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Does size really matter

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Title: Does size really matter- relationship of particle size to lung deposition and exhaled fraction.

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Abstract: Particle size is the major determinant in the deposition and distribution of inhaled drug within the lungs and hence is related to local efficacy. It has been previously thought that however, extra fine particles are mostly exhaled. Our data demonstrates that extra fine particles are not associated with an appreciably higher exhaled fraction.

1 **Does size really matter- relationship of particle size to lung deposition and exhaled fraction.**

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8 **Declaration of funding: Unrestricted grants from Department and from Chiesi**

9 **Capsule summary:** We demonstrate that extra-fine particles are not associated with an appreciably
10 higher exhaled fraction, hence explaining their efficacy profile in asthma.

11 **Keywords:** Particle size, exhaled, lung deposition, asthma

12 **Word Count:** 944

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14 Particle size is the major determinant in the deposition and distribution of inhaled drug within the lungs
15 and hence is related to local efficacy . The particle size distribution of an aerosol is usually expressed in
16 terms of its mass median aerodynamic diameter (MMAD). Particles deposit in the respiratory tract by
17 inertial impaction (3-6 μ m), sedimentation (1-3 μ m) and diffusion (<1 μ m). In order to reach the lower
18 respiratory tract past the carina the MMAD of inhaled particles should be less than 5 μ m in diameter ,
19 specifically the particle size with the most efficient deposition in the small airways ,so called extra fine
20 particle fraction is said to be <2 μ m (1) . It has been demonstrated that smaller particles of inhaled
21 salbutamol achieve greater overall lung deposition, along with greater peripheral lung distribution (2).
22 Moreover smaller particles of long acting beta-agonist are also associated with improved small airways
23 responses measured by impulse oscillometry (3).

24 Whilst it is widely accepted that for efficient lung deposition, the MMAD should be lower than 5 μ m, it is
25 more controversial what happens to small particles with MMAD lower than 1 μ m. It conventionally
26 believed that, particles <1 μ m are mainly exhaled and therefore may not able to elicit any therapeutic
27 activity within the lungs, due to their extremely low settling velocity. Conversely, it could be argued that
28 although small particles have a greater potential to be exhaled, this is counterpoised by their capability

29 to be distributed throughout the whole lungs and reach the distal airways with a high pulmonary
30 deposition .We have therefore evaluated the relationship between in vitro MMAD and in vivo lung
31 deposition (LD), and the exhaled fraction (EF) expressed as fraction of the delivered dose, using pooled
32 analysis from relevant literature using scintigraphic studies conducted in healthy volunteers and
33 asthmatic patients using pMDI or DPI. Moreover the relationship between the ratio of EF to LD and
34 MMAD was also evaluated.

35 We used pooled data (supplementary table) from 18 different studies ,comprising 32 separate inhaled
36 formulations , in healthy subjects (n=173) and asthmatics (n=124) ,21 formulations in healthy
37 volunteers, 15 with pressurised metered dose inhalers (pMDI) and 6 with dry powder inhalers (DPI); and
38 11 formulations in asthmatic patients, 8 with pMDI and 3 with DPI were evaluated. All participants were
39 aged 18-65, and asthmatic patients had a mean FEV₁ of 85% predicted, we combined the data in asthma
40 patients with that of healthy volunteers. All subjects were non smokers .

41 Lung deposition increased in relation to decreased MMAD, such that when the MMAD was around 1 μm
42 the lung deposition exceeded 50% of the delivered dose and became markedly lower when MMAD
43 approaches 4 μm (Figure 1a). Pointedly this pattern was similar in healthy and asthmatic patients. The
44 exhaled fraction remained low irrespective of particle size. The mean amount of particles exhaled
45 amounted to approximately 5 % of the emitted dose thus demonstrating that such extra fine particles
46 are suitable for inhalation. Furthermore, the ratio of the amount exhaled to the amount deposited in
47 the lung was found to be independent from the MMAD (Figure 1b).

48 Our findings are consistent with previous data with inhaled salbutamol which similarly demonstrated
49 that total lung deposition was greatest in particles with a MMAD of 1.5 μm compared to particles of 3 μm
50 and 6 μm (4). It could be argued that the ability to correctly perform the inhalation including an
51 adequate breath-holding is likely to decrease the amount of exhaled drug. In this regard in all of the
52 included studies in our cohort , inhaler technique with a given device was standardised .Previous data(5)
53 have demonstrated that extra-fine particles are able to reach the small airways more effectively and
54 hence achieve better drug distribution throughout the whole bronchial tree. Interestingly they also
55 indicate that the exhaled fraction is approximately 12 % of the dose deposited in the lung and is totally
56 independent from the MMAD further confirming that extra-fine particles are suitable for inhalation. The
57 clinical relevance of extra-fine particles <2 μm has been demonstrated by Nicolini and colleagues (6)
58 who compared extra-fine (MMAD 1.1 μm) versus coarse particle HFA-beclometasone (MMAD 3.5 μm) ,
59 in individuals with asthma, and demonstrated the extra-fine particles significantly reduced both

