DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 21(12), 1399-1409 (1995)

A NEW APPARATUS FOR THE DETERMINATION OF THE EMITTED DOSE FROM PRESSURIZED METERED DOSE INHALATION AEROSOLS WITH INHALATION DEVICES

N. Gaddipati[1], M. Graziosi[2], and M. Ganesan[3]
Medical Research Division
American Cyanamid Company, Pearl River, New York 10965

ABSTRACT

A new *in vitro* test apparatus is described in this report to test the emitted dose from the pressurized metered dose inhalation aerosols (MDI) with inhalation devices. Drug deposition from MDIs in conjunction with different inhalation chambers was studied using a new apparatus and compendial apparatuses. The new apparatus is simple and offers an alternate method to determine the small particle fraction delivered from MDI aerosols with inhalation devices.

INTRODUCTION

MDI suspension formulations are polydisperse aerosols and the drug particles delivered from these aerosol sprays contain broad range of particle sizes. Differences in size distributions of these drug particles influence the quantity of drug available at the site of action. The particle size of the active drug discharged from the MDI spray is monitored by measuring the small-particle fraction of the active present in the aerosol sprays. Previously small-particle fractions of the sprays were tested by custom designed simulated respiratory systems[1-4]. The apparatuses commonly used to determine the small-particle fraction of aerosol sprays are: a) *Unit Spray Sampling Apparatus,* described in the United States Pharmacopeia (USP XXII)[5], and b) *Apparatuses A and B for the Deposition of Emitted Dose,* described in the British Pharmacopoeia (BP)[6]. The BP apparatuses are more versatile than the USP apparatus and have been introduced into the

[1]Correspondence
Present Address: [2]Pfizer Central Research, Groton, CT
[3] Solvay Pharmaceuticals, Marietta, GA

United States Pharmacopeia (USP 23)[7]. However the BP apparatuses are complex requiring assembly of several precisely molded glass parts for Apparatus A and metal parts for Apparatus B. In an attempt to design a compact inhalation device to use with MDIs, we have developed a simple laboratory apparatus to determine the small-particle fraction delivered from MDIs using inhalation chambers. Inhalation chambers of different sizes and shapes were tested to determine the emitted dose using this new test apparatus, USP Spray Sampling Apparatus and the BP Apparatus A. Data from these *in vitro* studies are presented in this report.

MATERIALS AND METHODS

Materials

Azmacort™ MDI manufactured by Rhone Poulanc Rorer (Collegeville, PA) was utilized. HPLC grade tetrahydrofuran and acetonitrile, and reagent grade sodium phosphate were obtained from J. T. Baker (Phillipsburg, NJ).

Inhalation Device Test chambers for *In Vitro* Tests: The inhalation device chambers (prepared by Cyanamid Mechanical R&D group, Pearl River, N.Y.) tested for this study are shown in Figure 1 and a description of each device is shown in Table 1.

The inhalation flow rate of the test devices 1 through 7 is controlled by the flow-through design of nine "1" mm diameter orifices (not shown in the Figure) present on the far-end of the chamber. All test devices were fitted with InspirEase^{R} mouth pieces except where indicated. When an MDI is sprayed into the test chamber the spray is delivered into the device in the opposite direction of the inhalation air flow. A spacer device used with Azmacort™ MDI was included in this study as a control. The Azmacort™ spacer delivers the spray in the same direction as the inhalation air flow.

Methods

Respirable (small particle) and Non-Respirable Fractions

When an MDI is sprayed into an inhalation device chamber, the delivered dose can be classified into two fractions: (a) non-respirable particle fraction (NRPF) containing particles collected on the chamber walls due to propellant impaction and gravitational sedimentation of large particles and (b) respirable particle fraction (RPF) containing small particles suspended in the device chamber. The NRPF and RPF of inhalation devices are affected by the aerosol formulation as well as the chamber size and shape. If the NRPF and RPF values are known for different size/shape chambers, a device that is compact and offers greater RPF can be selected to enhance pulmonary deposition from MDIs. To accomplish this, NRPF and RPF were determined for the test chambers using a new Cyanamid Test (CT) apparatus (prepared by Cyanamid Mechanical R&D Group, Pearl River,

