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DEVELOPMENT OF A HIGH-DOSE TECHNETIUM Tc 99M LABELED SULFUR COLLOID METERED DOSE INHALATION AEROSOL

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ABSTRACT

Radiolabeled Technetium sulfur colloid metered dose inhalation aerosol (MDI) suitable to evaluate pulmonary deposition from inhalation devices has been developed by using a lyophilization process to prepare the radiolabeled material for aerosolization. The reproducibility of the manufacturing process was demonstrated by characterizing the aerosol performance with respect to dose delivery, particle size, and valve delivery.

INTRODUCTION

Radiolabeled pressurized metered dose inhalation aerosols (MDI) are used to determine pulmonary and oropharyngeal deposition of inhaled drugs delivered via MDIs and also to evaluate performance of inhalation devices used in conjunction with MDIs. Radiolabeled MDIs containing bromine-77[1] and Technetium 99m were utilized to determine lung

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deposition of drugs from MDI's[2-5], drug deposition from extension devices[6], and dry powder inhalers[7].

Several studies have shown that the pulmonary deposition of the dose delivered from MDIs is only about 10%. This is primarily due to the turbulence caused by the propellant and impaction of larger particles in the oropharynx[3,8-11]. In view of the poor drug delivery problems associated with MDIs, simple spacer (e.g. Aerochamber™, Breathancer™,) and chamber shape (e.g.InspirEase®, Inhal-Aid®, Nebuhaler®) extension devices that are interposed between the MDI and the patient's mouth have been developed. The use of extension devices with the MDIs have been shown to enhance pulmonary deposition and minimize oropharyngeal deposition[12-17].

Pulmonary deposition performance of these inhalation devices which are different in design and shape can be evaluated by administering a radioactive MDI aerosol spray via these devices and monitoring the pulmonary deposition profiles. Pulmonary deposition studies conducted earlier required administration of several sprays of radiolabeled material (Table 1) to obtain adequate dose for imaging. Normal inhalation dosage of MDIs is usually one or two sprays. Development of a high dose radiolabeled aerosol that can deliver a sufficient radioactive dose within a single spray will allow to evaluate pulmonary deposition of different inhalation devices under normal MDI usage conditions.

The purpose of the present study is to develop a high dose radiolabeled MDI that delivers not less than one millicurie of radioactivity per spray. Additionally, manufacturing process reproducibility would be evaluated by testing dose delivery performance, content uniformity, and particle size analysis of the aerosol.

MATERIALS AND METHODS

Materials

TSC Kit for the Preparation of Technetium Tc 99m Sulfur Colloid (TSC) Injection was obtained from Medi-Physics Inc. (Paramus, NJ).

TABLE 1

Number of doses, radioactivity per spray, and total radioactive dose administered for lung imaging studies with MDIs

Study	Radioactivity per spray (uCi)	Number of sprays administered	Total radioactivity administered* (uCi)
Newman et al.,[2]	10	6	60
Newman et al.,[3]	10	10	100
Vidgren et al.,[4]	10	10	100
Vidgren et al.,[7]	20	5	100
Zainudin et al.,[6]	81	4	324

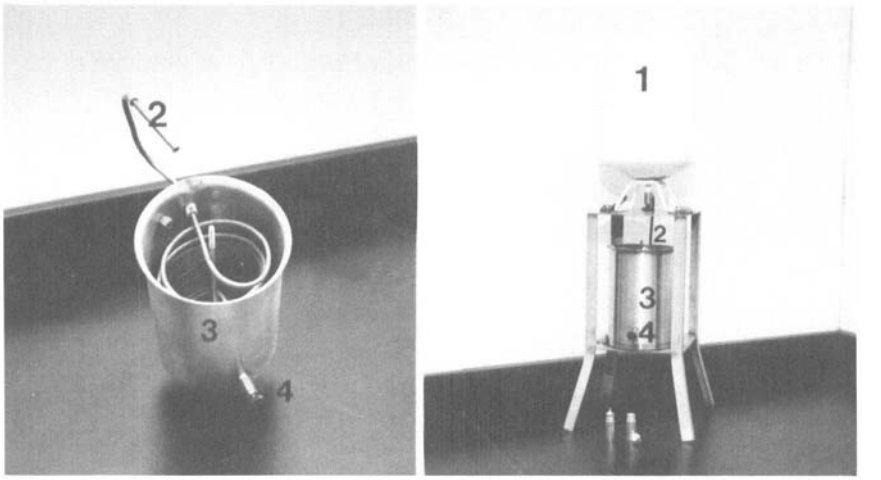
* Calculated by multiplying the radioactivity per spray by the number of sprays administered for imaging.

