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Tests for foreign particles in metered-dose aerosols

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A simple method for the determination of foreign particulate matter in metered-dose aerosols (MDA's) has been developed. The method compares favourably with a procedure currently used in pharmaceutical industry and has the advantage of providing information on container to container variation. A linear relationship between log particle count and particle size was found for a number of MDA's, although there was considerable product-to-product variation. On the basis of the results obtained in this study, commercially available MDA's would in general comply with a limit for foreign particles greater than 100 μm of not more than 150 particles per container with the sum of the mean count and twice the standard deviation not more than 200.

Metered-dose aerosols for oral inhalation (MDA's) are a widely used dosage form. Development of appropriate test methods to control these products presents problems, especially with regard to methods of sampling the MDA's and determining the particle size distribution of the active ingredient. One aspect of MDA testing which has received scant attention is the detection and quantitation of foreign particles. Foreign particles present in these products are typically fragments of aluminium, plastic and rubber which may be present in the MDA at the completion of the manufacturing process or generated by abrasion during activation of the metering valve. A proportion of the foreign particles included in a metered-dose delivered by an MDA will be deposited in the airways of a patient using this medication. These deposited particles have a potential to cause adverse reactions and it appears reasonable that the likelihood of future adverse reaction will be proportional to the numbers of foreign particles small enough (<10 μm) to be deposited in the lungs. A patient may use MDA's in the relief or control of symptoms for many years, so that there is a possibility that numbers of foreign particles in the non-ciliated airways of the lungs in the respiratory system will build up over a period of time. In addition excessive numbers of foreign particles in an MDA container could adversely affect the operation of the metering value, causing inaccuracies in the delivery of active substance per dose or possibly complete failure of the valve mechanism. Control on the numbers of foreign particles present in doses from MDA's therefore seems desirable in the interests of user safety.

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There are a number of difficulties associated with the development of a requirement limiting the number of foreign particles in MDA's. The analytical method must use a sampling system which collects the MDA discharge with reasonable efficiency, so that significant numbers of foreign particles are not lost to the system. The design and operation of the collection system must be such that extraneous particles are not introduced. Apparatus should preferably be cheap and simple in design with a detection system which will permit quantitation of all types of particle likely to be encountered. Because of the probable involvement of the metering valve in the generation of particles, with the possibility of increasing numbers of particles being formed after many valve activations, it seems appropriate for the sampling procedure to require the entire contents of an MDA container to be sampled through the metering valve. Any limit for particulate matter must however take into account the level of cleanliness that is realistically achievable by manufacturing industry. While the objective of the method is to control the number of small foreign particles (<10 μm) reaching the patient, the size range of the particles to be detected will depend on the detection method used. Some instrumental methods require large numbers of counting events for adequate precision, implying the use of a relatively small particle size, possibly in the range 0·5 μm–10 μm.

Considerable difficulties may be encountered when using these instrumental techniques owing to the wide size range of foreign particles encountered in these products. In particular, the frequent blocking of cells or apertures may occur when small particles are being counted. Use of a larger particle

size might be more appropriate if microscopy is used. Finally, some assessment of the quality of a batch of MDA's can be obtained if more than one container is sampled. Measurement of container to container variation in particulate contamination, possibly using a measure such as standard deviation, gives some insight into the chance of a badly contaminated MDA container being available for use. The value of this information must be weighed against the tedium of procedures which involve the emptying of MDA containers by successive activation of the metering valves and the sizing and counting of particles by microscopy.

Initial specification of a method

The initial procedure proposed for the Australian test for foreign particles in MDA's required a sample of ten MDA containers each of which was individually sampled by evacuating its contents into a 100 ml conical filter flask with an internally-ground neck and fitted with a stainless steel adapter (Fig. 1). The lower end of the delivery tube was approximately 2 cm above the floor of the flask. After evacuation of an MDA container, the contents of the flask were transferred to a membrane holder and filtered through a 47 mm diameter membrane of nominal pore size not greater than 5 μm. The number of particles present on the membrane of length greater than 100 μm along their longest axis were then counted microscopically. Filtered, particle-free solvents were used in the transfer operations and the membrane was checked for absence of particles prior to filtration. A problem arose with this method (Method A) because of leakage of the aerosol from the adapter during activation of the valve. The leakage could be reduced by use of an adapter into which the aerosol valve fitted closely, but this led to particle generation by abrasion of the valve stem and housing on the wall of the adapter. In addition, because various brands of MDA products had slightly different dimensions, a range of adapter sizes was necessary. It was therefore necessary to modify the collection method.

