ABSTRACT

Powder aerosols are being considered as treatment for patients with Cystyic Fibrosis because powders can deliver amiloride hydrochloride directly to airway surfaces more quickly and easily than is possible when the drug is administered in solution. The goals of this research were: 1) to increase the fraction of respirable amiloride hydrochloride mass generated, 2) to remove larger, non-respirable particles from the aerosol before inhalation, and 3) to assess the effectiveness of these aerosol generation techniques for delivering amiloride to the lower airway surfaces. Three independent variables were tested, each at three levels: 1) size range of lactose powder flow-aid used to help disperse the amiloride aggregates 2) ratio of amiloride to lactose in the capsule, and 3) total mass of amiloride and lactose in the capsule. For the particle size of interest, 0.7 to 3.3 micrometers, all three independent variables had a significant effect on the fraction of respirable amiloride hydrochloride mass generated. For size range of lactose flow-aid used to disperse amiloride aggregates, the trend indicated that smaller lactose particles, <38 um, were most effective.

For ratio of amiloride to lactose, a 1:2 ratio of lactose flow-aid to amiloride drug was most effective. For total mass of amiloride and lactose in the capsule, the least mass, 30 mg, was most effective in dispersing amiloride aggregates.

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INTRODUCTION

Powder aerosols are being considered to deliver amiloride, or other therapeutic agents, to patients with CF because they may deliver a relatively large amount of drug directly to airway surfaces. Dry aerosols are of particular importance because they enable delivery of dry amiloride which should remain in the airway surface liquid longer than a solution of the same drug. As a result, higher drug concentrations on the airway surfaces can be achieved more quickly and easily than is possible when the drug is administered in solution. Further, delivery of less soluble forms of the drug may lengthen the residence time of an effective concentration of drug on airway surfaces.

Because amiloride is a diuretic, a concern is that the drug will impact in the mouth and throat, be ingested, and induce renal diuresis and vascular volume depletion. To minimize ingestion, yet deliver sufficient drug for a therapeutic airway surface concentration, the aerosol particles must have the appropriate size distribution. Developing a powder delivery system that can target conducting airways of the lung has been difficult because no present method is avail-

able to quantify drug concentrations in distal airways. Even though lung deposition models are helpful to predict where particles of any given size may collect, it is difficult to document the predicted concentration of particles in targeted lung surfaces.

Particles from 0.5 to 10 um aerodynamic diameter deposit in the lungs (1); however, due to the decreased airway diameters in distal conductive airways, deposition of 10 % would be optimistic for particles in this size range (2). Most particles larger than 6 um aerodynamic diameter will collect in the nose and mouth and be swallowed (3) thus being of no use in the treatment of CF airway dysfunction. Particles <4 um aerodynamic diameter are of primary interest in this study.

Pulmonary deposition of these particles occurs primarily by three mechanisms: 1) inertial impaction 2) diffusion and 3) gravitational sedimentation. For particles > 3 um, deposition occurs by inertial impaction in the conducting airways; for smaller particles that penetrate to distal regions, diffusion may predominate.

Small particles are bound to surfaces by van der Waals and electrostatic forces. The magnitude of these binding forces depends on the nature of the material,

the shape and the size of the particles, the roughness of surfaces, relative humidity, duration of particle contact, and initial contact velocity. Current theory cannot predict adhesive forces accurately, even for the simplest case of a single particle attached to a defined substrate (4). To seperate an agglomerate into constituent particles, sufficient energy must be supplied to disperse the particles to the point that attractive forces become negligible.

The goals of the research were 1) to increase the fraction of respirable amiloride hydrochloride particles being generated 2) to remove larger, non-respirable particles from the aerosol before inhalation, and 3) to assess the effectiveness of these aerosol generation techniques for delivering amiloride to the lower airway surfaces.

METHODS

APPARATUS

To predict particle deposition patterns, control must be achieved over the rate and volume of inspiration because these factors play a major role in determining the region of particle deposition within the airways. The Spinhaler turbo-inhaler from Fisons, Inc. was selected for this study because it is activated by the patient's inspiration and automatically synchronizes the release of drug with the intake of a breath (5,6).

Air inhaled through the mouth piece of the Spinhaler causes vibratory motion of the rotating impeller (5,6). The impeller, in turn, imparts energy to the drug particles causing agglomerated drug in the capsule to break up and disperse into the inhaled air.

The May multistage liquid impinger was designed to fractionate viable organisms by size (7). This three stage impinger was designed to approximate the particle collection characteristics of the oropharynx, tracheobronchial, and alveolar regions of the respiratory system. At the recommended flow of 55 liters per minute, 50% of particles greater than 6 um in

diameter, with estimated specific gravity of 1.5, are expected to collect on the first stage; the corresponding cut sizes for the second and third stages are 3.3 and 0.7 microns. Amiloride hydrochloride has a specific gravity of 1.53.

EXPERIMENTAL DESIGN

The experiments reported here determine the mass and size distribution of amiloride hydrochloride powder dispersed by a Spinhaler over 27 experiments. Three independent variables were tested each at three levels: 1) size range of lactose powder flow-aid used to help break up the amiloride aggregates a) <38 um b) 38-53 um c) 53-75 um; 2) the mass ratio of amiloride to lactose in each capsule a) 2:1 b) 1:1 c) 1:2; and 3) the total mass of the amiloride and lactose in the capsule a) 30 mg b) 40 mg c) 50 mg. In addition to the three independent variables, data were collected for chronological experiment number, relative humidity, chronological Spinhaler number, and chronological experiment number for each Spinhaler.

Five additional experiments were conducted at the intermediate level of each variable to determine experiment reproducibility, and seven impactor experiments were conducted to evaluate a specially designed particle collection device. See figures (1,2,3) for experimental set-up. All 39 experiments were run in random order.

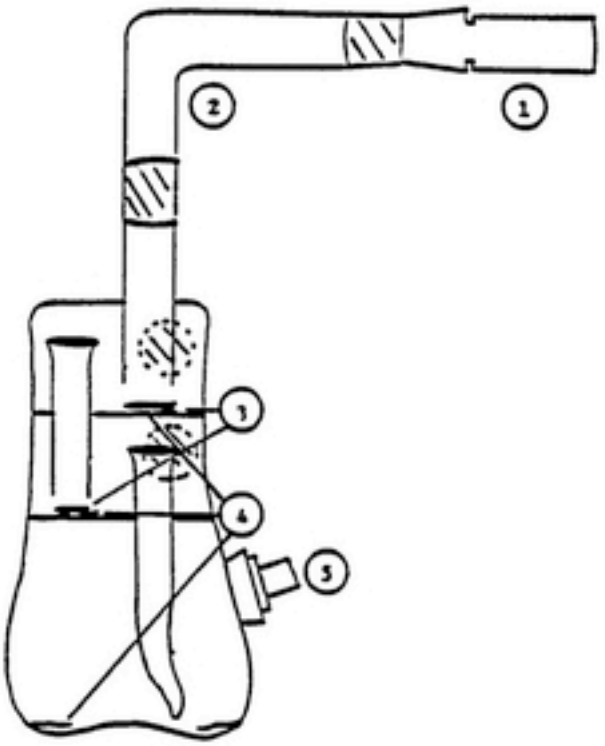

Figure 1. May multistage liquid impinger.
Key: 1. Spinhaler; 2. artificial throat; 3. impaction stages; 4. impingment liquid.