Dichlorodifluromethane (Freon 12) was obtained from Dupont (Deepwater, NJ). 100 ul, Model DF10 aerosol valves and 19 ml Presspart anodized aluminum cans were obtained from Valois (France). Sodium standards used for sodium analysis were obtained from Orion Research (Cambridge, MA). Mo 99 Technetium generator used to prepare sodium pertechnetate solution was obtained from Mallinkrodt Medical Inc. (Maryland Heights, MO)

Methods

Manufacturing Procedure

A metered dose Technetium Sulfur Colloid (TSC) aerosol was prepared using the TSC kit from Medi-Physics. Before making the radiolabeled aerosols, all process conditions were fully evaluated and optimized by preparing the aerosols without radioactivity. One complete



1. Propellant tank 2. Propellant fill line 3. Chill chamber
4. Propellant pour-out spout

FIGURE 1
Cold-Fill Equipment

TSC kit was used for each TSC aerosol and the processing steps are as follows:

TSC injection kit was reconstituted following the manufacturer's directions described in the package insert. The reconstituted TSC injection was poured into a glass petri dish and lyophilized using a Virtis Bench Top 3 Model lyophilizer (The Virtis Co., Gardiner, NY). The lyophilized TSC powder from the petri dish was transferred to a tared 19 ml aluminum aerosol canister and the net TSC powder in the canister was determined. The total number of doses per canister was determined based on 4 mg of TSC powder dosing per spray, and the quantity of Freon 12 required was determined based on 100 ul spray per each dose. Sufficient quantity of Freon 12 was added to the TSC powder aerosol canister using a cold-fill equipment (see Figure 1) fabricated in our laboratory.

A high intensity ultrasonic processor (Daiger Scientific, USA) fitted with a micro tip was pre-chilled, placed into the aerosol canister containing

the TSC powder, sonicated for sixty seconds, and a 100 ul metered dose aerosol valve was crimped on using a Socoge (France) aerosol valve crimper. The crimped TSC aerosol was leak-checked by immersing in a water bath at 40-50^{O}C, and valve delivery was checked by testing the spray weight and/or radioactivity per spray.

TSC Aerosol Test Methods - Process Evaluation

Sodium Ion Analysis: The dried TSC powder contains 28% sodium. Content uniformity of TSC aerosol canisters and the valve delivery performance were evaluated by testing the sodium content using a Orion Research Model 940 Expandable Ion Analyzer (Boston, MA) equipped with Model 84-11 Ross^{TM} sodium electrode supplied by Orion Research.

Particle Size Distribution: Particle size distribution of TSC aerosol sprays was measured using Anderson Mark II, 8 stage cascade impactor (Atlanta, Georgia) equipped with a preseparator. The air flow rate was maintained at 21 liters per minute. TSC aerosol canister was shaken and 5 sprays were actuated into the preseparator. After 1 minute an additional 2 sets of 5 sprays were dispensed into the preseparator allowing a 1 minute interval between each set. After a 15 minute settling interval TSC powder deposited on stages 0 thru 5 were collected into separate 25 ml volumetric flasks using purified water. The TSC powder collected on stages 6 and 7 was combined by washing into the same 25 ml volumetric flask. The amount of TSC powder deposited on each stage was determined by testing the sodium content of the samples collected from each stage.

