ELSEVIER

International Journal of Pharmaceutics 173 (1998) 93–102

international journal of pharmaceutics

Effect of formulation factors on the observed bounce in cascade impactors used to measure the spray particle size of metered dose inhalers

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Received 27 February 1998; received in revised form 17 June 1998; accepted 25 June 1998

Abstract

This study was conducted to investigate the extent of particle reentrainment, or bounce, in cascade impactors used to measure the size of the spray from single and multiple doses of metered dose inhalers (MDIs), and to determine the effect of some common formulation properties on the observed bounce. MDIs were formulated as suspensions or solutions, with varying levels of surfactant. These were fired into two impactors (the Andersen Sampler Mark II and the Marple-Miller model 150), the collection surfaces of which were uncoated or coated with silicone oil or glycerin. The amount of drug from a formulation collected on each stage was determined and comparison was made between results with coated and uncoated stages. Efficacy of the coating for eliminating bounce was demonstrated by comparing single shots with multiple shots. Different ways of describing bounce effects offer varying indications of its significance. The suspension formulations (containing surfactant) all showed evidence of bounce, but solution formulations showed little or none. Silicone oil and glycerin were equally effective in eliminating bounce. Results with impactors of two different designs were similar. Particle bounce was shown to occur with a variety of formulations when impactor stages are not coated.

Keywords: Aerosol; Size; Metered dose inhaler; Cascade impactor; Bounce

1. Introduction

Cascade impactors are instruments used to measure the size of gas-borne particles in the micrometer size range. Instruments have been

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0378-5173/98/$ - see front matter
PII S0378-5173(98)00217-8

Table 1
Properties of formulations tested

	Code	Albuterol (% w/w)	Oleic acid (%)	Ethanol (%)	Propellant (%)
Suspension, low surfactant (I and II)	LI	0.141	0.1	—	28/P11
	LII				71.8/P12
Suspension, high surfactant	H	0.169[a]	0.5	1.0	98.3/blend[b]
Solution, no surfactant	N	0.141	—	1.0	98.3/blend[b]
Solution, surfactant	S	0.141	0.5	1.0	98.3/blend[b]
Proventil®	P	0.141	?	—	P11, P12

[a]Albuterol sulfate, equivalent to 0.142% Albuterol base.
[b]Blend composition is 25% P11, 25% P114, 50% P12. P11 is dichlorofluoromethane, P12 is dichlorodifluoromethane, P114 is diclorotetraflouroethane.

available for many years, and are widely used in atmospheric and environmental studies. The instruments measure size by collecting, by the mechanism of inertial impaction, successively smaller particles on a series of collection surfaces. Guidelines for operation (e.g. Moss and Kenoyer, 1986) usually include recommendations for coating collection surfaces to control particle bounce.

Bounce is the term applied to the phenomenon of reentrainment in the moving air stream of a particle that had previously been deposited on a collection surface, and was recognized by the designer of the first cascade impactor (May, 1945). The likelihood of a particular particle bouncing depends on a range of variables, including the hardness and surface characteristics of the particle, the velocity of the air stream in the impactor nozzles, and the texture of the impaction surface (John, 1995). The end result is that some particles of a given size finally end up on a collection stage whose cut point is smaller than the size corresponding to those particles, thus causing errors in the reported size distribution. Because some, but not all, particles are treated as though they were smaller than they truly are, the distribution becomes wider and is shifted towards the smaller end (Esmen and Lee, 1980).

The recommendations for controlling bounce were developed primarily to address the problem of stage overloading, which occurs when so much material has deposited on a collection surface that it becomes unable to retain all of the incoming particles, and some 'falls off' into the air stream. Pharmaceutical applications for measuring the size of MDIs are somewhat different from the more usual applications in air monitoring studies because the stage loadings are ordinarily quite low, and the more popular suspension-based formulations all have a significant amount of nonvolatile liquid in them, which might be supposed to act as an adherent when the particles contact the collecting surfaces. Probably for this reason, not much attention has been given to the presence of bounce in cascade impactor measurements on MDIs. However, recent studies (Graham et al., 1995; Nasr and Allgire, 1995) on the effects of measuring single shots have shown a difference in the reported size related to the number of shots fired into the impactor.

This study was undertaken to determine the presence and possible effect of bounce on cascade impactor measurements, using a formulation range sufficient to encompass many marketed products and formulations in development.