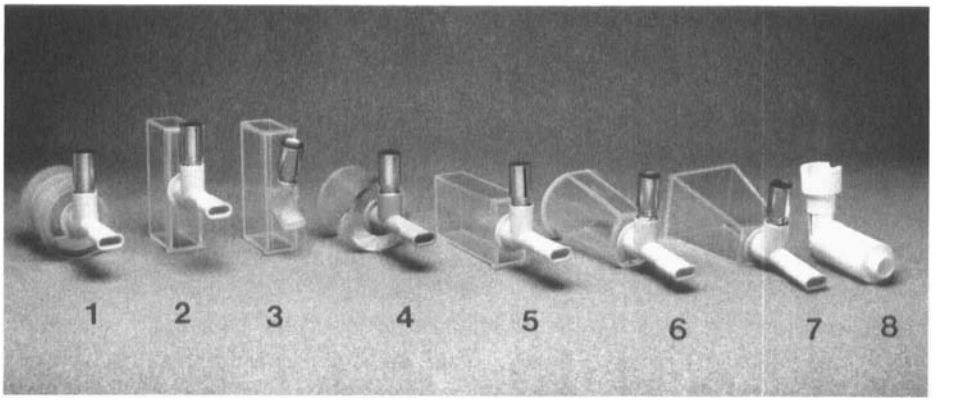

FIGURE 1
Different Shape and Size Inhalation Device Test Chambers

TABLE 1
Description of Test Devices for *In Vitro* Evaluation

Device No.	Shape	Chamber Volume (ml)	Plume Length in the Chamber (cm)
1	Cylindrical	225	6
2	Rectangular	225	6
3	Rectangular[1]	225	6
4	Conical	225	6
5	Rectangular	225	12.5
6	Elliptical	300	12.5
7	Pyramid	320	12.5
8	Spacer[2]	100	9.5

[1]Device fitted with a prototype actuator (prepared by G R Tech. Services, Clark, NJ); all other devices were fitted with the InspirEase[R] actuator (manufactured by Schering Corporation, Kenilworth, NJ).
[2]Spacer device from Azmacort™

N.Y.), BP "Apparatus A for Determination of the Emitted Dose" (Twin Impinger - Model T12 from Erweka Instrument Corporation, Milford, CT), and USP "Spray Sampling Apparatus". The Azmacort™ (delivers approximately 200 mcg of triamcinolone acetonide per spray[8]) MDI was used to determine the NRPF and RPF for different inhalation device chambers.

CT Apparatus

A typical assembly of the test apparatus is shown in Figure 2. The apparatus consists of a two piece threaded acrylic housing that holds a 0.45 μ membrane filter (Pall Process Filtration Corporation, East Hills, N.Y.) supported by a stainless steel screen backing. The housing can be easily dismantled by unthreading the acrylic pieces for clean-up of the apparatus, sampling or replacement of the membrane filter. The filter-end of the housing was connected to the device mouth piece and the other end was connected to a vacuum source via a flow meter (Cole Parmer, Chicago, IL). Air-flow through the apparatus was maintained at 18 liters per minute simulating the slow inhalation flow rate preferred for more uniform deposition[9].

The Azmacort™ valve was primed, and shaken for not less than 5 seconds prior to each actuation. For each measurement 5 actuations were made into the device chamber. The apparatus was dismantled, the triamcinolone acetonide i) deposited within the chamber including the mouth-piece (NRPF) and ii) deposited on the filter plus filter housing (RPF) were collected separately by rinsing with methanol, and quantitated by HPLC. NRPF and RPF were expressed as percentages of the total triamcinolone acetonide recovered from the chamber and the filter.