Particle size distribution of TSC aerosols was also measured by laser ensemble light scattering technique using Malvern Series 2600c Droplet and Particle Sizer Analyzer (Malvern, England). TSC aerosol powder collected from the sprays was suspended in hexane and the particle size measurements were made.

Radioactivity Measurement: Radioactivity of the TSC aerosol canister and the dose delivered per each spray were measured using a Radioisotope Dose Calibrator^{R} CRC-30B6 (Pittsburgh, PA).

RESULTS AND DISCUSSION

Reconstituted TSC injection is an aqueous colloidal dispersion that is not miscible with the propellants used in MDIs. The removal of water from the reconstituted TSC solution allows to prepare TSC aerosol by dispersing the dried TSC in a suitable propellant. Spray drying, vacuum drying and lyophilization techniques were evaluated to dry the reconstituted TSC solution. Vacuum drying resulted in agglomerates of large particles and the TSC powder was unsuitable for MDIs. Spray drying yielded a TSC powder acceptable for MDI use, however this process has the disadvantage of TSC powder losses via the filter bag. Lyophilization process used in this study minimizes powder losses during drying and the dried material is suitable for use in MDIs.

TSC aerosol manufacturing process time was optimized to complete the aerosol preparation within 6 hours. Because of the 6 hr. half-life of Technetium Tc 99m, the finished TSC aerosol retains half the initial radioactivity.

Content Uniformity

The quantity of TSC powder for one TSC injection based on theoretical calculations is 200 mg. After lyophilization, the average TSC powder yield in the petri dish per TSC injection was 184 mg (n=6, % RSD=1.5). During the transfer of TSC powder from the petri dish to the canister some of the powder adheres to the petri-dish, and the average net weight of TSC powder transferred to the canister was found to be 172 mg (n=8, % RSD=1.7).

The theoretical sodium content of one reconstituted TSC injection is 56 mg. Content uniformity by sodium ion analysis after lyophilization in petri dish and sonication in the aerosol canister, the average sodium content per canister was found to be 49.5 mg (n=3, %RSD 1.3) and 46.6 mg (n=3, %RSD 2.1) respectively.

Sodium content for all the above samples was found to be between 28 to 29% w/w (theory 28% w/w sodium). These data show the process to

TABLE 2

Dose delivery performance of TSC aerosol canisters

Canister No.	mcg of sodium per spray			
	Beginning	Middle	End	Mean (%RSD)
1	975	970	885	943 (5.4)
2	990	950	995	978 (2.5)
3	995	1010	935	980 (4.0)
	(All sprays from 3 canisters)			967 (4.0)

be reproducible and the small TSC powder losses observed at each stage are consistent.

Dose Delivery Performance

The theoretical sodium content of TSC aerosol spray is 1120 mcg for the 4 mg TSC powder dose. Individual sprays collected from the beginning, middle, and end portions of the canister showed an average sodium content of 967 mcg per spray. These data presented in Table 2 show the dose delivery from 3 cans ranged from 885 to 1010 mcg which is well within the acceptable range (75 to 125% of theory) expected for inhalation aerosol formulations.

Valve Delivery Performance

Valve delivery test results presented in Table 3 show that each TSC aerosol canister delivered not less than 30 doses and the variability between the canisters for the average spray weight is within $\pm$3%. Individual sprays within the canister show little variation with a RSD of less than 3% for all canisters.

TABLE 3

Valve delivery performance of TSC aerosol canisters

Canister No.	No. of sprays delivered	Ave. spray wt. in mg (% RSD)
1	30	131 (1.7)
2	33	128 (1.9)
3	30	128 (1.4)
4	30	128 (3.0)

Particle Size Distribution

Laser light scattering method: Mean particle size diameter of TSC aerosols was 19.5 ± 1.4 microns (n=4 canisters, %RSD 1.8), and 7.2% of particles are between 1 and 5 microns (n=4 canisters, %RSD 8.8).