2. Materials

Two impactors were evaluated; the Andersen Sampler Mark II (Andersen-Graseby, Smyrna, GA) and the Marple-Miller Impactor model 150 (MMI) (MSP, Minneapolis, MN). The stainless steel plates in the AI were roughened with fine abrasive prior to use, to facilitate wetting of the surface by the coating materials.

A variety of experimental formulations were tested, all based on albuterol or albuterol sulfate. Solution- and suspension-based formulations con-

Table 2
Mean albuterol recovery (μg per shot basis) in single spray content and particle size determinations

Experiment	Andersen impactor		Marple-Miller impactor	
	n	Albuterol recovered (μg/puff)	*n*	Albuterol recovered (μg/puff)
LI, single spray content	60	78	24	73
One puff	4	79	4	82
Ten puffs	2	71	2	91
LII, single spray content	20	66	24	72
One puff	3	83	3	86
Ten puffs	2	84	2	76
H, single spray content	100	59	52	57
One puff	10	62	8	60
Ten puffs	8	64	6	64
S, single spray content	88	77	58	76
One puff	7	75	9	69
Ten puffs	7	74	5	76
N, single spray content	24	58	24	58
One puff	4	55	4	57
Ten puffs	3	66	2	66

n indicates the number of replicates.

taining both low (or no) and high levels of surfactant were tested, along with a commercial product as reference. The composition of the formulations is described in Table 1. All except the commercial formulation were prepared in small quantities of a few units, and stability of the formulations was not a criterion. Generally, the measurements were conducted on one coating/no coating condition, and repeated for the second coating some time later. However, the low surfactant suspension formulation proved to be unstable over the nine months in which data were gathered. The size was stable over short periods of time between the uncoated and coated tests with a single coating, so results for this formulation are reported as though there were separate formulations for each coating.

3. Methods

Experimental procedures have been described in detail (Nasr et al., 1997). In summary, prior to each measurement, the stages were thoroughly cleaned with water and solvents. Stages were either left uncoated, or were coated with glycerin, or with silicone oil. In the case of glycerin coating, a few drops of a solution of 95% glycerin in ethanol were placed in the center of the collecting surface. The liquid spread easily over the surface to form a uniform coating, and was then allowed to air dry for a few minutes to evaporate ethanol. Silicone oil (Cling Surface, ITW Fluid Products Group, St. Louis, MO) was applied by directing the spray from a pressurized can onto the collecting surface for a few seconds.

For each experiment in the series, a sample vial was primed by actuating to waste, then the valve stem cleaned. Two or five unit sprays were collected using the same initially clean actuator, which was not cleaned in the course of a single measurement. The vial was then actuated into the impactor for a single shot, then an additional two to five units sprays were collected. The collection stages were quantitatively washed with buffered methanol/water solution, and the amount of drug recovered was determined by HPLC, using a coulometric electrochemical detector (Nasr and Allgire, 1995). Ten-shot measurements differed only in the number of shots fired into the impactor and the quantities of dilution solvent, with a pause of 10 s after each shot. Table 2 shows recovery for all of the formulations except Proventil, which previously has been reported (Nasr et al., 1997).

