

INTRODUCTION

- The Respira™ inhaler is a passive dry powder device, which utilizes the inhalation energy of the patient, transferring this energy to efficiently detach and deaggregate micronized drug particles

- Fine particle fractions in excess of 80% have been achieved across several drug classes (1)

- It is largely flow-rate independent (2-5) and, due to its simple and original design, delivers the pure drug particulates without the need for lactose carriers or costly electronic drivers

- The Respira technology is uncomplicated and consists simply of a millimeter-sized bead coated with pure micronized drug powder (2-5)

- The energy of inhalation effort alone, even at very low inspiratory efforts, is sufficient to induce rapid oscillations of the bead within the device, thus generating large forces that detach the drug particles from the bead surface, producing an aerosol of fine drug

The purpose of the present *in vivo* study

- To compare the Respira technology to a leading marketed inhaler via a blinded, cross-over lung scintigraphy study investigating the regional deposition of inhaled radiolabeled Albuterol (ALB) from Respira's technology compared to the traditional lactose blend of radiolabeled ALB (1% w/w)

- Notably, the Respira technology was not optimized for performance, but rather designed to enable appropriate blinding. Thereby, a head-to-head comparison of radiolabelled-ALB lung deposition from the Spiriva Handihaler®, versus the Respira bead technology housed within a Handihaler could be achieved (Fig 1)

MATERIALS AND METHODS

Test Inhaler (Respira): Albuterol sulfate (ALB) was radiolabeled with technetium (^{99m}Tc)

Reference Inhaler (Handihaler®): A lactose blend of radiolabeled ALB (1% w/w)

Blinding the Inhalers: The Respira technology was blinded to the patients by containing it within a Handihaler® device

In vitro Validation of ^{99m}Tc Labeling: In order to validate the labeling technique, linearity of deposition of radiolabeled ALB with ^{99m}Tc radiolabel was assessed using a Next Generation Impactor (NGI) at 45L/min (4kPa pressure drop)

In vivo Study:

- A single dose was inhaled (ALB; 150-200µg labeled with ^{99m}Tc) on separate randomized study days from either device, Respira Technology or Handihaler

- The subject was instructed to target an inhaled flow rate of 45L/min using a pneumotach device, followed by breath holding for 10 sec. Exhalation onto a filter trapped any exhaled radioactivity

- A cobalt 57 transmission scan prior to inhalation was used to define the lung borders. Immediately after dosing, posterior planar images of the head and torso were taken using a gamma camera

- The doses of radioactivity inhaled from the Respira and the Handihaler devices were kept constant. Any disparity between devices was accounted for through normalization to the same median count

- Deposited counts in the head, lung, and stomach were corrected for tissue attenuation, as appropriate

- Percentage doses remaining in the device, deposited in the lungs, oropharynx and exhaled air were quantified

RESULTS AND DISCUSSION

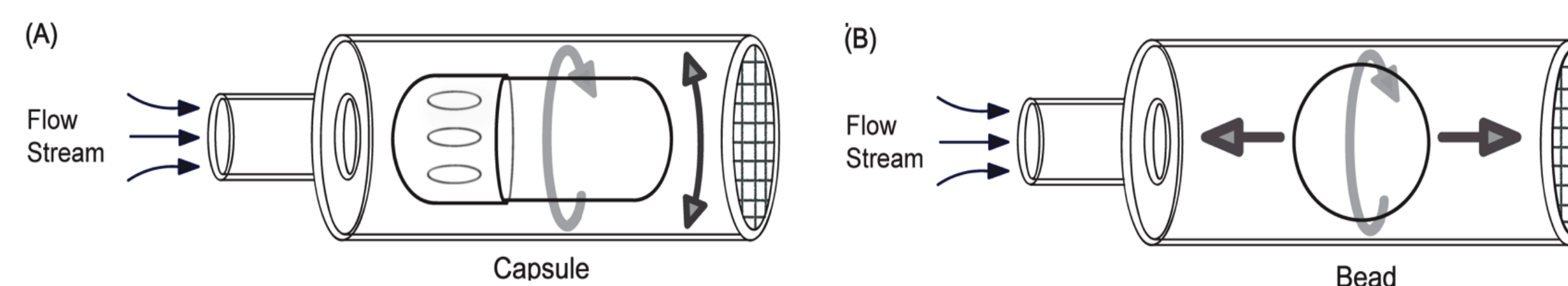


Figure 1. Illustration depicting the relative motions of: (A) a gelatin capsule; and (B) a Respira™ bead (Respira technology), which occur within the Handihaler® cartridge upon inhalation.