Cascade Impactor method: Particle size fraction collected between stages 3 and 5 (1.1 - 4.7 microns[18]) was 8.1% (n=3 canisters, %RSD 17.8).

Particle size analysis of TSC aerosols by two separate methods show similar values for the percent respirable particles between 1 and 5 microns.

Dose Delivery from Radiolabeled TSC Aerosol

Radiolabeled TSC aerosol was prepared using sodium pertechnetate solution containing 250 millicurie of radioactivity. After the 6 hr. manufacturing process, based on 50 doses per canister the theoretical radioactive dose expected through the valve was 2.5 millicuries. The mean radioactive dose delivered through the valve for this canister was 2.45 millicuries (n=6) with a RSD of 3.4%.

CONCLUSIONS

The process characterization data presented in this paper for the non-radioactive TSC aerosol show the manufacturing process to be reproducible, delivers TSC doses satisfactorily from the valve, and exhibit similar particle size profiles. Radioactive TSC aerosol data show that the aerosol made by this process delivers high doses of radioactivity accurately for each dose.

Radiolabeled TSC aerosols made by this process were later successfully used in two separate gammascintigraphic studies in human volunteers by the administration of a single dose of TSC aerosol. These In vivo studies conducted to evaluate the pulmonary deposition profiles of different inhalation devices are the subject of a separate research publication.

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REFERENCES

1. M.D. Short, C.A. Sing, F.D. Few, P.T. Studdy, J.D. Heaf, and S.G. Spiro, Chest, 80 Suppl. 918 (1981).

2. S.P. Newman, F. Moren, D. Pavia, F. Little, and S.W. Clarke, Rev Respir. Dis. 124 317 (1981b).

3. S.P. Newman, D. Pavia, N. Garland, and S.W. Clarke, Air. J. Raspier. Dis., 63 Suppl. 119, 57 (1982).

4. M.T. Vidgren, A. Karkkainen, P. Karjalainen, and T. Paronen, Int. J. Pharm., 37 239 (1987).

5. M. T. Vidgren, T.P. Paronen, A. Karkkainen, and P. Karjalainen, Int. J. Pharm., 39 107 (1987).

6. B.M.Z. Zainudin, S.E.J. Tolfree, M. Biddiscombem, M. Whitaker, M.D. Short, and S.G. Spiro, Int. J. Pharm. 51 67 (1989).

7. M. T. Vidgren, T.P. Paronen, P. Vidgren, P. Vainio, and J. Nuutinen, Int. J. Pharm., 64 1 (1990).

8. D.S. Davies, Postgrad. Med., 51, Suppl. 7, 69 (1975).

9. D.S. Davies, J. Resp. Dis., 63 Suppl. 119, 67 (1982).

10. S.P. Newman, D. Pavia, F. Moren, N.F. Sheahan, and S.W. Clarke, Thorax, 36 52 (1981).

11. M.B. Dolovich, R.E. Ruffin, R. Roberts, and M.T. Newhouse, Chest, 80 Suppl. 911 (1981).

12. J. J. Sciarra, and A. Cute, J. Pharm. Sci., 67 1428 (1978).

13. B. Freigang, Can. Med. Assoc. J., 117 1308 (1977).

14. F. Moren, Int. J. Pharm., 1 205 (1978).

15. D. Corr, M.B. Dolovich, D. McCormik, R. Ruffin, G. Obminski, and M.T. Newhouse, J. Aerosol. Sci., 13 1 (1982).

16. M.J. Tobin, J. Janouri, I. Danta, C. Kim, H. Watson, and M.A. Sackner, Am. Rev. Respir. Dis., 126 670 (1982).

17. J.H. Toogood, B. Jennings, J. Baskerville, and S.A. Johansson, Eur. J. Respir. Dis., 63 Suppl. 122, 100 (1982).

18. Anderson cascade impactor operating manual