Comparison of different collection methods

The procedure described above was compared with two alternative collection systems. In both alternatives, the MDA was fitted with a mouthpiece, so that the mode of discharge bore more resemblance to normal usage. The first alternative method (Method B) consisted of evacuating the MDA directly into a 500 ml conical flask. The flask was held horizontally and the MDA actuated with the end of the mouthpiece on the central axis of the neck and 1 cm away from the lip of the neck of the flask. After every twenty activations of the MDA valve, the contents of the flask were transferred to the membrane filter by rinsing with 10 ml of filtered ethanol. In the second alternative (Method C), the sample collector consisted of a 300 ml modified Millipore filter funnel and with a 3 cm diameter hole in the wall near the top of the dome (Fig. 2). The open end of the vessel was mounted on a 47 mm diameter stainless steel filter assembly (Millipore) fitted to a 500 ml filter flask. Suction was applied using a rotary pump. The MDA was actuated with the end of the mouthpiece inside the hole near the dome, and the inner surfaces of the

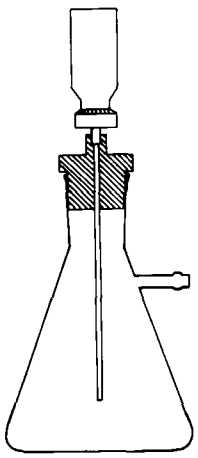

FIG. 1. Collection apparatus used for Method A.

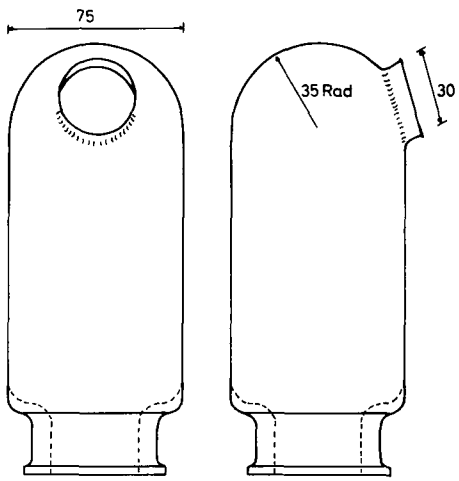

FIG. 2. Collection Apparatus used for Method C.

sample collector were rinsed with ethanol to remove any deposited particles. The three collection procedures were compared using ten containers of a commercially available MDA. In order to reduce the effect of container to container variation, each container was sampled by all three methods. Sequences of twenty doses from each container were sampled alternately by each method until 180 doses from each 200 dose container had been collected. The number of doses collected by each method was then reduced to four and the sequence continued until the container was emptied. The inside surfaces of the collection vessels were rinsed with 10 ml ethanol after each sequence of twenty doses had been delivered. The numbers of particles detected using Method B were found to be significantly lower (paired t-test, $P > 0{\cdot}001$) than the counts obtained using the other methods. The lower count with this method may have been due, in part, to the tendency for the aerosol to rebound from the walls of the collection vessel and escape. In addition, particles of both the active substance and foreign material adhered to the inner surface of the collecting flask and proved difficult to remove during the rinsing step. The other methods gave comparable results and it was decided to carry out further work with Method C in view of the applicability of the apparatus to all MDA's.

Survey of available products

A number of commercially available MDA's were tested for particulate contamination using Method C. For the purposes of this study, six 0·45 μm collection filters (Millipore No. FHLP 01300) were assembled on a manifold (Millipore No. XX2504758), connected to a rotary pump capable of providing a pressure differential of about 750 mm Hg.

Twenty doses from each container were expelled into a sample chamber while the apparatus was under vacuum. The inner walls of the sampling apparatus were washed with 10 ml of filtered ethanol and the process was repeated until the container was empty. The membrane filters were dried under reduced pressure and covered with Millipore cover slips. The entire filtering surface of the membrane, which was illuminated by reflected light incident at 45°, was examined microscopically using a micrometer eye piece and a magnification of 100×. Ten cans from each sample were processed in this manner.

The study was carried out in two stages. In the first, the number of particles in ten size ranges were determined for six MDA products. In three cases, two samples of ten containers were tested. In the second part of the investigation the results obtained for samples of nine batches of a commercial MDA product using Method C were compared with the results obtained by the manufacturer. The method used by the manufacturer also employed microscopy to determine the number of particles greater than 100 μm but utilized a collection procedure in which the MDA was not fitted with a mouthpiece. For each sample, ten MDA's were discharged through adaptors and the aerosol passed through a delivery tube and into a solvent. The suspension of foreign particles was transferred to a membrane filter, and the total count of particles greater than 100 μm per 100 doses obtained. The manufacturer's method, therefore, provides a mean particle count for ten containers but does not give an estimate of container-to-container variation.