- In vitro* validation of the radiolabeling technique was demonstrated by the codeposition of radiolabeled ALB with ^{99m}Tc radiolabel across the NGI stages at 45L/min (Fig 3).

- A high coefficient of correlation for both devices (Handihaler $r^2 = 0.88$; Respira $r^2 = 0.96$) indicated a strong linear association of radiolabeled drug with radiolabel.

- Previously documented *in vitro* fine particle fraction (%FPF; fine particle dose as a percentage of emitted dose) data for the Handihaler device of 23-25% FPF (6) matched the values obtained in our study of $21 \pm 4\%$ FPF at an equivalent flow rate.

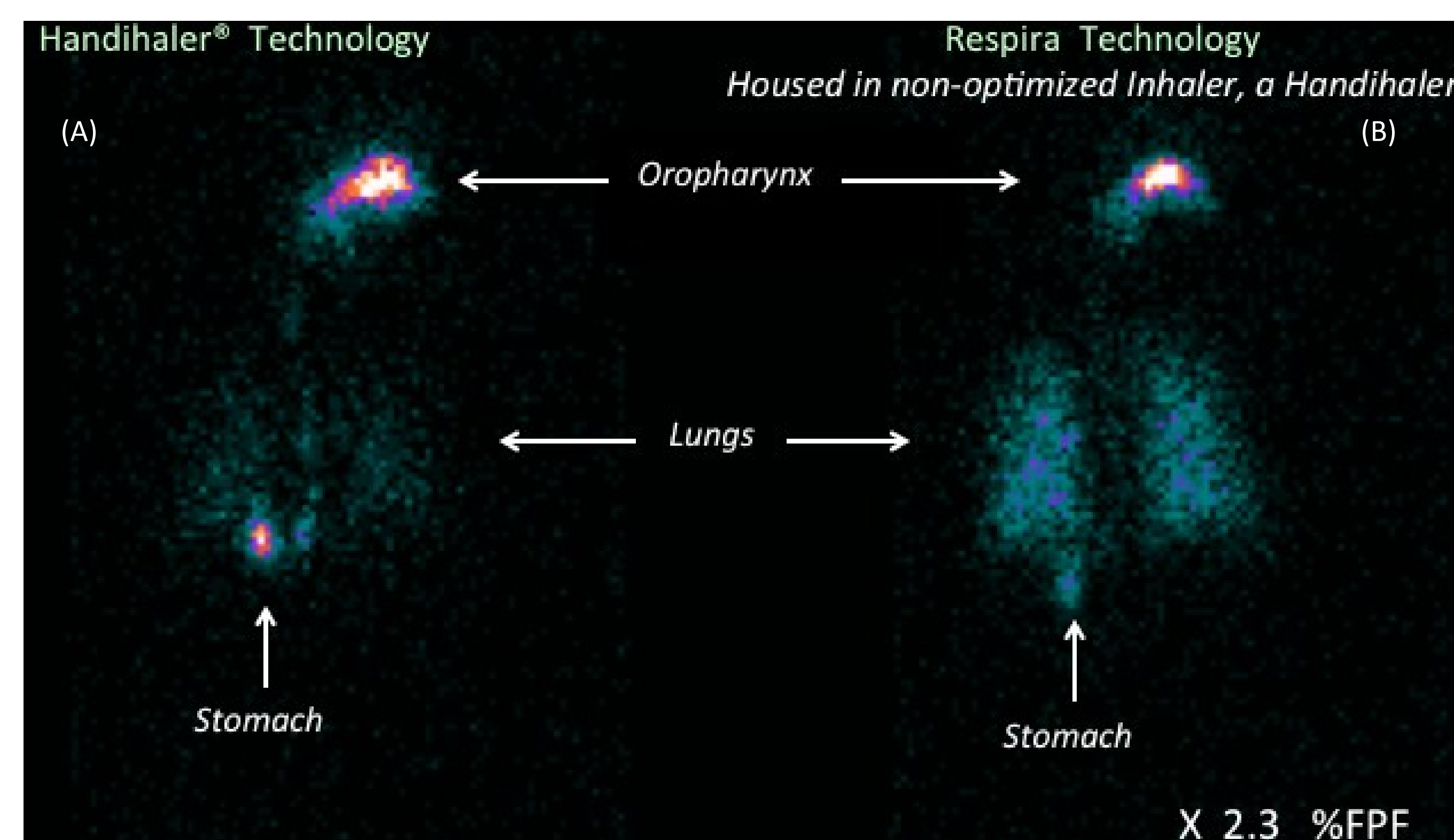


Figure 2: ^{99m}Tc planar scintigraphy depicting the deposition pattern of the radiolabeled drug, albuterol sulfate (ALB), aerosolized from two DPI devices composed of: (A) Handihaler with capsule containing the radiolabeled ALB lactose blend (1%w/w); (B) Respira technology with pure radiolabeled ALB. Both images were normalized to the same median count