BP Apparatus

Twin Impinger Apparatus was assembled, and the inhalation device test chamber was connected to the throat of the apparatus. Methanol was added to the upper and lower impingement chambers. Following the BP procedure, air flow through the apparatus was maintained at 60 liters per minute as ten sprays of Azmacort™ were discharged into the test chamber. The apparatus was then dismantled, the triamcinolone acetonide deposited in the i) device chamber, ii) throat and neck, iii) upper impingement chamber, and iv) lower impingement chamber were collected separately by rinsing with methanol, and quantitated by HPLC testing. The deposition results were expressed as percentages of the total triamcinolone acetonide recovered from the above four fractions. NRPF was calculated by combining the percent triamcinolone acetonide collected in the device chamber, throat and neck, and the upper impingement chamber. The BP requires to measure the drug fraction only from the lower impingement chamber to determine the emitted dose from the MDI, and this fraction was considered as the RPF for this study.

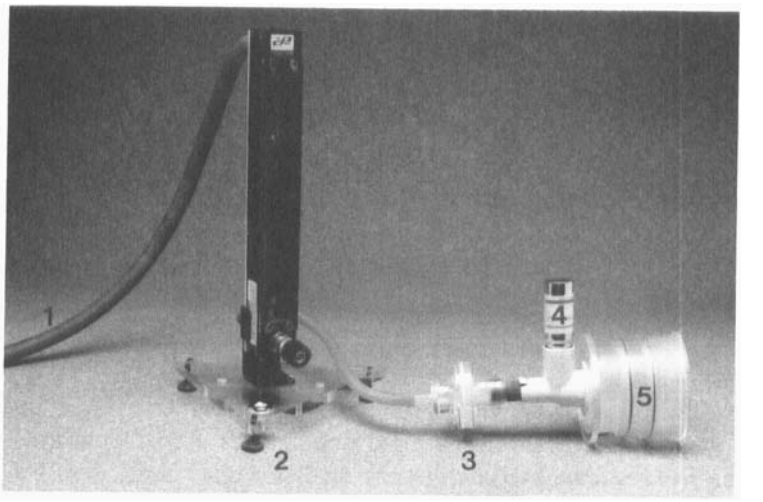

FIGURE 2
Cyanamid Test Apparatus
1. To vacuum pump, 2. Flow meter, 3. Housing for the membrane filter and stainless steel backing, 4. MDI, 5. Device chamber.

USP Apparatus

The apparatus was assembled, and the inhalation device test chamber was connected to the intake adapter of the apparatus. Methanol was used as the absorbing solution in the collection chamber. Following the USP procedure, air flow through the apparatus was maintained at 12 liters per minute as five sprays of Azmacort™ were discharged into the test chamber. The RPF was determined by quantitating the triamcinolone fraction collected in the absorbing solution.

HPLC Method

Triamcinolone acetonide content of samples was quantitated by reverse phase chromatography using a 15cm Microbondapak (Millipore, Milford, MA) C18 column, with a mobile phase containing tetrahydrofuran, acetonitrile and 0.005M sodium phosphate buffer (1:37:62). The flow rate was 1ml per minute, with UV detection at 254nm.

RESULTS AND DISCUSSION

Triamcinolone Deposition in Test Chambers

The USP method yielded RPF values of less than 0.5% for all the test chambers except for the Azmacort™ spacer device which showed 25% RPF. This

result is not surprising because the spray for the Azmacort™ device is delivered in the same direction as the inhalation air-flow, while for all the test chambers the spray was delivered toward the opposite direction of inhalation air-flow. Increasing the flow rate up to 20 liters per minute did not increase the RPF emitted per spray for any of the test chambers. No further testing was done by the USP method and the results from BP and CT apparatuses are discussed.

Evaluation of BP and CT Apparatuses

The triamcinolone acetonide distribution for different inhalation devices with the CT and BP apparatuses is shown in Tables 2 and 3 respectively.

The triamcinolone deposited within the inhalation chambers, NRPF and RPF are compared to determine if the BP and CT apparatuses are suitable to discriminate the deposition performance from different inhalation chambers.