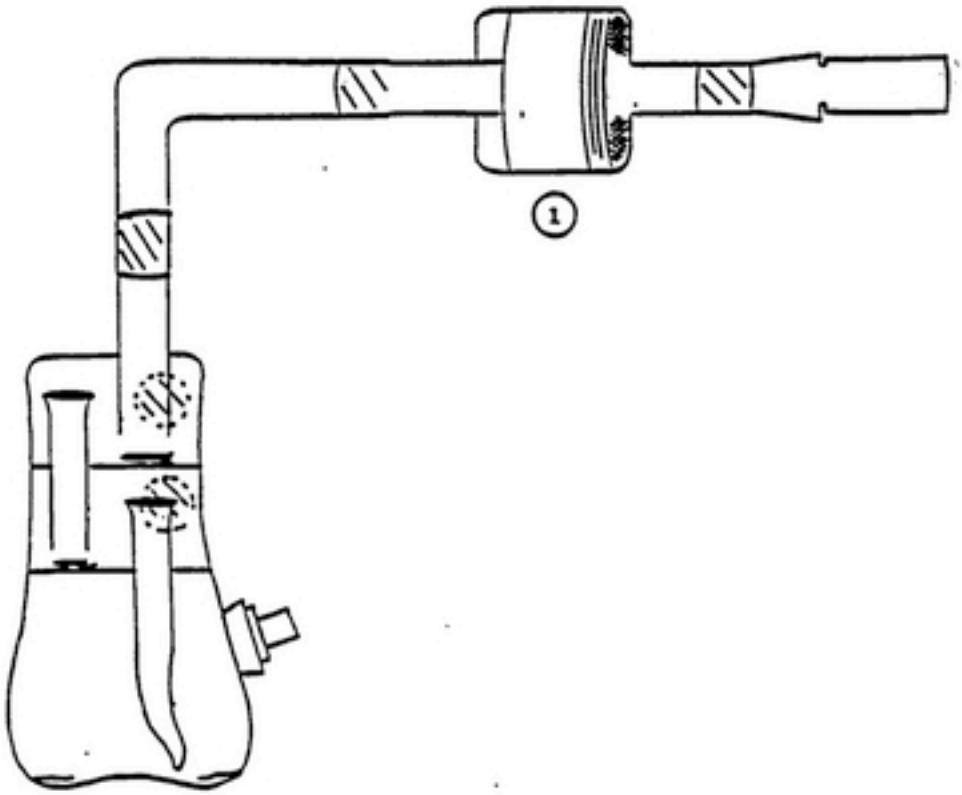

Figure 2. May multistage liquid impinger with the impactor in line. Key: 1. impactor

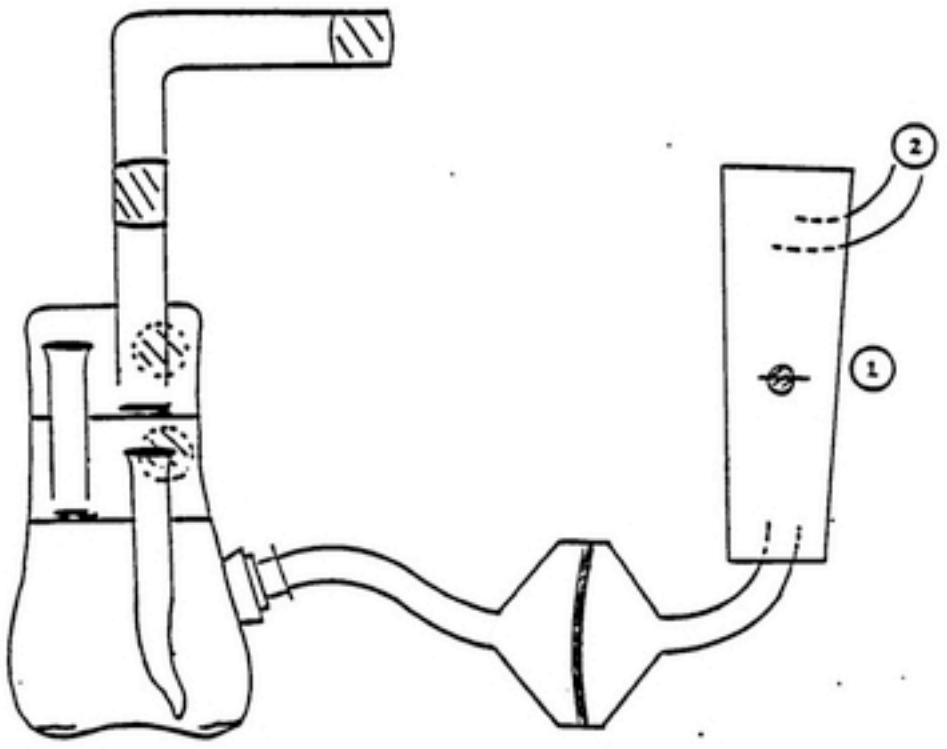

Figure 3. Experimental apparatus.
Key: 1. rotameter
2. to vacuum

Figure 4. Impactor

The amiloride was hand milled to a CMD of 0.96 um and a GSD of 1.8. The lactose flow-aid was sieved into three size fractions 1) < 38 um, 2) 38-53 um, and 3) 53-75 um.

One portion of this research involved design and evaluation of an impactor to remove drug particles larger than approximately 4 um aerodynamic diameter as they left the Spinhaler, see Figures (2,4). The impactor was included in the sampling train for the seven impactor experiments.

The Spinhaler was connected to the May impinger by glass tubing (3.5 cm) with an approximate 90 degree bend to simulate the trachea. The top two stages of the May impinger were filled with enough double-distilled water to maintain wetted impactor surfaces. The bottom stage was filled with 8 ml of double distilled water. The May impinger was connected to a glass fiber filter downstream to collect the finest particles.

Air flow was set at 55 Lpm using a calibrated rotameter. 1.5 mm holes were hand drilled into standard #2 gelatin capsules. Three capsules were filled with the appropriate quantities of amiloride and lactose. Then the capsule was placed in the rotor cup of the Spinhaler and suction was applied for 30 seconds.

This sequence was repeated for the other two capsules, for a total collection time of 90 seconds.

Liquid was syringed, then rinsed from each impinger stage into 100 ml flasks. Residual amiloride in the Spinhaler and glass throat were rinsed with double distilled water and also collected. The mass of amiloride in each sample was determined by visible spectrophotometry using the peak absorbtion wavelength for amiloride of 361 nm. The lower limit of sensitivity for the standard curve was 1.0 ug/ml, or an absorbance of 0.069.

RESULTS

Amiloride that deposited on the third stage of the May impinger or on the final filter, particles smaller than 3.3 um diameter, were of primary interest to this study, as they should be most likely to collect on airway surfaces.

In chart 1, total mass in capsule in mg, is plotted against percent amiloride mass on stage three. This chart shows that the less amiloride in the capsule the greater the percent recovery for the 3rd stage.

In chart 2, total mass in capsule in mg, is plotted against amiloride mass on stage three. This chart shows that the more amiloride present per capsule the more amiloride recovered on stage 3.

In chart 3, amiloride to lactose mass ratio is plotted against percent amiloride mass on stage three. This chart shows that the less amiloride to lactose per capsule the greater the percent recovery of amiloride for the 3rd stage.

In chart 4, amiloride to lactose mass ratio is

plotted against amiloride mass recovered on stage 3. This chart shows that the more amiloride present in the capsule the more amiloride recovered on stage 3.

In chart 5, lactose size range in um, is plotted against percent amiloride mass on stage 3. This chart shows that the smaller the lactose particles the greater the percent recovery for stage 3.

In chart 6, lactose size range, in um, is plotted against amiloride mass recovered for stage 3. This chart shows that the smaller the lactose particles the greater the mass recovery of amiloride on stage 3.

In summary the trend showed that to disperse amiloride into particles 0.7 - 3.3 um, use less total mass per capsule, use a high ratio of lactose flow-aid to amiloride drug, and use small lactose particles in the capsules. For example, with 10 mg amiloride in a capsule and the reported combination of variables; 1.4 mg of amiloride would be deposited in the region of interest.