Table 3
Single shot size measurement results with Andersen Sampler

	n	MMAD (μm)	GSD	Mass <4.7 μm (μg)	Percent <4.7 μm	fp[a] (μm)	Mass $<$ fp(μg)	Percent $<$ fp
Suspension, low surfactant, glycerin series: code LI								
No coat	2	1.90 (0.19)	1.90 (0.07)	41.1 (0.7)	91.2 (1.6)	1.1	9.3 (4.4)	20.1 (6.5)
Glycerin	1	2.08	1.88	35.3	89.2		5.9	14.8
Suspension, low surfactant, silicone series: code LII								
No coat	2	3.99 (0.20)	2.26 (0.02)	19.5 (0.4)	55.5 (4.8)	1.1	2.4 (0.1)	6.9 (0.8)
Silicone	2	4.35 (0.11)	2.05 (0.04)	22.6 (0.5)	51.6 (1.6)		1.3 (0.1)	2.9 (0.3)
Suspension, high surfactant: code H								
No coat	6	3.31 (0.16)	1.63 (0.04)	25.8 (5.5)	75.9 (4.2)	2.1	4.7 (0.9)	14.1 (2.8)
Glycerin	2	3.59 (0.13)	1.55 (0.03)	28.3 (2.1)	75.8 (3.7)		3.0 (0.1)	7.8 (0.5)
Silicone	2	3.47 (0.13)	1.60 (0.02)	20.6 (0.18)	74.8 (3.3)		3.7 (0.4)	13.3 (0.8)
Solution, with surfactant: code S								
No coat	3	2.10 (0.08)	1.81 (0.06)	59.4 (8.4)	91.4 (2.3)	1.1	12.3 (3.5)	18.9 (4.6)
Glycerin	2	2.33 (0.01)	1.78 (0.01)	51.8 (4.7)	89.2 (0.1)		9.1 (1.0)	15.7 (3.0)
Silicone	2	2.23 (0.15)	1.76 (0.2)	55.1 (6.3)	90.5 (1.5)		6.5 (4.6)	11.0 (8.6)
Solution, no surfactant: code N								
No coat	2	1.45 (0.21)	2.09 (0.08)	34.5 (5.3)	92.7 (4.5)	0.65	7.6 (1.3)	20.2 (1.6)
Glycerin	2	1.52 (0.04)	2.20 (0.18)	33.1 (9.8)	92.2 (1.5)		7.0 (1.1)	19.8 (2.3)
Proventil®: code P								
No coat	4	1.93 (0.25)	1.80 (0.16)	34.9 (2.5)	93.1 (1.4)	1.1	8.0 (2.4)	21.4 (6.6)
Glycerin	2	2.32 (0.17)	1.62 (0.11)	35.8 (0.6)	89.4 (8.1)		2.2 (0.1)	5.4 (0.3)
Silicone	2	2.35 (0.16)	1.72 (0.09)	32.9 (1.9)	82.1 (16)		2.6 (0.1)	6.5 (1.2)

Values are given as mean (standard error).
n indicates the number of replicate experiments.
[a] Fine point (fp): the cut-size of the stage corresponding approximately to the smallest 10% of sample.

4. Results and discussion

Several measures of the effects on the size distribution between coated and uncoated conditions were compiled.

4.1. Summary parameters

For each data set the mass median aerodynamic diameter (MMAD) and the geometric standard deviation (GSD) were determined by fitting data to a lognormal distribution by means of linear regression of probit values to logarithm of aerodynamic diameter (Nasr, 1993; Nasr and Allgire, 1995) For the AI, the mass and percentage of total sample mass recovered from the impactor that was smaller than 4.7 μm are tabulated. For the MMI, corresponding data are recorded for material smaller than 5 μm. This value was used because it is one of the commonly used defining points for the so-called 'respirable mass' or 'respirable fraction' (Adjei et al., 1996); these terms are still commonly used to describe MDI size properties, despite being of limited descriptive capability for size distributions. In addition to the above parameters, the mass and percentage values were determined for material smaller than a second size, designated for ease in discussion as the 'fine point'. The fine point was selected as the size of the stage below which approximately 5–10% of the cumulative mass was collected on the coated stages, and was not the same for all formulations due to their inherent size differences. Values of MMAD, GSD, and mass and percentages smaller than the indicated sizes are recorded in Table 3 for data obtained from single shot determinations with the AI and in Table 4 for data from the MMI. Because of the small number of replicates at each condition, the standard error rather than the standard deviation is tabulated for each