60 bronchial and alveolar exhaled nitric oxide unlike coarse particle, which only reduced bronchial exhaled
61 nitric oxide. Moreover, extra-fine HFA-flunisolide (MMAD 1.2 μ m) has been shown to reduce histological
62 evidence of eosinophilic and interleukin 5 mediated inflammation in peripheral and central airways after
63 6 weeks of treatment (7). If these extra-fine particles were mostly exhaled, as conventionally believed,
64 one would not expect there to be an improvement in small airway inflammation as evidenced invasively
65 and non-invasively. It should be appreciated that there will be a normal distribution of particle size
66 around the MD ,such with an MMAD of 1.1 μ m there will be a proportion of particles <1 μ m. In this
67 regard such smaller particles may be absorbed from the alveoli and potentially increase systemic
68 adverse effects , although such alveolar deposition might also contribute to anti-asthmatic efficacy as
69 shown in association with the nocturnal phenotype (8). Our asthma cohort of asthma patients had an
70 FEV1 of 85% predicted, in this regard it has been shown that there is evidence of small airways
71 dysfunction in terms of a raised peripheral airways resistance occurring in approximately of half of
72 patients who have a preserved FEV1 >80% predicted (9).

73 In summary the present data demonstrate that the EF/LD ratio is independent from the MMAD,
74 suggesting that extra-fine particles will not be associated with an appreciably higher exhaled fraction.
75 Further prospective studies are required to assess how this relates to clinical efficacy in patients with
76 more severe asthma, perhaps using impulse oscillometry to better assesses the small airways (10).

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Does size really matter – relationship of particles size to lung deposition and exhaled fraction.

Figure 1.a

Lung deposition (circles) and Exhaled drug (squares) as function of MMAD (μm). Regression line and the 95% confidence intervals are also shown.
Pooled data from 18 different studies, comprising 32 separate inhaled formulations, each point represents a particular formulation. Lung deposition (circles) and Exhaled drug (squares) as function of MMAD (μm). Regression line and the 95% confidence intervals are also shown.

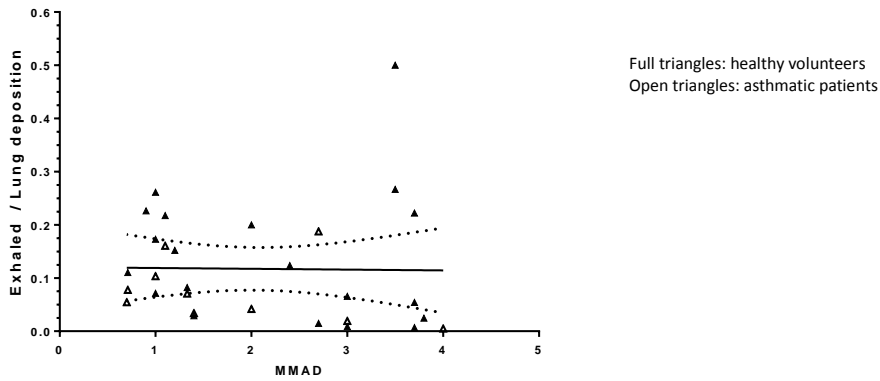
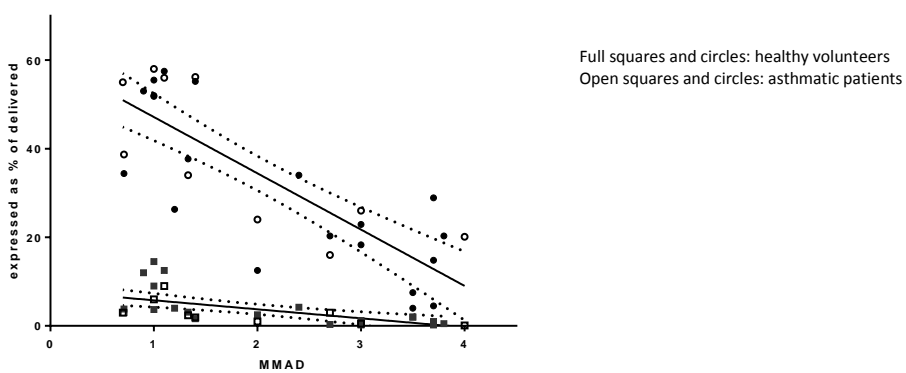


Figure 1.b

Ratio of Exhaled vs lung deposited drug as function of MMAD (μm). Regression line and the 95% confidence intervals are also shown.