As shown in table 1, with the impactor in line, less amiloride is deposited on the 1st and 2nd stages without affecting 3rd stage deposition.

For other variable data recorded during the

experiments no clear trends emerged for the amount of amiloride collected on stage 3.

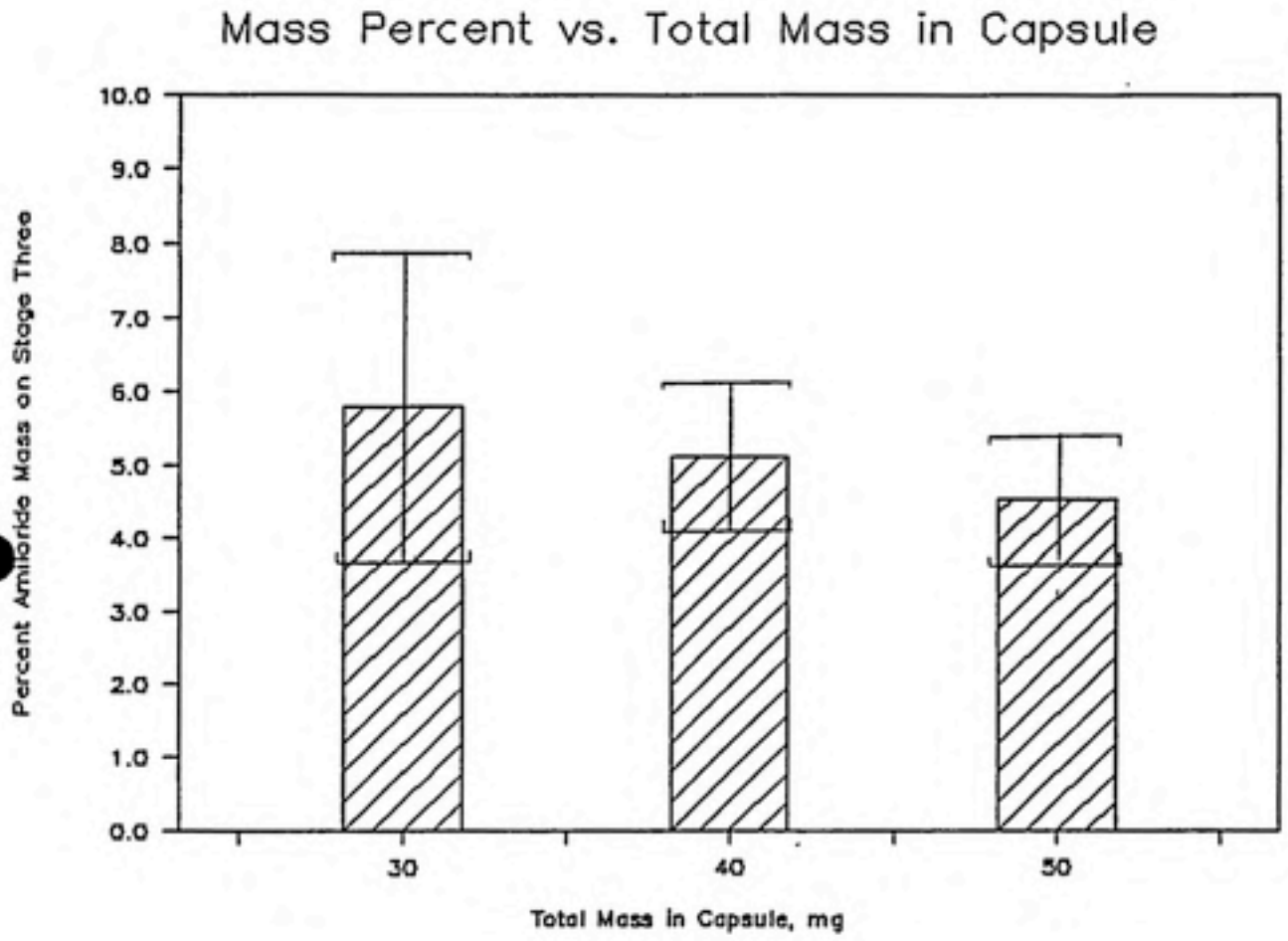

Chart 1

Percent Amiloride Mass on Stage Three is plotted against Total Mass of Amiloride in Capsule. The Standard Deviations are indicated by brackets.

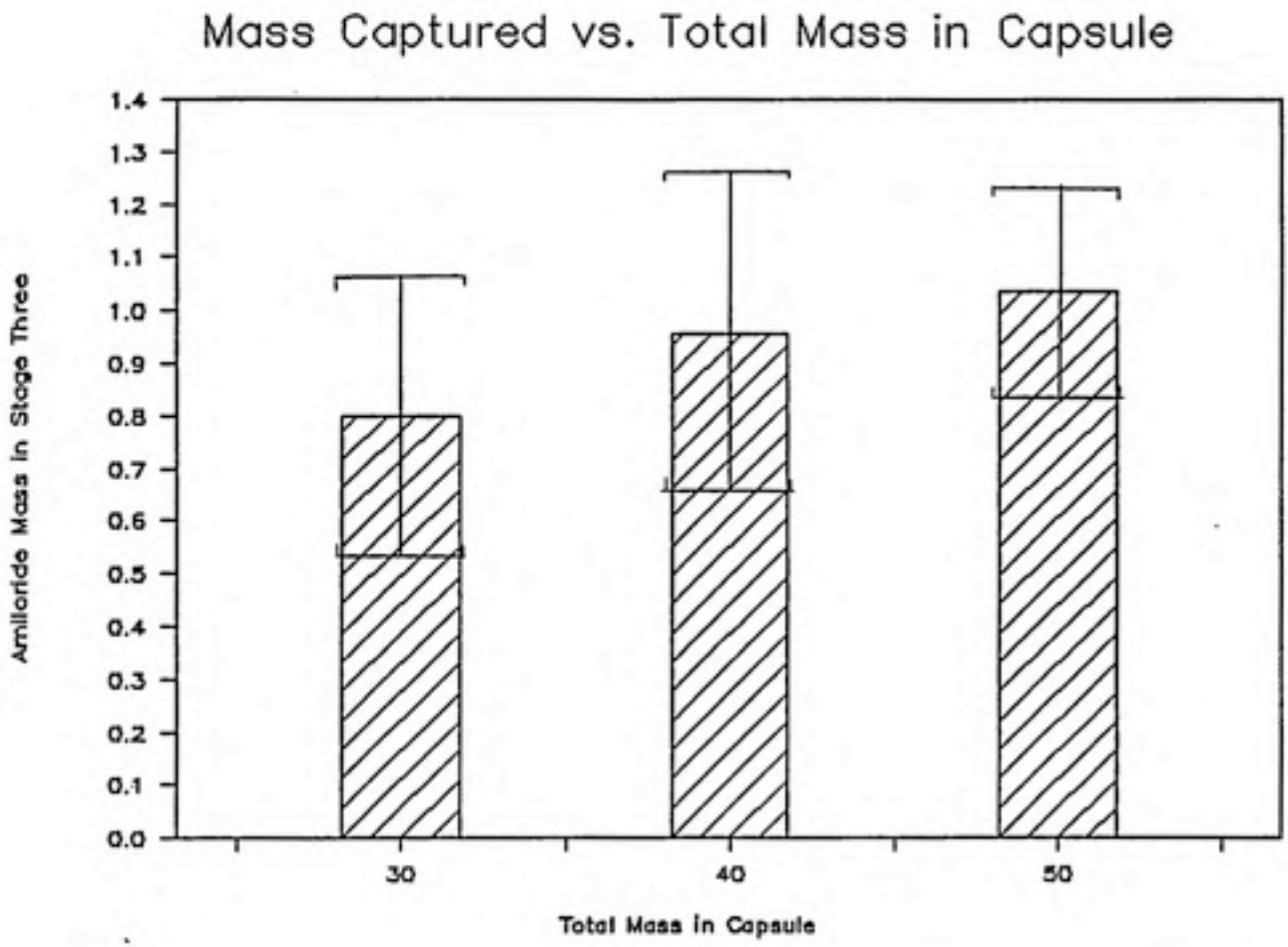

Chart 2

Amiloride Mass in Stage Three is plotted against
Total Mass of Amiloride in Capsule.
Standard Deviations are indicated by brackets.

