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Particle Size of Inhalation Aerosol Systems II: Uniformity of Delivery of Some Commercial Inhalation Aerosols

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Using controlled sampling conditions (described in Part I) an examination of the uniformity of delivery of some commercially available aerosols has been made. The uniformity of delivery is very high for most products intended solely for inhalation. One dual purpose aerosol was found extremely variable and it is concluded that needs of oral and nasal applications are not compatible.

INTRODUCTION

The use of inhalation aerosols for treatment of respiratory tract diseases presents a number of problems. One of the most important of these is the formulation of the system to produce a suitable size and size range of particles released in the aerosol cloud. It is also essential that the same weight of medicament having similar particle distributions must be delivered at each actuation. These characteristics however, can be modified by the co-ordination of the breathing cycle and actuation of the device by the patient (Palmes et al (1967; 1971)).

Methods of measurement of the size of the particles released has been discussed in Part I. The literature on formulation problems of inhalation aerosols is not extensive. Contractor and colleagues (1970) and Morén (1978) examined the effect of valve and actuator design on the dose delivered. Other workers (Bell, Brown & Glasby (1973); Chowhan and Amaro (1977)) investigated the dose collected in an impingement device in relation to the mass of drug delivered.

The purpose of this paper is to examine the uniformity of size distribution for a number of commercially available inhalation aerosols as determined by light scattering measurement.

APPARATUS

A Royco 225/508 particle size analyser unit as described in Part I was used. The pressurised aerosol units were actuated into the cabinet, mixed for 10 seconds and then sampled over a one minute period.

Table 1. Uniformity of Delivery of Some Inhalation Aerosols

Product	Mean Number of Particles Greater Than Stated Size (μm) for 10 Repeats					Mean Size	
	0.50	1.6	3.0	5.0	7.0	by no.	by wt.*
1	430220	78275	10361	1045	125	1.30	2.1
Standard Deviation	29208	6896	806	128	-		
2	310894	26283	1272	75	9	1.0	1.98
Standard Deviation	12368	1438	141	13	-		
3	527992	27927	19731	2486	434	0.84	2.02
Standard Deviation	21102	4970	1540	268	-		
4	113730	20044	3109	158	18	1.26	1.86
Standard Deviation	4513	924	203	20	-		
5	478813	88557	13745	2832	551	1.18	2.20
Standard Deviation	19560	4565	1013	297	-		
6	141728	58075	34166	14934	6035	1.35	26.73
Standard Deviation	23597	11413	6416	2667	-		
7	365619	53883	7948	619	43	1.20	1.76
Standard Deviation	15372	4102	853	95	-		
8	690952	11565	3049	467	64	1.24	1.54
Standard Deviation	2382	486	180	39	-		
9	172751	45667	3917	126	10	1.40	1.97
Standard Deviation	12293	3731	325	17	-		

* $\ln d_{gw} = \ln d_{gn} + 3\ln^2 \sigma_g$ (assumes a log normal distribution)

Table 2. Uniformity of Inhalation Aerosols

Product No.	Mean of % Coefficient Variance	Mean Variation of Delivery (±%)
1	8.8	4.1
2	9.4	4.4
3	10.1	4.7
4	6.8	3.2
5	6.8	3.1
6	18.3	8.6
7	9.5	4.4
8	5.6	2.2
9	9.3	4.3

EXPERIMENTAL AND RESULTS

When examining inhalation aerosols, not only must a size analysis be carried out but studies must also examine the effect of use on delivery and the effect of actuator on the spray characteristics.

Nine commercially available aerosol units were examined for uniformity of size distribution delivery.

The reproducibility of count each one product after ten actuations is quite notable (Tables 1 and 2). There is one exception, product 6; this result probably reflects the intended purpose of the product which is a dual purpose unit intended for nasal or upper respiratory tract treatments. It would be expected that such a product should have larger particles than one intended for treatment of mid-lung conditions. This product does have significantly larger particles than the other units tested but also has a much greater degree of variation. A possible explanation is that the large particles are obtained by aggregation of smaller particles and this leads to wide size variations.