Table 4
Single shot size measurement results with Marple-Miller impactor

	n	MMAD (μm)	GSD	Mass < 5 μm (μg)	Percent < 5 μm	fp[a] (μm)	Mass < fp (μg)	Percent < fp
Suspension, low surfactant, glycerin series: code LI								
No coat	2	2.66 (0.12)	2.85 (0.02)	28.3 (5.1)	57.6 (10.4)	1.25	22.3 (7.5)	40.2 (22.6)
Glycerin	1	3.69	2.16	23.3	65.5		2.3	8.0
Suspension, low surfactant, silicone series: code LII								
No coat	2	3.65 (0.54)	2.56 (0.21)	21.0 (2.6)	62.6 (4.9)	2.5	12.7 (3.1)	39.2 (5.6)
Silicone	2	5.50 (0.49)	2.31 (0.13)	20.5 (0.4)	45.9 (5.7)		7.8 (0.4)	17.6 (3.4)
Suspension, high surfactant: code H								
No coat	6	3.34 (0.45)	1.69 (0.13)	20.7 (6.0)	73.2 (4.4)	2.5	7.8 (1.6)	26.8 (5.1)
Glycerin	2	3.72 (0.04)	1.78 (0.15)	23.2 (1.6)	71.5 (1.3)		6.6 (0.4)	20.6 (2.0)
Silicone	2	3.75 (0.03)	1.63 (0.0)	20.6 (1.4)	71.8 (0.6)		6.4 (0.0)	21.1 (0.4)
Solution, with surfactant: code S								
No coat	3	2.30 (0.09)	1.82 (0.07)	56.0 (6.2)	91.1 (1.7)	1.25	2.1 (0.3)	13.4 (2.0)
Glycerin	2	2.37 (0.01)	1.84 (0.07)	53.3 (4.6)	89.4 (1.7)		2.2 (0.1)	15.2 (1.2)
Silicone	2	2.23 (0.10)	2.16 (0.08)	41.3 (1.6)	84.5 (3.0)		2.6 (0.3)	19.9 (0.8)
Solution, no surfactant: code N								
No coat	2	1.42 (0.04)	2.02 (0.01)	37.6 (0.8)	96.0 (0.6)	0.62	5.8 (0.5)	14.8 (1.1)
Glycerin	2	1.58 (0.25)	2.23 (0.20)	34.9 (8.9)	92.2 (1.6)		4.5 (0.2)	12.5 (3.8)
Proventil®: code P								
No coat	4	1.82 (0.02)	2.11 (0.26)	39.5 (4.4)	90.9 (3.7)	0.62	5.5 (0.2)	12.0 (1.3)
Glycerin	2	2.31 (0.0)	1.65 (0.03)	41.4 (5.3)	94.0 (0.5)		2.0 (0.8)	4.6 (2.5)
Silicone	2	2.22 (0.04)	1.66 (0.04)	40.5 (5.9)	93.0 (0.1)		0.3 (0.1)	0.6 (0.4)

Values are given as mean (standard error).
n is the number of replicate experiments.
[a] Fine point (fp): the cut-size of the stage corresponding approximately to the smallest 10% of sample.

parameter. Tables 5 and 6 record similar data for measurements made on ten shot samples for the AI and MMI, respectively.

Considering first the ten shot data recorded in Tables 5 and 6, no discernable pattern in summary parameters is apparent between the coated and uncoated conditions for either the AI or the MMI. Three situations would account for the observation: no bounce occurs with any of the formulations, the coatings are ineffective in preventing bounce, or any bounce may be concealed by experimental variability.

Considering next comparisons between one and ten shot measurements on coated surfaces for the tabulated parameters in Tables 3 and 5 for the AI, and Tables 4 and 6 for the MMI, no pattern emerges and observed differences are small compared to standard errors. Since bounce is related to stage loading levels, the similarity in results for one and ten shot measurements is evidence that the results for single shots collected on coated stages, as well as those for ten shots on uncoated stages, are not affected by bounce, i.e. both of the coatings are effective in eliminating bounce.

In contrast, there is a striking pattern of variation between MMAD and GSD measurements on single shots with coated and uncoated stages for both impactors on all formulations. Without exception, the average MMAD is larger for measurements made with coated stages, consistent with the occurrence of bounce from uncoated stages; although for all comparisons, differences are not large compared with the standard error. With the AI, except for the no-surfactant solution formulation, the average GSD is larger for uncoated stages, again consistent with the apparent distribution broadening as a result of bounce. The pattern in GSD does not hold for formulations tested with the MMI. With either impactor, no pattern is seen between glycerin and silicone oil coatings.