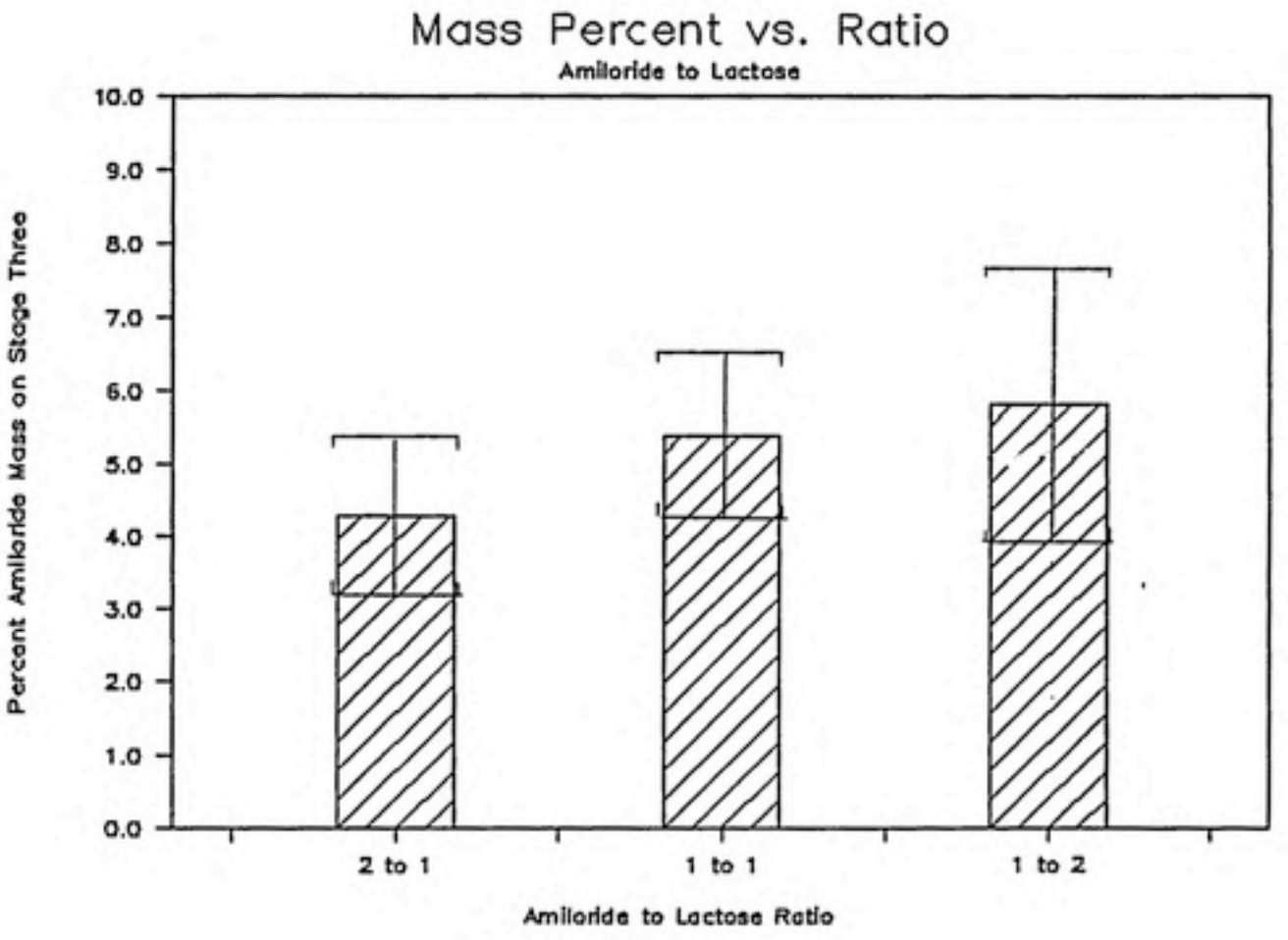

Chart 3

Percent Amiloride Mass on Stage Three is plotted against Amiloride to Lactose Ratio. Standard Deviations are indicated by brackets.

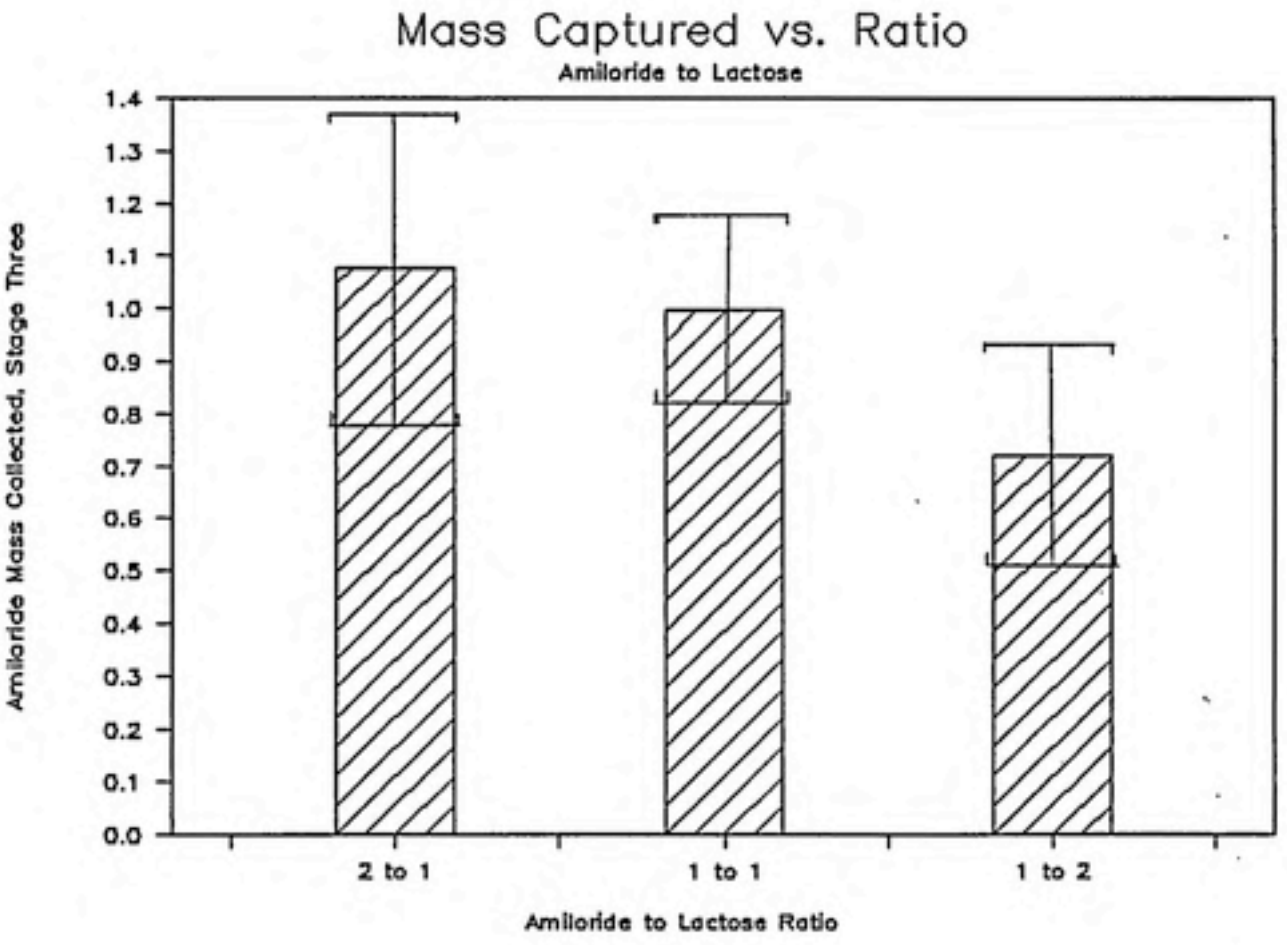

Chart 4

Amiloride Mass Collected on Stage Three is plotted against Amiloride to Lactose Ratio. Standard Deviations are indicated by brackets.