Changes in the number of small particles will have little effect on the efficacy of the product because the total mass involved is small. However, significant changes in the larger size groups will cause considerable differences in delivery and deposition. An examination of the variations in delivery with confidence limits of 95% shows that in general the variation in delivery is ±4.3% but varies between ±2.2% and ±8.6% (Table 2). As previously stated product 6 is the only exception to a very close tolerance of delivery when assessed by number of particles delivered.

Batch to batch variations must be controlled within strict limits. Four batches of two of the products (units 8 and 9) were examined for uniformity of delivery. The results in Table 3 indicate that for these two products a good degree of reproducibility is achieved.

Table 3. Batch to Batch Variations of Delivery for Two Products

Product No.	Mean Number of Particles Greater than Stated Size (μm) for 10 Repeats					Mean Size (number)
	0.5	1.6	3.0	5.0	7.0	
8 (1)	600772	11598	3052	467	61	1.42
(2)	609721	16757	2035	63	5	1.16
(3)	580620	11085	3265	560	77	1.24
(4)	690957	11565	3049	467	64	1.25
9 (1)	171613	44741	3940	129	12	1.33
(2)	191725	48920	2512	42	3	1.40
(3)	187384	45007	882	53	7	1.31
(4)	172751	45667	3917	126	10	1.40
	% Coefficient of Variance					
8 (1)	4.1	4.0	6.8	7.0	-	5.7
(2)	8.2	6.4	4.7	17.0	-	9.1
(3)	6.2	6.8	7.4	11.0	-	7.8
(4)	1.9	4.2	5.9	8.3	-	5.6
9 (1)	7.4	8.0	9.7	16.8	-	10.5
(2)	6.7	5.9	15.0	16.1	-	10.9
(3)	5.2	10.5	9.8	20.0	-	11.4
(4)	7.1	8.2	8.3	13.4	-	9.3

Contractor et al (1970) investigated changes in the delivery of medicament as the containers became progressively emptier. In our studies we have found no change in the variation of size and delivery as the container was emptied (Table 4).

Actuator design was investigated by Morán (1978). He showed that design changes play an important rôle in the size of the particles produced. We investigated how minor alteration caused by actuator production variables might affect the distribution.

Five previously unused actuators were fitted in turn to one aerosol unit and actuated 10 times. It was found that there were no dectable changes in spray characteristics for these five units (Table 5).

Table 4. Uniformity of Delivery as the Containers are Emptied

Actuation No.	% Used	Mean Number of Particles Greater Than Stated Size (μm) for 10 Repeats					Mean Size	
		0.5	1.6	3.0	5.0	7.0	No.	wt.
5- 14	5	174833	42926	2047	47	4	1.36	1.77
45- 54	25	164490	40014	1922	48	4	1.31	1.77
95-104	50	170080	41391	1981	45	4	1.31	1.76
145-154	75	183619	48746	2397	52	4	1.34	1.79
185-194	95	190209	48907	2245	44	4	1.33	1.78

* 30 second interval allowed between actuations

Table 5. Effect of Different Actuators on Delivery

Product and Adapter No.	Mean Number of Particles Greater Than Stated Size (μm) for 10 Repeats					Mean Size	
	0.5	1.6	3.0	5.0	7.0	No.	wt.
9 (1)	169604	45417	2411	68	5	1.35	1.80
(2)	169865	45687	2259	45	2	1.35	1.80
(3)	182818	49457	2352	46	2	1.35	1.80
(4)	187616	51561	2497	47	2	1.36	1.81
(5)	192324	52845	2523	49	2	1.36	1.81

CONCLUSIONS

The overall picture of commercial inhalation aerosols is one of great reproducibility and uniformity of delivery. Only one of nine products showed any great variation and this one was a dual purpose unit. Actuator characteristics appear uniform and have little effect on the product delivery. The spray characteristics are consistent over the whole life of the device. Batch to batch variation is small.

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