Table 5
Ten shot size measurement results with Andersen Sampler

	n	MMAD (μm)	GSD	Mass[a] <4.7 μm (μg)	Percent <4.7 μm	fp[b] (μm)	Mass[a] $<$ fp (μg)	Percent $<$ fp
Suspension, low surfactant, glycerin series: code LI								
No coat	1	2.02	1.89	43.3	90.3	1.1	8.6	17.8
Glycerin	1	1.97	1.89	45.0	90.8		8.8	17.7
Suspension, low surfactant, silicone series: code LII								
No coat	1	3.97	2.06	18.4	54.7	1.1	1.47	4.4
Silicone	1	4.36	2.02	16.6	51.9		0.92	2.9
Suspension, high surfactant: code H								
No coat	4	3.39 (0.15)	1.54 (0.03)	22.7 (6.7)	77.9 (2.5)	2.1	3.3 (0.9)	11.7 (3.6)
Glycerin	2	3.58 (0.04)	1.60 (0.01)	25.4 (7.2)	72.1 (1.9)		3.2 (1.4)	9.0 (1.7)
Silicone	2	3.52 (0.31)	1.57 (0.13)	18.5 (3.5)	75.4 (4.7)		2.7 (0.5)	11.5 (5.0)
Solution, with surfactant: code S								
No coat	3	2.21 (0.09)	1.83 (0.09)	53.4 (5.8)	89.4 (2.7)	1.1	9.1 (1.9)	15.6 (2.0)
Glycerin	2	2.29 (0.2)	1.78 (0.01)	54.1 (5.8)	89.4 (0.8)		8.2 (1.6)	13.5 (1.3)
Silicone	2	2.24 (0.20)	1.97 (0.0)	50.7 (0.8)	85.4 (4.1)		10.0 (1.8)	16.9 (3.5)
Solution, no surfactant: code N								
No coat	1	1.48	1.98	39.6	94.8	0.65	5.8	13.8
Glycerin	1	1.47	2.04	40.9	94.7		8.0	18.6
Proventil: code P								
No coat	4	2.23 (0.03)	1.62 (0.03)	36.3 (1.6)	93.6 (1.0)	1.1	2.8 (0.4)	7.3 (0.8)
Glycerin	3	2.16 (0.18)	1.30 (0.54)	34.7 (5.3)	94.0 (1.2)		4.5 (2.5)	12.5 (7.0)
Silicone	3	2.33 (0.14)	1.71 (0.20)	37.9 (2.8)	89.2 (7.8)		3.1 (1.7)	7.1 (2.8)

Values are given as mean (standard error).
n is the number of replicate experiments.
[a] Measured mass divided by 10.
[b] Fine point (fp): the cut-size of the stage corresponding approximately to the smallest 10% of sample.

The fractions of drug mass smaller than 5 μm (4.7 μm for the AI) also show very small differences, although for the most part these are in the expected direction, with greater proportions of sample for uncoated stages being deposited in the smaller stages of the impactor.

In contrast to the two previous comparisons, when the mass or the fraction containing about 10% of the sample is examined, a large and significant difference is seen between coated and uncoated measurements. Without exception, larger amounts of sample appear on the smallest cutsize impactor stages for measurements using uncoated collection surfaces, although a few relatively large standard errors can be seen. No apparent systematic difference is seen between the glycerin- and silicone-coated stages.

These results demonstrate one inadequacy of using only MMAD and GSD or the portion less than 5 μm to characterize distributions: Both descriptors fail to convey potentially important characteristics of the size distribution. This might be expected, since MMAD and GSD are a representation of central tendency of the data, which is little affected by the small portions of the sample at the extremes of the distribution. Similarly, mass and percentage less than 5 μm includes the majority of the sample which reaches the impactor, and changes in the distribution within this size range have no effect on the parameters. Therefore, neither of these quantities should be anticipated to give a strong indication of the changes in the measured distribution which are seen at the smallest sizes. Examination of the cumulative mass collected on the finer stages, in contrast, shows the distributions to be consistently different.