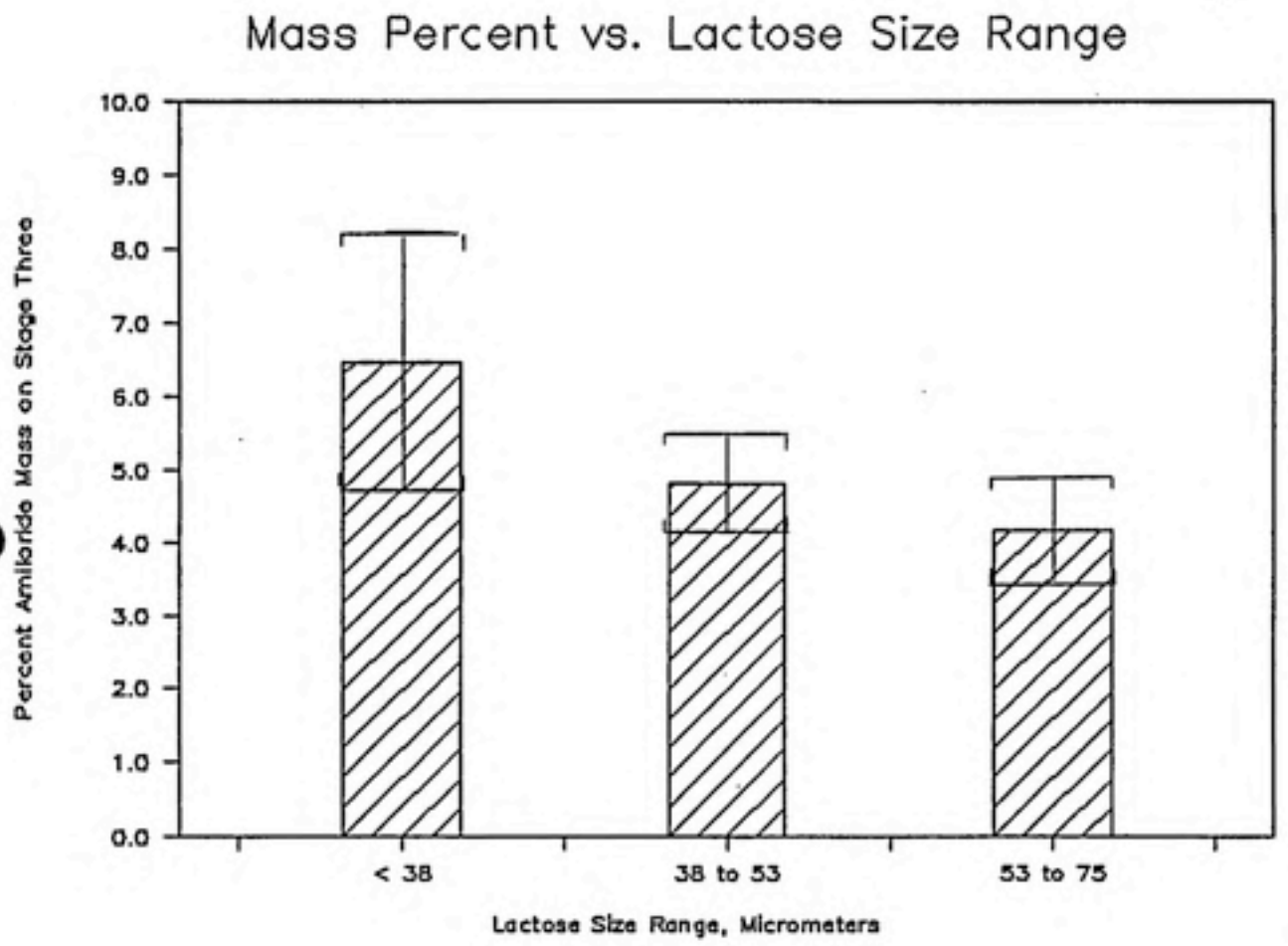

Chart 5

Percent Amiloride Mass on Stage Three is plotted against Lactose Size Range.
Standard Deviations are indicated by brackets.

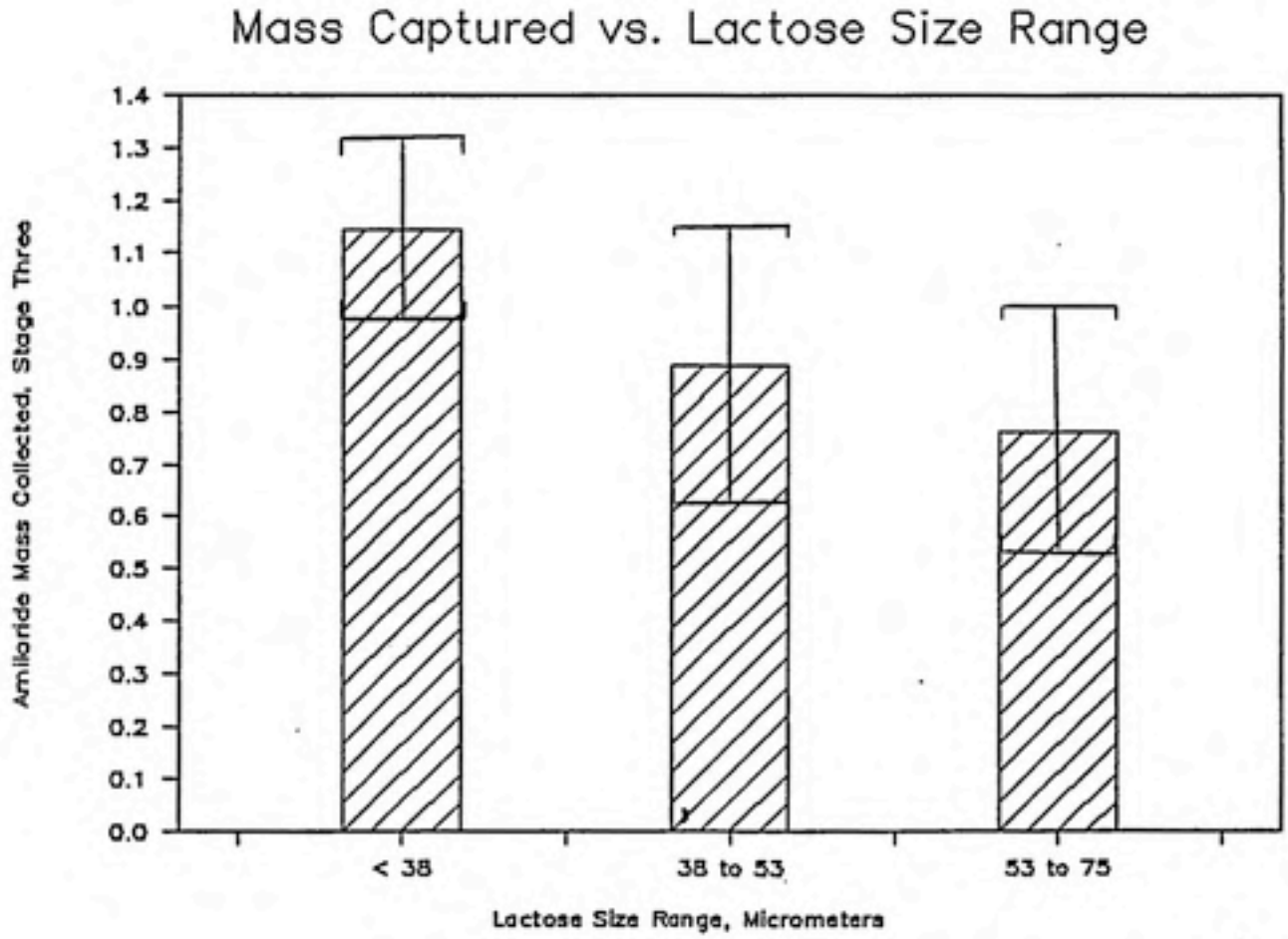

Chart 6

Amiloride Mass Collected on Stage Three is plotted against Lactose Size Range.
Standard Deviations are indicated by brackets.