RESULTS AND DISCUSSION

The particles observed were predominately metal, rubber and plastic. The products examined were manufactured using either the 'through-the-valve pressure filling system' or the 'cold fill' process and the results obtained showed, in general, that foreign particulate contamination was higher for the former process. The 'cold fill' products contained predominantly metallic particles whereas the 'through-the-valve pressure filled' products contained both rubber and metal particles. Long fibrous plastic particles were obtained from the mouthpieces of both types of aerosol and large particles of plastic liner were observed in some products. Dust and other fibres were observed in some containers and glass particles were observed in sample D. A batch of sample D that was six months beyond its expiry date gave a high particle count. In this case, most of the particles were of rubber and may possibly have been associated with perishing of the rubber components in the metering valve.

The results of the measurements on particle size distribution are given in Table 1 and Fig. 3. The nature of the particle size distribution appeared to vary from product to product. With Brands B and D, there appears to be a linear relationship between log particle count and particle size over the range of sizes considered. A similar log-normal relationship was observed with Brand E over the range 50–200 μm, but a log-log plot gave better linearity over the range 25–125 μm. In the other products, plots of log particle count against particle size showed a change of slope after either 75 or 100 μm (Fig. 3). Two of

Table 1. Counts of foreign particles in metered-dose aerosol products.

	Size range (μm)*										
Product	25–49	50–74	75–99	100–124	125–149	150–174	175–199	200–400	> 400	Total > 100	Total > 100** per dose
A (1)	92	66	46	22	10	3	1	1	2	38	0·08
	(10)	(9)	(11)	(6)	(3)	(2)	(1)	(1)	(2)	(7)	(450)
A (2)	96	66	49	23	11	3	2	1	2	43	0·10
	(11)	(8)	(7)	(7)	(2)	(2)	(2)	(1)	(2)	(7)	(446)
B (1)	592	256	99	59	19	9	4	3	2	96	0·38
	(77)	(39)	(26)	(8)	(4)	(2)	(2)	(2)	(1)	(11)	(252)
B (2)	555	257	116	65	19	10	4	4	3	105	0·40
	(90)	(56)	(34)	(9)	(7)	(3)	(2)	(2)	(2)	(7)	(265)
C (1)	58	24	14	8	1	1	<1	1	1	11	0·03
	(7)	(5)	(3)	(2)	(1)	(1)	(1)	(1)	(1)	(2)	(334)
C (2)	57	27	14	8	1	<1	<1	1	2	13	0·04
	(11)	(5)	(5)	(3)	(1)	—	—	(2)	(2)	(3)	(322)
D	868	369	164	52	20	8	5	4	1	91	0·28
	(50)	(41)	(28)	(8)	(3)	(2)	(1)	(1)	(1)	(8)	(324)
E	689	214	124	79	51	26	14	7	2	178	0·63
	(62)	(29)	(17)	(12)	(16)	(4)	(3)	(1)	(2)	(31)	(282)
F (1)	426	216	102	60	20	9	3	4	2	98	0·40
	(50)	(23)	(19)	(9)	(4)	(2)	(1)	(2)	(1)	(11)	(243)
F (2)	414	214	114	60	27	11	7	3	2	110	0·45
	(27)	(24)	(25)	(8)	(4)	(2)	(1)	(2)	(1)	(10)	(246)
D (expired)	953	529	234	87	27	12	6	3	1	136	0·40
	(41)	(39)	(32)	(9)	(6)	(2)	(2)	(1)	(1)	(11)	(337)

Notes:
All results are the mean of measurements on ten separate MDA containers with the exception of those for Brand F, sample 1, which were obtained using seven containers.
* Standard deviation is given in parentheses below each mean particle count.
** The mean total number of doses is given in parentheses below each value of counts per dose of particles > 100 μm.

these MDA's (A and C) had low particle counts and the change of slope might be related to the very small number of particles at sizes greater than 100 μm. The predominantly log-normal relationship found between particle count and particle size is in contrast to the power law relationships found for atmospheric particulates by Cadle (1965) and for foreign particles in large volume parenterals by Vessey & Kendall (1966), Kendall & Peters (1968) and Blanchard et al (1976, 1977).

The results from the second part of the study are given in Table 2. Similar results were obtained by each method, and there is no significant difference between the results on the basis of a paired *t*-test ($P > 0{\cdot}30$). The batch-to-batch variation in particle count obtained by Method C (with mouthpiece attached to the container) was significantly less at the 95 per cent level than that found using the manufacturer's method (F-test).

The container to container variation in counts of particles greater than 100 μm was narrower than the distribution typically found in containers of large volume parenterals (Kendall 1969). The samples tested, with one exception, would have complied with the limit $x + 2s < 200$; $x < 150$ where x is the mean count (ten containers) of particles greater than 100 μm and s is the standard deviation.