Table 6
Ten shot size measurement results with Marple-Miller impactor

	n	MMAD (μm)	GSD	Mass[a] < 5 μm (μg)	Percent < 5 μm	fp[b] (μm)	Mass[a] < fp (μg)	Percent < fp
Suspension, low surfactant, glycerin series: code LI								
No coat	1	3.37	2.23	20.3	70.9	1.25	3.7	12.8
Glycerin	1	4.04	2.52	18.2	61.1		3.6	12.0
Suspension, low surfactant, silicone series: code LII								
No coat	1	3.87	2.21	22.0	63.3	1.25	3.0	8.7
Silicone	1	5.17	2.14	17.8	48.3		1.0	2.6
Suspension, high surfactant: code H								
No coat	2	3.57 (0.10)	1.59 (0.04)	21.2 (3.7)	77.3 (1.8)	2.5	5.7 (1.0)	20.7 (0.7)
Glycerin	2	3.69 (0.08)	1.60 (0.01)	23.2 (3.9)	72.8 (5.4)		7.2 (3.2)	21.9 (4.8)
Silicone	2	3.78 (0.31)	1.81 (0.18)	20.2 (5.6)	68.2 (2.7)		5.1 (0.7)	17.5 (1.7)
Solution, with surfactant: code S								
No coat	2	2.30 (0.01)	1.94 (0.09)	55.1 (7.6)	89.5 (0.4)	1.25	9.5 (2.9)	15.3 (2.7)
Glycerin	2	2.19 (0.37)	1.95 (0.16)	65.1 (9.1)	89.4 (2.4)		15.1 (9.4)	20.8 (10.7)
Silicone	1	2.74	2.25	42.0	79.6		7.3	13.8
Solution, no surfactant: code N								
No coat	1	1.78	2.05	31.5	91.7	0.62	3.2	9.2
Glycerin	1	1.29	2.21	45.3	95.3		4.8	10.1
Proventil: code P								
No coat	7	2.24 (0.15)	1.73 (0.18)	37.2 (7.5)	92.4 (3.1)	0.62	1.7 (0.5)	4.3 (1.4)
Glycerin	2	2.68 (0.11)	1.79 (0.06)	27.6 (1.1)	86.9 (3.0)		1.0 (0.1)	3.0 (0.6)
Silicone	3	2.36 (0.27)	1.75 (0.19)	38.0 (6.8)	88.8 (7.9)		0.6 (0.1)	1.4 (0.4)

Values are given as mean (standard error).
n is the number of replicate experiments.
[a] Measured mass divided by 10.
[b] Fine point (fp): the cut-size of the stage corresponding approximately to the smallest 10% of sample.

4.2. Stage mass comparisons

In an effort to identify a measure of bounce that would indicate the effects concisely, without strong dependence on the particular size distribution under consideration, a novel term, 'bounce ratio', was defined as the ratio of the mass collected on a stage when it was uncoated, to the mass on the same stage when it was coated. In the absence of bounce, this ratio would be expected to remain constant at 1.0 for each of the stages. Figs. 1 and 2 show bar charts of the bounce ratio for each of the stages for the AI and MMI, respectively, as functions of the collection site and formulation. With the exception of the low surfactant suspension formulation (L), all measured values with uncoated stages were averaged over the respective stages for each formulation, and the coated stages were averaged over the combination of glycerin and silicone coatings. The bounce ratios for glycerin and silicone coating conditions are reported separately for the low-surfactant suspension formulation because the formulation showed changes in size over time, as noted previously.

The bounce ratio charts in Figs. 1 and 2 appear to be sensitive indicators of formulations which show bounce. The ratios less than 1.0 in the upstream stages of the impactor (those with larger cut-sizes) are consistent with relatively greater amounts being retained on the coated surfaces, as compared to the uncoated surfaces. The ratios greater than 1.0 in the downstream stages correspond to a smaller amount of oversized material reaching the finest coated stages since that portion was retained in the intended larger-sized stages, on the coated surfaces. The no-surfactant solution (N) shows no indication of bounce with either impactor, and the surfactant-solution formulation (S) shows no bounce with the MMI, and little or none with the AI.