Table 1

	AVERAGE % RECOVERY OF AMILORIDE	
	FOR 27 CONDITIONS	FOR IMPACTOR STUDY
SPINHALER	5.5	6.9
CAPSULES	3.4	2.8
IMPACTOR	----	28.4
THROAT	4.1	2.0
1ST STAGE	68.7	49.7
2ND STAGE	13.2	5.4
3RD STAGE	5.1	3.7
	AVERAGE MASS RECOVERY OF AMILORIDE IN MG	
	FOR 27 CONDITIONS	FOR IMPACTOR STUDY
SPINHALER	3.2	4.1
CAPSULES	2.0	1.6
IMPACTOR	----	16.6
THROAT	2.2	1.2
1ST STAGE	39.7	29.0
2ND STAGE	7.7	3.1
3RD STAGE	2.8	2.2

DISCUSSION

The reproducibility study confirmed that the experimental procedure could be repeated effectively. For particles < 3.3 um, all three independent variables had a significant effect on the total amiloride mass and the percent total amiloride dispersed into this range, $p<0.050$ for mass, and $p<0.001$ for percent. See Table 2. These results suggest that maximum dispersion occurs with 30 mg of amiloride and lactose in a 1:2 ratio and use of <38 um lactose. No significant interactions were found.

Analysis of variance found that the impactor significantly reduced the percent recovery for the top and middle stages, particles > 3.3 um $p<0.001$, but not for the bottom stage $p>0.429$.

Four Spinhalers were used during this work. After eleven experiments the amiloride HCL and flow-aid failed to discharge from the capsules on some trials. Spinhalers were replaced once they functioned inconsistantly.

ANALYSIS OF VARIANCE P VALUES

	STAGE 1	STAGE 2	STAGE 3
TOTAL PERCENT AMILORIDE RECOVERED			
MASS IN CAPSULE	<0.539	<0.220	<0.001
RATIO OF AMILORIDE TO LACTOSE	<0.651	<0.388	<0.001
LACTOSE SIZE RANGE	<0.732	<0.927	<0.001
PRESENCE OF IMPACTOR	<0.001	<0.001	<0.429
TOTAL MASS AMILORIDE RECOVERED			
MASS IN CAPSULE	<0.001	<0.025	<0.002
RATIO OF AMILORIDE TO LACTOSE	<0.001	<0.076	<0.001
LACTOSE SIZE RANGE	<0.841	<0.821	<0.001
PRESENCE OF IMPACTOR	<0.001	<0.099	<0.050

SUMMARY

Using lactose as a flow aid, results indicate that most amiloride dispersed is >3.3 um and too large to reach the tracheobronchial region. The fraction that is respirable depends on the size of amiloride particles, the amount of lactose flow-aid in capsule, the size of lactose particles and the ratio of amiloride to lactose. To maximize dispersion of respirable sizes use small <38 um size lactose particles, a 2:1 ratio of the flow-aid to drug, and 30 mg total mass in the capsule. The impactor can reduce the amount of large particles that reach the patient, without significantly diminishing the amount of particles 0.7 to 3.3 um that reach the patient.

ACKNOWLEDGEMENTS

I would like to extend special thanks to my advisor Dr. David Leith and the committee members Dr. Michael Flynn and Dr. Michael Knowles for their support and guidance during my study at the University of North Carolina. I would also like to thank Dr. Robert Harris for showing great patience and understanding.

I would especially like to thank Pat Gallarelli, (soon to be) Dr. Donna Lee Iozia, Dr. Chung-Te Lee, David and Donna Eley, and Dennis and Cynthia George for their friendship.

FUTURE WORK

- test < 30 mg total mass of drug and flow aid per sule
- test higher ratio of flow aid to drug per capsule
  - 3:1, 4:1, 5:1
- test < 38 um lactose particles
- test impactor with optimized combination of variables
- test with alternate flow aid

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APPENDIX

PERCENT PER CAPSULE
spinhaler

total mass in mg	ratio amiloride to lactose	size of lactose in microns	SPINHALER
		< 38	7.10 %
	two to one	< 53	6.10 %
		< 75	5.70 %
		< 38	3.90 %
30.00	one to one	< 53	8.30 %
		< 75	4.20 %
		< 38	4.70 %
	one to two	< 53	4.10 %
		< 75	7.40 %

total mass in mg	ratio amiloride to lactose	size of lactose	
		< 38	4.00 %
	two to one	< 53	5.30 %
		< 75	11.90 %
		< 38	5.50 %
40.00	one to one	< 53	6.50 %
		< 75	4.50 %
		< 38	3.70 %
	one to two	< 53	3.70 %
		< 75	6.30 %

total mass in mg	ratio amiloride in lactose	size of lactose	
		< 38	5.50 %
	two to one	< 53	4.50 %
		< 75	7.20 %
		< 38	4.10 %
50.00	one to one	< 53	7.10 %
		< 75	4.30 %
		< 38	3.10 %
	one to two	< 53	4.70 %
		< 75	3.90 %

PERCENT PER CAPSULE
capsule

total mass in mg	ratio amiloride to lactose	size of lactose in microns	CAPSULE
	two to one	< 38	3.50 %
		< 53	3.50 %
		< 75	4.40 %
30.00	one to one	< 38	4.40 %
		< 53	4.10 %
		< 75	3.00 %
	one to two	< 38	3.70 %
		< 53	3.80 %
		< 75	4.60 %

total mass in mg	ratio amiloride to lactose	size of lactose	
	two to one	< 38	5.00 %
		< 53	4.00 %
		< 75	6.60 %
40.00	one to one	< 38	2.20 %
		< 53	3.00 %
		< 75	3.30 %
	one to two	< 38	3.00 %
		< 53	1.90 %
		< 75	2.30 %

total mass in mg	ratio amiloride in lactose	size of lactose	
	two to one	< 38	3.40 %
		< 53	4.00 %
		< 75	3.40 %
50.00	one to one	< 38	3.50 %
		< 53	2.80 %
		< 75	2.10 %
	one to two	< 38	2.60 %
		< 53	1.60 %
		< 75	2.60 %

PERCENT PER CAPSULE
spinhaler & capsule

total mass in mg	ratio amiloride to lactose	size of lactose in microns	SPIN& CAP
		< 38	10.60 %
	two to one	< 53	9.60 %
		< 75	10.10 %
		< 38	8.30 %
30.00	one to one	< 53	12.40 %
		< 75	7.30 %
		< 38	8.50 %
	one to two	< 53	7.90 %
		< 75	12.00 %

total mass in mg	ratio amiloride to lactose	size of lactose in microns	
		< 38	8.90 %
	two to one	< 53	9.50 %
		< 75	18.40 %
		< 38	7.80 %
40.00	one to one	< 53	9.50 %
		< 75	7.80 %
		< 38	6.70 %
	one to two	< 53	5.60 %
		< 75	8.60 %

total mass in mg	ratio amiloride in lactose	size of lactose in microns	
		< 38	9.00 %
	two to one	< 53	8.50 %
		< 75	10.60 %
		< 38	7.60 %
50.00	one to one	< 53	9.90 %
		< 75	6.40 %
		< 38	5.80 %
	one to two	< 53	6.40 %
		< 75	6.60 %