Deposition in Test Chambers

A comparison of the data obtained using CT and BP apparatuses for the quantity of triamcinolone deposited in different test chambers is presented in Figure 3. These data show that the deposition in the chamber is consistently lower by the BP method which can be attributed to the rapid clearance of triamcinolone particles from the device chamber because of the high inhalation flow rate used by the BP method.

NRPF and RPF

The NRPF and RPF ranged from 96.4 to 98.4% and 1.8 to 3.6% respectively for the BP apparatus, while the data ranged from 86.9 to 94.8% and 5.2 to 13.1% for the CT apparatus. Comparison of these data are depicted in Figures 4 (NRPF) and 5 (RPF). Data from both CT and BP apparatuses is compared to evaluate if either of the apparatus is suited to differentiate the deposition profiles based on the device size, shape or plume length.

Devices 1 to 4: These devices have identical volume and plume length. The mean NRPF & RPF values obtained using the BP (97.6 & 2.4%; std dev. 0.8) and CT (94.1% & 5.9%; std dev. 0.8) methods show small differences in deposition values. However the data from both the methods indicate that at the 225ml volume, and 6.5cm plume length the shape of the chamber (cylindrical, rectangular, or conical) did not have any major effect on the deposition patterns.

Devices 5 and 6: Device 5 is rectangular in shape and device 6 is elliptical shaped. These devices differ from devices 1-4 by having a larger plume length, and device 6 in addition has larger chamber volume. The NRPF & RPF data from BP method for devices 5 (97.2 & 2.8%) and 6 (98.0 & 2.0%) are similar to

TABLE 2
Triamcinolone Distribution in Test Chambers with CT Apparatus

Device No.	% Triamcinolone Deposition[1] NRPF (Chamber)	RPF (Filter)
1.	93.5	6.5(1.0)
2.	94.8	5.2(2.2)
3.	93.3	6.7(1.0)
4.	94.7	5.3(0.7)
5.	90.5	9.5(2.6)
6.	88.2	11.8(3.6)
7.	93.8	6.2(1.7)
8.	86.9	13.1(1.0)

[1]Each value is an average of six determinations; data in parenthesis is standard deviation.

TABLE 3
Triamcinolone Distribution in Test Chambers with BP Apparatus

Device No.	% Triamcinolone acetonide Deposition[1] Device Chamber (A)	Throat and Neck (B)	Upper Impinge. Chamber (C)	NRPF (A+B+C)	RPF Lower Impinge. Chamber
1.	86.0(3.2)	9.9(2.9)	2.3(0.4)	98.2	1.8(0.4)
2.	74.5(5.1)	18.6(2.5)	3.4(1.5)	96.5	3.5(1.5)
3.	82.9(3.0)	12.0(2.3)	2.8(0.8)	97.7	2.3(0.5)
4.	78.0(5.0)	16.4(3.5)	3.6(1.4)	98.0	2.0(0.7)
5.	78.3(2.4)	15.6(1.8)	3.3(0.5)	97.2	2.8(0.3)
6.	78.0(5.0)	16.4(3.4)	3.6(1.4)	98.0	2.0(0.7)
7.	87.0(4.1)	9.3(3.4)	2.1(0.5)	98.4	1.6(0.3)
8.	71.0(3.2)	21.1(2.9)	4.3(0.5)	96.4	3.6(0.6)

[1]Each value is an average of six determinations; data in parenthesis is standard deviation.