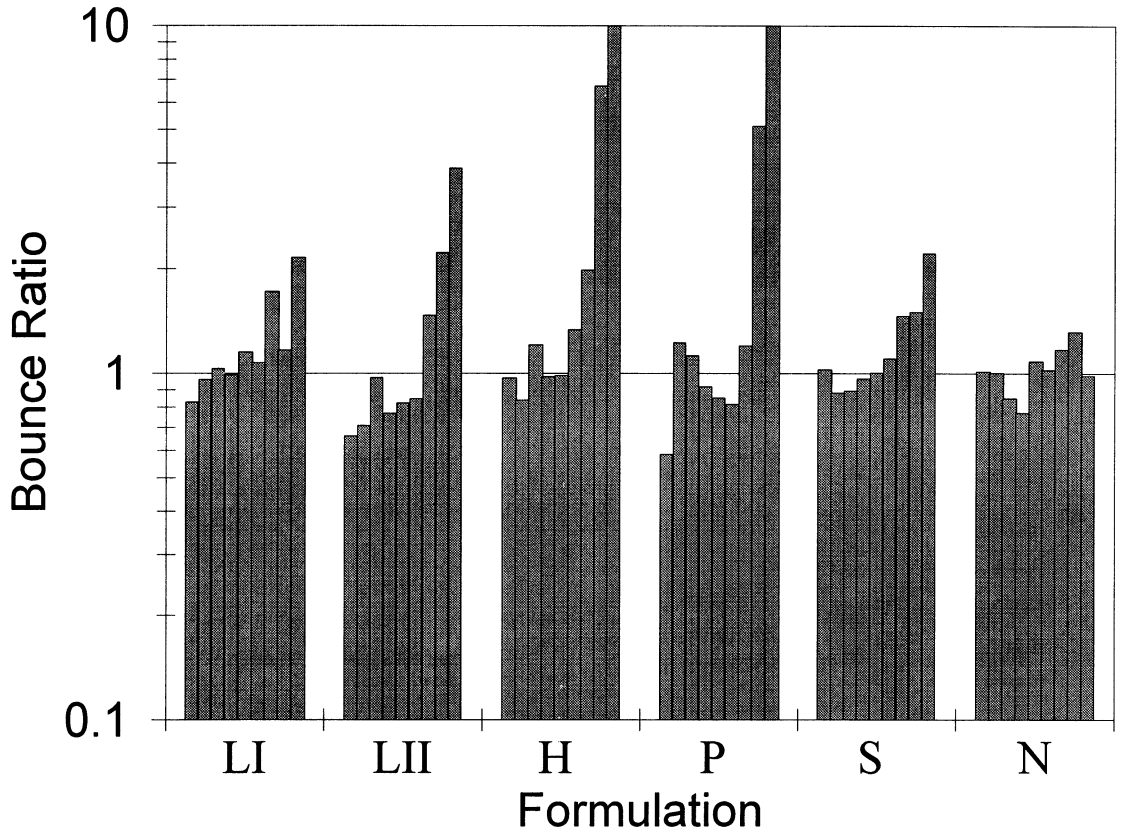

Fig. 1. Bounce ratios in Andersen sampler. Formulation codes are given in Table 1. For each formulation, results are shown for individual stages in the order of largest to smallest cut-size, beginning at stage 0 and ending with the filter.

Individual stage mass ratios were calculated for three other situations. In each case all replicate measurements (where they existed) were averaged, and those stages which contained less than 0.5% of the total recovered from the impactor were deleted from further consideration. First, the ratio of the masses collected with glycerin to that collected with silicone coatings were calculated for single shot measurements, for the three formulations for which appropriate data were available (high-surfactant suspension (H), Proventil (P), surfactant solution (S)). Values for all stages, reported as the mean (standard deviation), were 1.09 (0.33) and 1.14 (0.55) for the AI and MMI, respectively. The proximity to the expected value of 1.0 is evidence that the two coatings behaved similarly. Next, the corresponding ratios were calculated for the ten shot measurements, with values of 1.02 (0.36) and 1.16 (0.54) for the AI and MMI, respectively, indicating again that the two coating liquids are equivalent at the higher loadings of ten shot measurements. Finally, the ratio was calculated for both coated conditions for ten shot suspensions to those for one shot measurements, involving six formulations. In these ratios, the average of the two coated values were used, except for the low-surfactant suspension formulation (L). Values for the AI were 10.21 (2.96), and for the MMI, 10.01 (3.94), very close to the expected value of 10.0, consistent with bounce-free measurements. In none of these cases was any pattern discernable among the stages.

4.3. General comments

Although the configuration of these two impactors is quite different, each is a multiple-nozzle impactor operating at around 30 l/m, with the primary difference (for the purposes of this study) being that the AI uses polished stainless steel collection plates, while the MMI uses anodized aluminum (stainless steel collection cups are available, but were not evaluated).

The formulations all appeared to be stable with respect to particle size over the course of this study, with the exception of the low surfactant formulation (L). The drug in that formulation apparently formed stable agglomerates. Since several months elapsed between the experiments with glycerin and those with silicone, the aerodynamic size of the drug clusters emitted from the actuator was quite different. This shows up strongly in the MMAD values as well as other size description parameters. The replicate runs and the comparisons between coated and uncoated treatments on a given impactor were conducted within a few weeks and in randomized fashion, so that comparisons can be made between coated and uncoated conditions, but not between the two coated conditions.