PERCENT PER CAPSULE
throat

total mass in mg	ratio amiloride to lactose	size of lactose in microns	THROAT
		< 38	3.10 %
	two to one	< 53	3.00 %
		< 75	4.40 %
		< 38	4.20 %
30.00	one to one	< 53	3.40 %
		< 75	4.30 %
		< 38	5.80 %
	one to two	< 53	4.20 %
		< 75	6.40 %

total mass in mg	ratio amiloride to lactose	size of lactose in microns	
		< 38	4.50 %
	two to one	< 53	2.90 %
		< 75	4.10 %
		< 38	2.10 %
40.00	one to one	< 53	3.70 %
		< 75	4.10 %
		< 38	6.00 %
	one to two	< 53	4.20 %
		< 75	4.70 %

total mass in mg	ratio amiloride in lactose	size of lactose in microns	
		< 38	3.40 %
	two to one	< 53	3.10 %
		< 75	3.00 %
		< 38	3.80 %
50.00	one to one	< 53	3.00 %
		< 75	4.50 %
		< 38	5.10 %
	one to two	< 53	5.00 %
		< 75	4.70 %

PERCENT PER CAPSULE
top stage

total mass in mg	ratio amiloride to lactose	size of lactose in microns	TOP STAGE
		< 38	71.10 %
	two to one	< 53	82.50 %
		< 75	62.70 %
		< 38	59.10 %
30.00	one to one	< 53	64.40 %
		< 75	72.60 %
		< 38	62.20 %
	one to two	< 53	64.10 %
		< 75	69.10 %

total mass in mg	ratio amiloride to lactose	size of lactose in microns	
		< 38	68.60 %
	two to one	< 53	71.40 %
		< 75	52.00 %
		< 38	74.30 %
40.00	one to one	< 53	67.90 %
		< 75	76.80 %
		< 38	74.70 %
	one to two	< 53	73.30 %
		< 75	71.60 %

total mass in mg	ratio amiloride in lactose	size of lactose in microns	
		< 38	76.90 %
	two to one	< 53	64.70 %
		< 75	73.40 %
		< 38	56.50 %
50.00	one to one	< 53	75.10 %
		< 75	68.50 %
		< 38	47.00 %
	one to two	< 53	77.60 %
		< 75	79.30 %

PERCENT PER CAPSULE
middle stage

total mass in mg	ratio amiloride to lactose	size of lactose in microns	MIDDLE STAGE
	two to one	< 38	8.80 %
		< 53	1.10 %
		< 75	19.60 %
30.00	one to one	< 38	20.20 %
		< 53	14.20 %
		< 75	9.10 %
	one to two	< 38	13.40 %
		< 53	17.90 %
		< 75	8.40 %

total mass in mg	ratio amiloride to lactose	size of lactose in microns	
	two to one	< 38	11.90 %
		< 53	11.60 %
		< 75	21.80 %
40.00	one to one	< 38	9.50 %
		< 53	14.00 %
		< 75	8.60 %
	one to two	< 38	5.80 %
		< 53	11.90 %
		< 75	10.50 %

total mass in mg	ratio amiloride in lactose	size of lactose in microns	
	two to one	< 38	7.20 %
		< 53	19.60 %
		< 75	9.60 %
50.00	one to one	< 38	27.30 %
		< 53	7.40 %
		< 75	21.40 %
	one to two	< 38	36.70 %
		< 53	6.30 %
		< 75	4.80 %

PERCENT PER CAPSULE
bottom stage

total mass in mg	ratio amiloride to lactose	size of lactose in microns	BOTTOM STAGE
	two to one	< 38	6.30 %
		< 53	3.80 %
		< 75	3.10 %
30.00	one to one	< 38	7.80 %
		< 53	5.70 %
		< 75	5.20 %
	one to two	< 38	10.10 %
		< 53	5.90 %
		< 75	4.20 %

total mass in mg	ratio amiloride to lactose	size of lactos in microns	
	two to one	< 38	6.00 %
		< 53	4.70 %
		< 75	3.80 %
40.00	one to one	< 38	6.40 %
		< 53	4.80 %
		< 75	3.90 %
	one to two	< 38	6.80 %
		< 53	5.00 %
		< 75	4.70 %

total mass in mg	ratio amiloride in lactose	size of lactose in microns	
	two to one	< 38	3.50 %
		< 53	4.00 %
		< 75	3.30 %
50.00	one to one	< 38	4.80 %
		< 53	4.70 %
		< 75	5.00 %
	one to two	< 38	6.50 %
		< 53	4.70 %
		< 75	4.40 %

PERCENT PER CAPSULE
middle & bottom stage

total mass in mg	ratio amiloride to lactose	size of lactose in microns	MID & BOT STAGE
		< 38	15.10
	two to one	< 53	4.90
		< 75	22.80
		< 38	28.00
30.00	one to one	< 53	19.90
		< 75	14.30
		< 38	23.50
	one to two	< 53	23.80
		< 75	12.50

total mass in mg	ratio amiloride to lactose	size of lactos in microns	
		< 38	17.90
	two to one	< 53	16.30
		< 75	33.60
		< 38	15.90
40.00	one to one	< 53	18.90
		< 75	12.40
		< 38	12.60
	one to two	< 53	16.90
		< 75	15.30

total mass in mg	ratio amiloride in lactose	size of lactose in microns	
		< 38	10.70
	two to one	< 53	23.60
		< 75	13.00
		< 38	32.10
50.00	one to one	< 53	12.00
		< 75	26.30
		< 38	42.20
	one to two	< 53	11.00
		< 75	9.10

MASS PER CAPSULE
spinhaler

TOTAL MASS IN MG	RATIO AMILORIDE TO LACTOSE	SIZE OF LACTOSE IN MICRONS	SPINHALER
		< 38	1.40 mg
	two to one	< 53	1.07 mg
		< 75	1.10 mg
		< 38	0.57 mg
30.00	one to one	< 53	1.23 mg
		< 75	0.60 mg
		< 38	0.47 mg
	one to two	< 53	0.40 mg
		< 75	0.70 mg

TOTAL MASS IN MG	RATIO AMILORIDE TO LACTOSE	SIZE OF LACTOSE IN MICRONS	
		< 38	1.03 mg
	two to one	< 53	1.33 mg
		< 75	3.03 mg
		< 38	1.03 mg
40.00	one to one	< 53	1.27 mg
		< 75	0.87 mg
		< 38	0.50 mg
	one to two	< 53	0.47 mg
		< 75	0.77 mg

TOTAL MASS IN MG	RATIO AMILORIDE TO LACTOSE	SIZE OF LACTOSE IN MICRONS	
		< 38	1.80 mg
	two to one	< 53	1.43 mg
		< 75	2.33 mg
		< 38	1.00 mg
50.00	one to one	< 53	1.73 mg
		< 75	0.97 mg