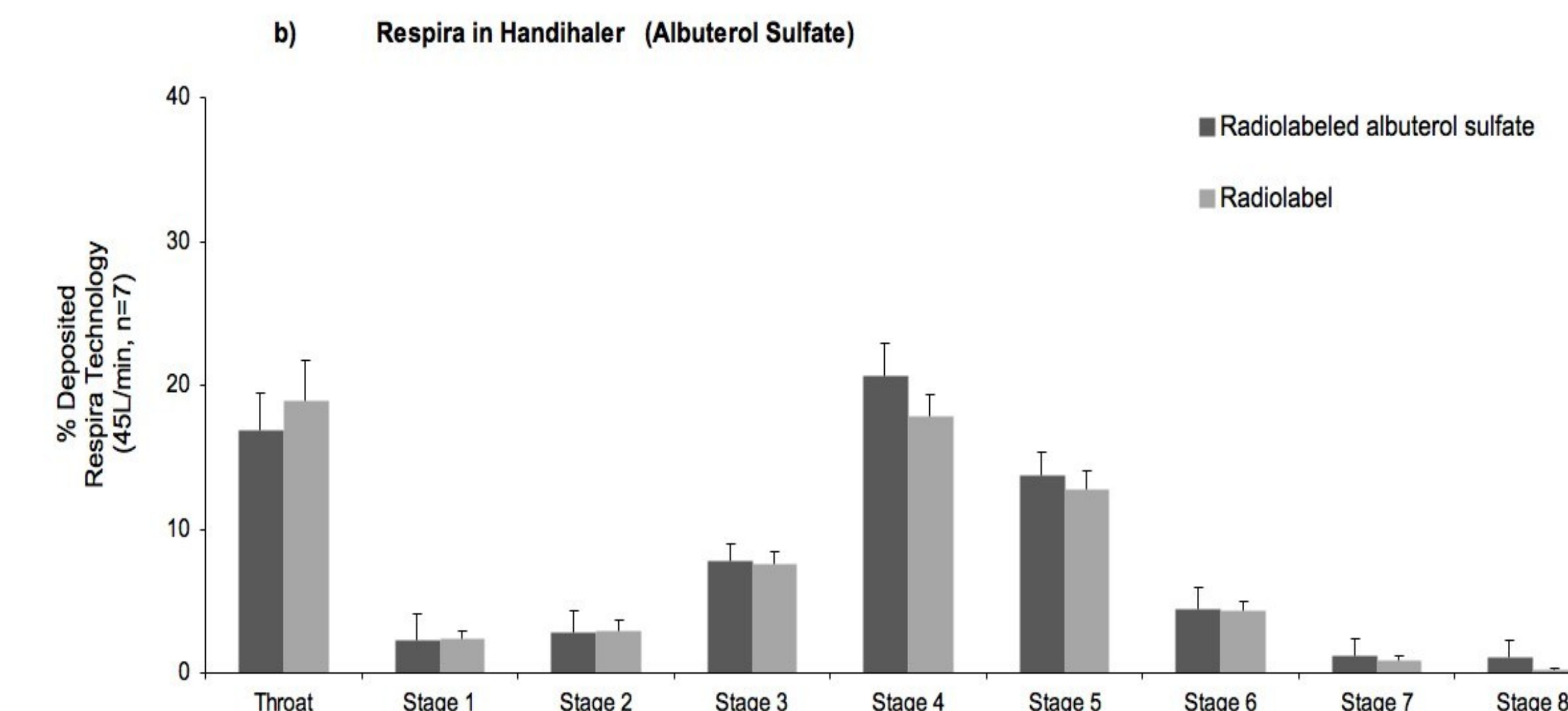
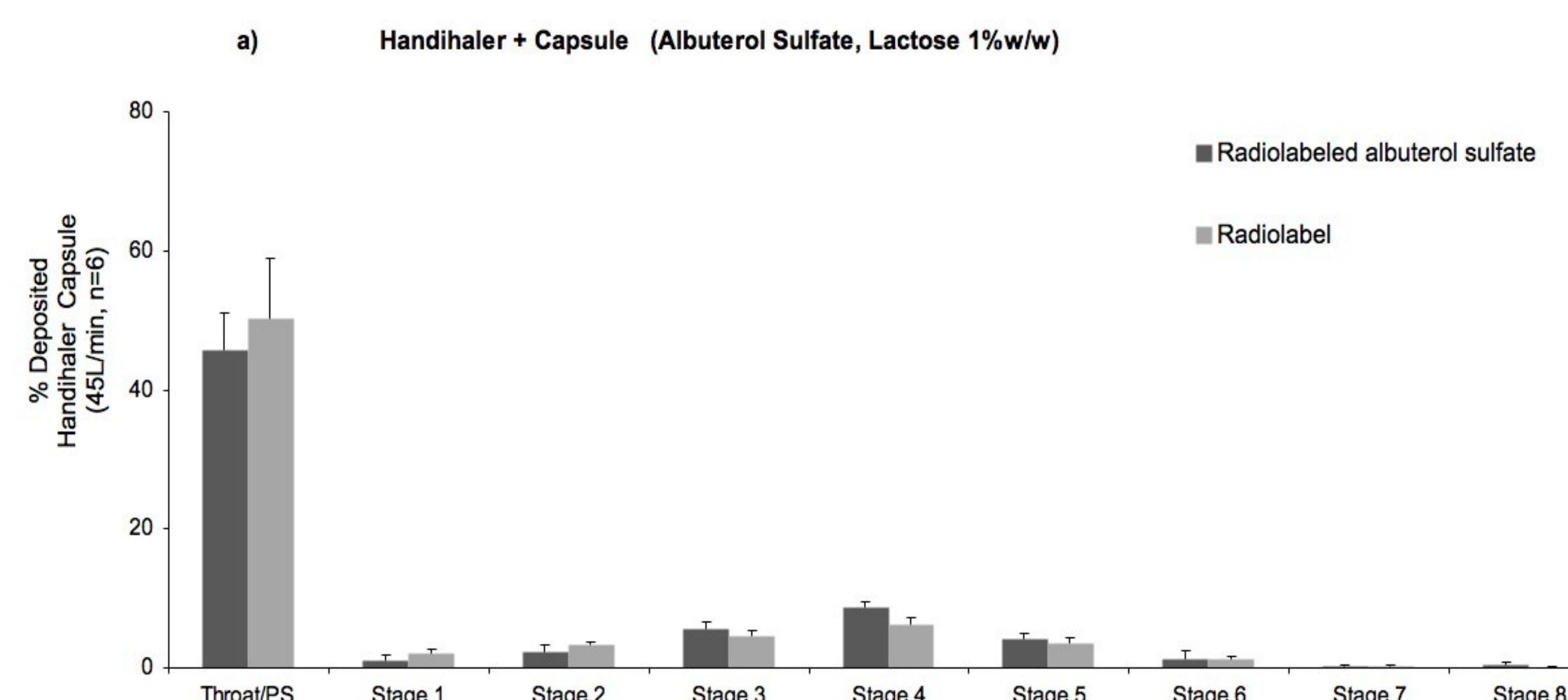