It is surprising that formulations containing significant amounts of surfactant still show bounce effects. The surfactant in these formulations was oleic acid, a material which often is used in the calibration of impactors because it is presumed not to bounce. Yet even when it was present at three times the solids content (by mass), the solid particles showed bounce at low stage loadings. Other work (Nasr et al., 1997) has shown that the bounce of Proventil is undetectable by ordinary measures when the stage loadings corresponding to ten shots are considered, indicating that a change in the efficiency of particle capture occurs as the stages become loaded with sample.

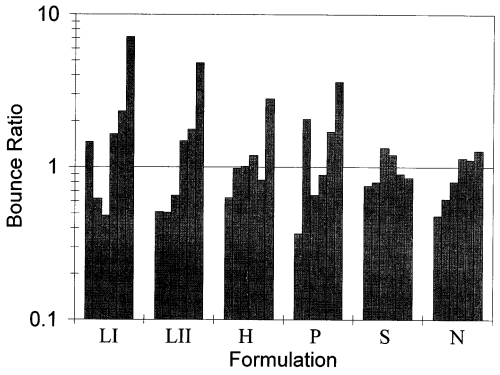

Fig. 2. Bounce ratios in Marple-Miller impactor. Formulation codes are given in Table 1. For each formulation, results are shown for individual stages in the order of largest to smallest cut-size, beginning at stage 1 and ending with the filter.

Differences might be expected between impactors due to the collection properties of the uncoated surfaces: the MMI collection surface is made of anodized aluminum, a relative hydrophilic material with a coarse structure on a microscopic scale, while the collection plates on the AI are made from smooth (even after roughening) and hard stainless steel. The two impactors showed qualitatively similar bounce characteristics, indicating that both of the uncoated surfaces resulted in bounce, while either coating was effective in eliminating bounce.

The significance of bounce on the reported results of size distributions for these formulations obviously would depend on which properties of the size distribution were considered. If the only properties considered were those of central tendency of the distribution, such as the MMAD/GSD or the mass or fraction below a size near the MMAD, distortions caused by bounce would not be so apparent. If, however, a more complete and accurate description of the characteristics of the distribution is intended, then the possible corrupting effects of bounce must be investigated.

Bounce shows up most strongly in summary parameters which show the smaller end of the distribution. A comparison of the masses recovered from individual stages, and patterns among the stages, gives a more sensitive indication of the occurrence of bounce than summary parameters.

5. Conclusions

Bounce effects are clearly seen in the measurement of suspension formulations, even those containing high levels of oleic acid surfactant

compared to solids. This appears not to be related to the material of construction of the impactor collection surfaces. Surprisingly, a solution formulation without surfactant, which might be expected to show relatively large effects due to the absence of non-volatile liquids, displayed no evidence of bounce. It would be prudent to suspect the presence of bounce in cascade impactor measurements on pharmaceutical products until it is demonstrated to be negligible.

Glycerin and silicone oil were seen to be equally efficacious in eliminating bounce. Detectable differences were not seen between anodized aluminum and stainless steel collection surfaces, either in the coated or in the uncoated condition.

Different measures of bounce show different sensitivities in detection, with the greater sensitivities associated with measures which focus on the collection stages corresponding to smaller sizes. The effect is most pronounced in the smallest 10% of the sample.

The examination of the ratios of mass collected on corresponding impactor stages is useful to develop a clear picture of artifacts which may be introduced into impactor data due to bounce-related phenomena. The expected value for each stage is equal to the ratio of total sample mass; deviations from the expected value shows a clear indication of the presence of bounce effects.

Acknowledgements

The authors are grateful to Sally Carlson and Sharon Saydah (3M Pharmaceuticals), Terry J. Tschappler and Christopher M. Stanley (US FDA) for laboratory assistance. We thank Wallace P. Adams and Guirag Poochikian of the Center of Drug Evaluation and Research (CDER), and James Allgire, Walter L. Zielinski, Henry D. Drew, and Thomas P. Layloff of the Division of Testing and Applied Analytical Development (DTAAD), US FDA for helpful discussions. Certain commercial equipment, instruments, or materials are identified in this report to specify adequately the experimental procedure. Such identification does not imply recommendation or endorsement by the FDA or 3M Pharmaceuticals, or does it imply that the materials or equipment identified are necessarily the best available for the purpose.

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