MASS PER CAPSULE
capsules

total mass in mg	ratio amiloride to lactose	size of lactose in microns	CAPSULE
		< 38	0.67 mg
	two to one	< 53	0.63 mg
		< 75	0.83 mg
		< 38	0.63 mg
30.00	one to one	< 53	0.57 mg
		< 75	0.47 mg
		< 38	0.37 mg
	one to two	< 53	0.40 mg
		< 75	0.43 mg

total mass in mg	ratio amiloride to lactose	size of lactose in microns	
		< 38	1.27 mg
	two to one	< 53	1.10 mg
		< 75	1.67 mg
		< 38	0.43 mg
40.00	one to one	< 53	0.60 mg
		< 75	0.60 mg
		< 38	0.37 mg
	one to two	< 53	0.20 mg
		< 75	0.27 mg

total mass in mg	ratio amiloride in lactose	size of lactose in microns	
		< 38	1.10 mg
	two to one	< 53	1.30 mg
		< 75	1.07 mg
		< 38	0.83 mg
50.00	one to one	< 53	0.67 mg
		< 75	0.47 mg
		< 38	0.43 mg
	one to two	< 53	0.23 mg
		< 75	0.43 mg

MASS PER CAPSULE
spinhaler & capsule

total mass in mg	ratio amiloride to lactose	size of lactose in microns	SPIN&CAP
		< 38	2.07 mg
	two to one	< 53	1.70 mg
		< 75	1.93 mg
		< 38	1.20 mg
30.00	one to one	< 53	1.80 mg
		< 75	1.07 mg
		< 38	0.83 mg
	one to two	< 53	0.80 mg
		< 75	1.13 mg

total mass in mg	ratio amiloride to lactose	size of lactose in microns	
		< 38	2.30 mg
	two to one	< 53	2.43 mg
		< 75	4.70 mg
		< 38	1.47 mg
40.00	one to one	< 53	1.87 mg
		< 75	1.47 mg
		< 38	0.87 mg
	one to two	< 53	0.67 mg
		< 75	1.03 mg

total mass in mg	ratio amiloride in lactose	size of lactose in microns	
		< 38	2.90 mg
	two to one	< 53	2.73 mg
		< 75	3.40 mg
		< 38	1.83 mg
50.00	one to one	< 53	2.40 mg
		< 75	1.43 mg
		< 38	0.93 mg
	one to two	< 53	0.97 mg
		< 75	1.07 mg

MASS PER CAPSULE
throat

total mass in mg	ratio amiloride to lactose	size of lactose in microns	THROAT
30.00	two to one	< 38	0.60 mg
		< 53	0.53 mg
		< 75	0.87 mg
	one to one	< 38	0.60 mg
		< 53	0.50 mg
		< 75	0.63 mg
	one to two	< 38	0.57 mg
		< 53	0.40 mg
		< 75	0.60 mg

total mass in mg	ratio amiloride to lactose	size of lactose in microns	
40.00	two to one	< 38	1.17 mg
		< 53	0.73 mg
		< 75	1.55 mg
	one to one	< 38	0.40 mg
		< 53	0.73 mg
		< 75	0.77 mg
	one to two	< 38	0.77 mg
		< 53	0.53 mg
		< 75	0.57 mg

total mass in mg	ratio amiloride in lactose	size of lactose in microns	
50.00	two to one	< 38	1.10 mg
		< 53	1.00 mg
		< 75	0.97 mg
	one to one	< 38	0.93 mg
		< 53	0.73 mg
		< 75	1.00 mg
	one to two	< 38	0.80 mg
		< 53	0.80 mg
		< 75	0.77 mg

MASS PER CAPSULE
top stage

total mass in mg	ratio amiloride to lactose	size of lactose in microns	TOP STAGE
		< 38	13.93 mg
	two to one	< 53	14.70 mg
		< 75	12.20 mg
		< 38	8.60 mg
30.00	one to one	< 53	9.47 mg
		< 75	10.67
		< 38	6.17 mg
	one to two	< 53	6.07 mg
		< 75	6.53 mg

total mass in mg	ratio amiloride to lactose	size of lactose in microns	
		< 38	17.83 mg
	two to one	< 53	18.17 mg
		< 75	13.33 mg
		< 38	14.00 mg
40.00	one to one	< 53	13.27 mg
		< 75	14.67 mg
		< 38	9.67 mg
	one to two	< 53	9.37 mg
		< 75	8.80 mg

total mass in mg	ratio amiloride in lactose	size of lactose in microns	
		< 38	24.93 mg
	two to one	< 53	20.77 mg
		< 75	23.67 mg
		< 38	13.80 mg
50.00	one to one	< 53	18.37 mg
		< 75	15.33 mg
		< 38	7.50 mg
	one to two	< 53	12.23 mg
		< 75	12.90 mg

MASS PER CAPSULE
middle stage

total mass in mg	ratio amiloride to lactose	size of lactose in microns	MIDDLE STAGE
		< 38	1.73 mg
	two to one	< 53	0.20 mg
		< 75	3.83 mg
		< 38	2.93 mg
30.00	one to one	< 53	2.07 mg
		< 75	1.33 mg
		< 38	1.33 mg
	two to one	< 53	1.70 mg
		< 75	0.80 mg

total mass in mg	ratio amiloride to lactose	size of lactose in microns	
		< 38	3.10 mg
	two to one	< 53	2.93 mg
		< 75	5.60 mg
		< 38	1.77 mg
40.00	one to one	< 53	2.73 mg
		< 75	1.63 mg
		< 38	0.73 mg
	two to one	< 53	1.50 mg
		< 75	1.30 mg

total mass in mg	ratio amiloride in lactose	size of lactose in microns	
		< 38	2.33 mg
	two to one	< 53	6.27 mg
		< 75	3.10 mg
		< 38	6.67 mg
50.00	one to one	< 53	1.80 mg
		< 75	4.77 mg
		< 38	5.70 mg
	one to two	< 53	1.00 mg
		< 75	0.77 mg

MASS PER CAPSULE
bottom stage

total mass in mg	ratio amiloride to lactose	size of lactose in microns	BOTTOM STAGE
30.00	two to one	< 38	1.23 mg
		< 53	0.67 mg
		< 75	0.60 mg
	one to one	< 38	1.13 mg
		< 53	0.83 mg
		< 75	0.77 mg
	one to two	< 38	1.00 mg
		< 53	0.57 mg
		< 75	0.40 mg

total mass in mg	ratio amiloride to lactose	size of lactose in microns	
40.00	two to one	< 38	1.53 mg
		< 53	1.20 mg
		< 75	0.97 mg
	one to one	< 38	1.20 mg
		< 53	0.93 mg
		< 75	0.73 mg
	one to two	< 38	0.87 mg
		< 53	0.63 mg
		< 75	0.57 mg

total mass in mg	ratio amiloride in lactose	size of lactose in microns	
50.00	two to one	< 38	1.13 mg
		< 53	1.30 mg
		< 75	1.07 mg
	one to one	< 38	1.17 mg
		< 53	1.13 mg
		< 75	1.07 mg
	one to two	< 38	1.03 mg
		< 53	0.73 mg
		< 75	0.70 mg

MASS PER CAPSULE
middle & bottom stage

total mass in mg	ratio amiloride to lactose	size of lactose in microns	M&B STAGE
		< 38	2.97 mg
	two to one	< 53	0.87 mg
		< 75	4.43 mg
		< 38	4.07 mg
30.00	one to one	< 53	2.90 mg
		< 75	2.10 mg
		< 38	2.33 mg
	one to two	< 53	2.27 mg
		< 75	1.20 mg.

total mass in mg	ratio amiloride to lactose	size of lactose in microns	
		< 38	4.63 mg
	two to one	< 53	4.13 mg
		< 75	6.57 mg
		< 38	2.97 mg
40.00	one to one	< 53	3.67 mg
		< 75	2.37 mg
		< 38	1.60 mg
	one to two	< 53	2.13 mg
		< 75	1.87 mg

total mass in mg	ratio amiloride in lactose	size of lactose in microns	
		< 38	3.47 mg
	two to one	< 53	7.57 mg
		< 75	4.17 mg
		< 38	7.83 mg
50.00	one to one	< 53	2.93 mg
		< 75	5.83 mg
		< 38	6.73 mg
	one to two	< 53	1.73 mg
		< 75	1.47 mg