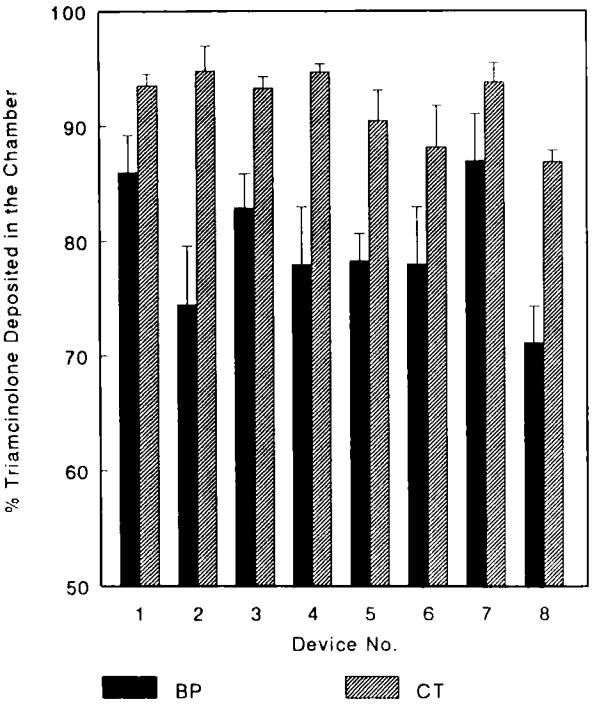

FIGURE 3
Comparison of Triamcinolone Deposition in the Test Chambers with the BP and CT Apparatuses

devices 1-4 indicating that the BP apparatus does not differentiate these devices despite of the increase in the chamber dimensions. The NRPF & RPF from the CT method for devices 5 (90.5 & 9.5%) and 6 (88.2 & 11.8%) are different from devices 1 to 4, indicating that the data from CT apparatus differentiate these devices.

Device 7: This inhalation chamber is pyramid shaped and has the largest chamber volume of all the test devices. The plume length of the chamber is similar to devices 5 and 6. This device did not show any increase in RPF with either of the methods indicating a possible shape/volume related effect for this device.

Device 8: Delivers the spray in the same direction as the inhalation flow, while for devices 1-7 spray is delivered in the opposite direction of inhalation flow. This device show NRPF (96.4%) and RPF (3.6%) values similar to the devices 1 to 7 by BP method. The data from CT method show the highest RPF (13.1%).which differentiates this device from other devices.

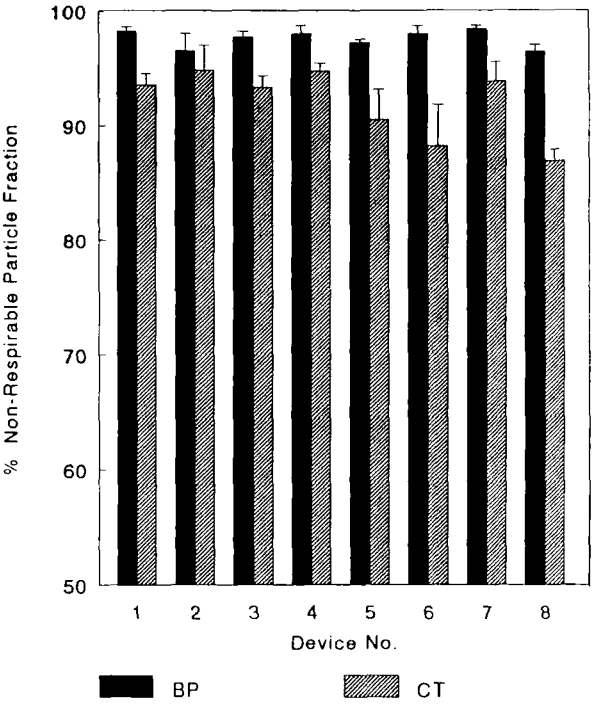

FIGURE 4
Non-Respirable Particle Fraction of Test Chambers by the BP and CT Test Methods

Comparative Evaluation

Inhalation chamber deposition data from the BP method (std. dev. range: 2.4 to 5.1) appears less precise than the CT method (std. dev. range: 0.7 to 3.6). However, when the deposition data from the various chambers of the BP apparatus is accounted for and the RPF values are compared, the precision of the BP apparatus is greatly improved. Comparison of the RPF data also show that the BP method (std. dev. range: 0.3 to 1.5) exhibits less scatter than the CT method (std. dev. range: 0.7 to 3.6) as evidenced by the standard deviation. Nonetheless, the RPF data from the BP method fails to discriminate for the size, shape or plume length of the device, while the CT method show differences in deposition patterns for different devices.