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Figure 1.a

Pooled data from 18 different studies, comprising 32 separate inhaled formulations, each point represents a particular formulation. Lung deposition (circles) and Exhaled drug (squares) as function of MMAD (μm). Regression line and the 95% confidence intervals are also shown.

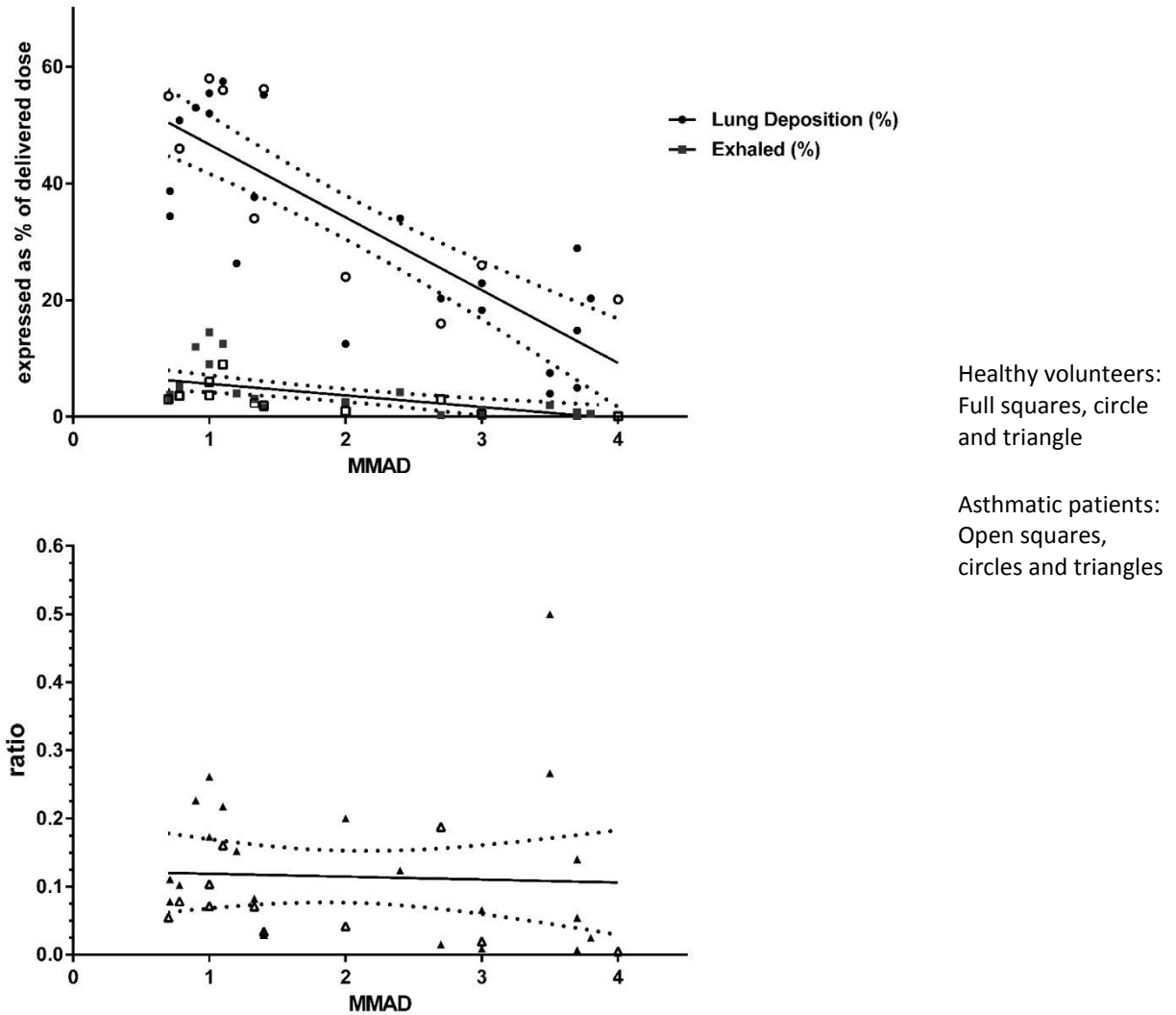


Figure 1.b

Ratio of Exhaled vs lung deposited drug as function of MMAD (μm). Regression line and the 95% confidence intervals are also shown.

Supplementary Table 1:

Source data

Häussermann S, Acerbi D, Brand P, Hederer B, AustenHerpich C, Poli G, Dewberry H, Sommerer K, Meyer T. Higher lungLung deposition with Respimat® Soft Mist™ Inhaler than of formoterol HFA-MDI (Atimos/Forair) in healthy volunteers, asthmatic and COPD patients with poor technique. International Journal of Chronic Obstructive Pulmonary Disease. 2008; J Aerosol Med. 2007 Fall;20(3(4):763-770):331-41.	
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