Single-point criteria of the sort used in this study are subject to criticism on the basis that the particles counted as exceeding a given diameter or other

Table 2. Comparison of method B with a manufacturer's method number of particles per 100 metered-doses > 100 μm.

Sample	Method B	Manufacturer's method	Difference
1	24 (8·9)	13	11
2	28 (6·9)	28	0
3	23 (4·7)	16	7
4	41 (17·2)	20	21
5	43 (19·4)	52	−9
6	35 (7·3)	52	−17
7	30 (6·5)	14	16
8	38 (2·6)	47	−9
9	39 (5·1)	31	8
Mean	33·4	30·3	3·1
s.d.	7·4	16·2	

Notes:
(1) Standard deviations for the ten individual determinations for method B are given in parentheses after the mean values.
(2) The results from the manufacturer's method refer to counts on the pooled particles from ten containers.

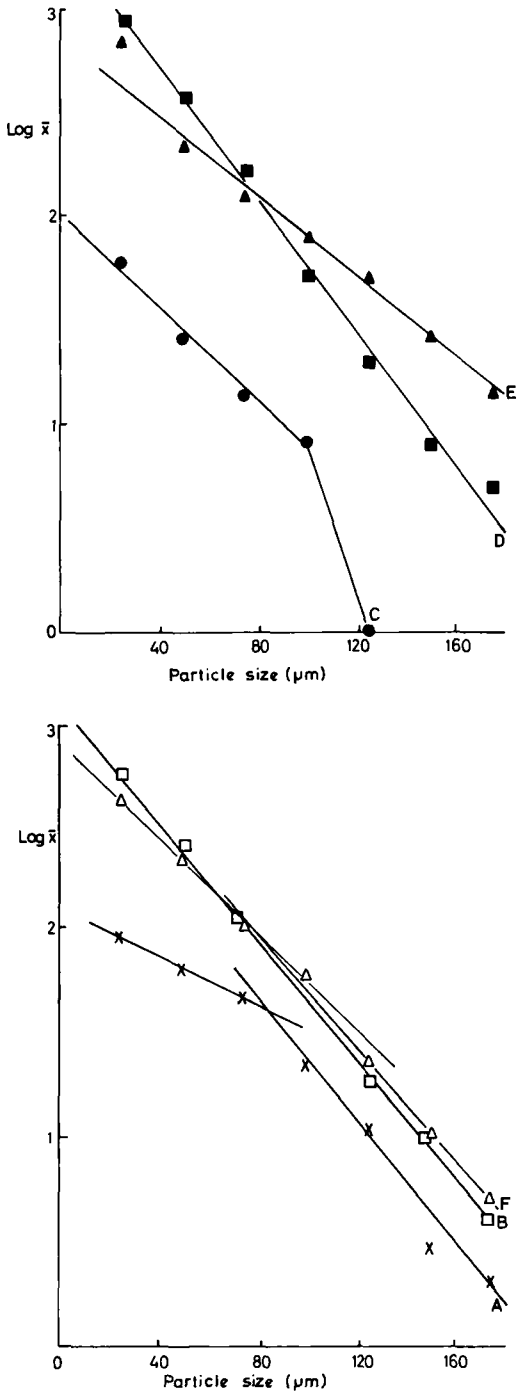

FIG. 3. Particle count – particle size relationships obtained for foreign particles from six brands of MDA.

dimension are not necessarily indicative of the number of particles in another size range. This shortcoming is illustrated by the change in slope observed in the log count-particle size relationship for products A, C and F at a particle size of about 100 μm. A single-point specification may be of limited utility as a control on the numbers of particles with appreciably larger or smaller dimensions than the value included in the specification. This limitation is also apparent from consideration of the results for the out-dated sample of product D, which would comply with a specification of not more than 150 particles greater than 100 μm, but contained large numbers of smaller particles. Use of a two point specification would give better assurance of low contamination in MDA products but is not realistic with currently available methodology because of the tedium, and expense of the counting procedure. A single-point specification seems at present to be a reasonable compromise between assurance of product quality, cost and speed of testing.

The method proposed for use in the testing of foreign particulate matter in MDA's has been shown to be applicable to a range of commercially available products. The method compares favourably with a method currently used by industry in which MDA's are discharged without the mouthpiece being fitted. By using the method, further information regarding the effectiveness of the manufacturer's quality assurance procedures can be obtained by consideration of the degree of individual can variation. Introduction of a test and requirement for MDA products of the type described is considered to be a desirable first stage in the provision of suitable quality assurance with respect to specifications for particulate contamination in the finished products. Introduction of more comprehensive test procedures and specifications must await the introduction of faster and more closely defined methods of analysis.

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