The data from the CT apparatus indicate similar chamber deposition for the inhalation devices 1 (cylindrical shape) and 2 (rectangular shape) which have identical volume and plume length. Further in an *in vivo* study[10] prototypes of

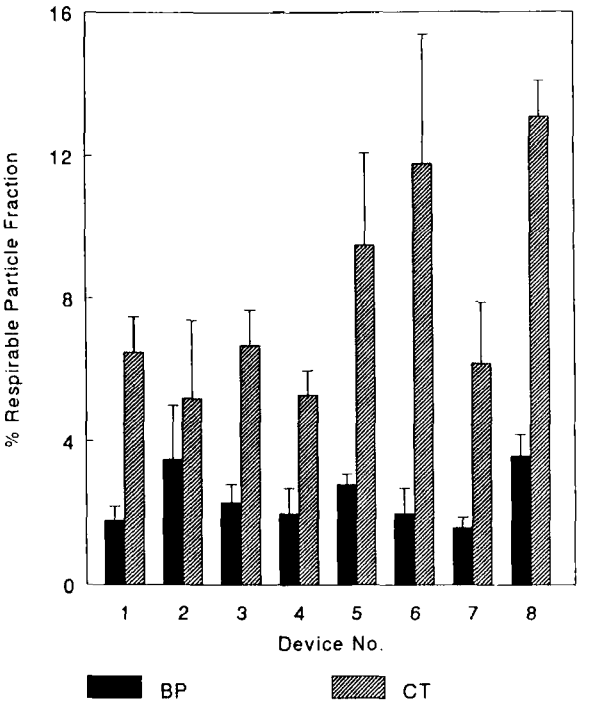

FIGURE 5
Respirable Particle Fraction of Test Chambers by the BP and CT Test Methods

device 1and 2 using a Technetium Tc 99M labeled sulfur colloid MDI[11] aerosol showed similar sulfur colloid deposition in lungs in the human volunteers.

CONCLUSIONS

The *in vitro* deposition profile data presented in this paper show that the CT apparatus is suitable to determine the small-particle fraction of MDIs with inhalation devices. Unlike the BP apparatus, CT apparatus is simple, easy to assemble and use, and allows easy change over between experiments. Furthermore, CT apparatus offers adequate precision to monitor the small particle fraction of MDIs, and can be easily adapted to accommodate the testing of emitted dose for MDIs with other commercial inhalation devices.

ACKNOWLEDGMENTS

The authors gratefully thank the support of Mr. B. Zoltan, Mechanical R&D, American Cyanamid Company for preparing the prototype inhalation chambers.

REFERENCES

1. W. A. Karig, E. G. Peck, and J. G. Sperandio
   J. Pharm Sci., 62 811(1973).
2. Z. T. Chowhan, and A. A. Amaro, J. Pharm Sci., 66 1254 (1977).
3. J. J. Sciarra, and A. Cute, J. Pharm Sci., 67 1428 (1978).
4. G. P. Martin, A. E. Bell, and C. Marriott, Int. J. Pharm., 44 57 (1988).
5. United States Pharmacopeia, XXII , U. S. Pharmacopeial Convention, Rockville, MD, 1556 (1988).
6. British Pharmacopoeia, Office of the British Pharmacopoeial Convention, London, 2 A204 (1988).
7. USP23/NF18, Unted States Pharmacopeial Conventon, Rockville, MD, 1762(1995).
8. Physician's Desk Reference, Medical Economics Data, Montvale, NJ 1838 (1992).
9. M. T. Newhouse and R. E. Ruffin, Deposition and Fate of Aerosolized Drugs, Chest, 6 936 (1978).
10. N. Gaddipati, M. Graziosi, K. Ellway, and M. Ganesan
    Submitted for publication to International Journal of Pharmaceutics.
11. N. Gaddipati, M. Graziosi, K. Ellway, and M. Ganesan,
    Drug Dev. and Ind. Pharm. 19(10) 1159 (1993).