted	Upright	Inverted	Upright	Inverted	Upright	Inverted	Upright	Inverted	Upright
Initial	67.0[a]/64.2[b]	30.3/64.2	74.4/71.1	24.9/71.1	82.6/80.0	54.3/80.0	73.8/72.7	71.5/72.7	97.2/96.7	94.9/96.7
80% *CE*	65.2/63.9	23.9/63.9	71.5/70.0	14.4/70.0	79.5/79.0	10.9/79.0	73.7/72.8	71.7/72.8	98.3/97.6	94.0/97.6

[a] Initial dose after 16-hr. storage (average of 10 values). [b] Doses obtained at 45-min. intervals (average of 40 values).

these effects are included, individual doses fall well within ±15% of mean for most of the valves and formulations.

Although the weight variation of doses delivered from meter valves would appear in most cases to meet USP and NF weight variation standards for capsules and small weight tablets, other areas of concern do exist. One major problem with most meter valves is the determination of the point at which the dose falls below acceptable limits. Using the arbitrary end-point of two successive individual doses being at least 10% less than the previous dose, the percent remaining in the aerosol package with each type of valve was determined. These values are shown in Table V. The results, to say the least, are disturbing, with the exception of three valves (V 50I-DA, R 50I-EC, and S 50I-EC). A significant quantity remains in the container beyond the point where doses fall below acceptable limits. In most cases the patient is not able to determine either visually or audibly that any change in dose has occurred. Such a phenomenon is not or would not be tolerated in any other dosage form. Its acceptance in aerosols becomes particularly questionable when it is obvious that valves do exist that effectively eliminate the problem. The apparent formulation effect which indicates that Formulation III is better than I or II is only a result of product densities. Approximately the same number of doses remains in the container for all formulations tested. The end-point for the upright valves is a function of the length of the dip

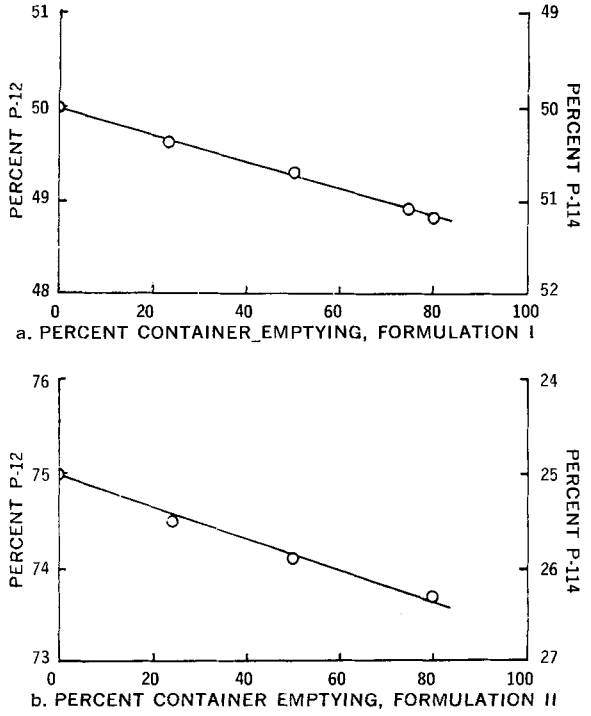

Figure 1—*Effect of container emptying on ratio of propellents 12/114.*

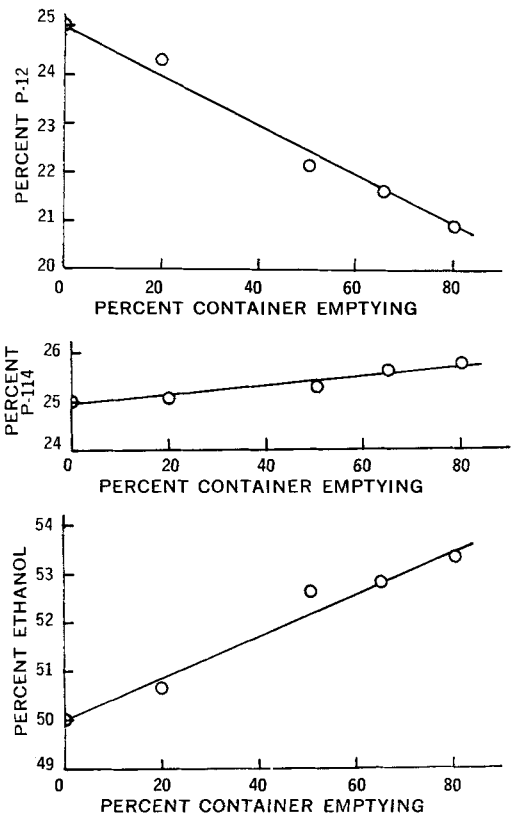

Figure 2—*Effect of container emptying on proportion of P-12/P-114/ethanol.*

tube and is generally more variable than that found in inverted valves.

The fact that initial doses from meter valves after a period of nonuse are often low has long been recognized. In many cases it was believed that the time necessary to cause a significant decrease in the weight delivered was longer than would ordinarily be encountered in practice. The data presented in Tables VI–VIII indicate that a problem does exist under ordinary use conditions for some valves. As can be seen in Table VI, no significant difference appears to exist with upright valves between the dose obtained after a 16-hr. storage and those obtained at 45-min. intervals. These data were collected from containers stored in the upright position. Observation of the bottles and dip tubes indicates that the liquid remains in the dip tube in contact with the bottom of the valve stem at all times, preventing drainback.

Inverted valves appear to exhibit a problem as can be seen in Table VII. Doses obtained from inverted valves after 16-hr. storage in the upright position showed a significant loss in weight, with the exception of only one valve (R 50I-EC). In addition, this loss of weight is even larger at later stages of container emptying, amounting to from one-third to one-half of the dose obtained from 45-min. actuations. Of equal importance is the fact that when inverted valves are stored in the inverted position, no significant differences occur, as can be seen from the data for valves R 50I, V 50I-DA, R 50I-EC, and S 50I-EC.

To verify the importance of storage position and eliminate any variations due to fractionation, valves E 50I, V 50I, V 50I-DA, R 50-I-EC, and S 50I-EC were studied in both upright and inverted storage conditions, using Formulation IV. The results of the study are shown in Table VIII. These data show conclusively that drainback does occur in inverted valves without efficient emptying cups and that this drainback is a function of storage position. Although the cause is not obvious, container emptying accentuates the drainback problem. Unfortunately, data were not collected at intermediate levels of container emptying in such a form to indicate when this effect first begins to occur. At least one manufacturer has designed an inverted valve, which effectively decreases drainback, by adding a chamber around the lower tank opening. At least one commercial product avoids the problem because packaging and labeling are designed so that containers are customarily stored in the inverted position. It would appear that all producers using inverted valves might well adopt this policy.

SUMMARY AND CONCLUSIONS

1. Container-emptying effects resulting from propellent fractionation and causing changes in the weights of doses delivered do occur in inhalation formulations.

2. A new simple technique is described to measure the extent of fractionation, using a gas chromatograph.

3. A significant decrease in dose weights at the latter stages of container emptying is a serious problem in metered aerosols. Three valves appear to be significantly superior to all others in minimizing variation of dose through the latter stages of container emptying.

4. Doses delivered from inverted meter valves after standing all night in an upright position are significantly lower than those delivered at 45-min. intervals. These effects are magnified at latter stages of container emptying. The problems can be solved by designing packaging and labeling so that containers with inverted valves are stored in an inverted position.

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