Figure 3. In vitro validation of the radiolabeling process: NGI deposition profiles from a) Handihaler® and b) Respira™ of ^{99m}Tc radiolabeled ALB powder from both inhalers were assayed by UV (at 230nm) and gamma radiation (counts/second).

- In vivo* scintigraphy scans demonstrated the superiority of the Respira technology in delivering radiolabeled ALB to the lungs in this single subject, as can be seen from Figure 2.

- Respira technology successfully targeted ALB particles to the lungs, delivering 49% of the nominal dose.

- The Handihaler device performed as expected of a capsule-based lactose formulation with 18% lung deposition, and as previously reported (7).

- High extrathoracic deposition (68% of nominal dose) and concomitant high drug levels in the stomach, detected seconds post inhalation were also observed for the Handihaler device (as indicated in Fig 2).

CONCLUSIONS

- This *in vivo* scintigraphy study demonstrated the superior performance of Respira technology in:

- Delivering larger fractions of drug to the lungs, and
- Minimizing extrathoracic deposition compared to a leading commercial DPI, the Handihaler

- This was despite the fact that in this study, the Respira technology was not optimized for performance, housed instead within a Handihaler DPI.

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REFERENCES

- Donovan MJ, et al., (2012), *RDD*, Phoenix, Arizona
- Donovan MJ, et al., (2011), *AAPS*, Washington D.C.
- Donovan MJ, et al., (2011), *AAPS*, Washington D.C.
- Donovan MJ, et al., (2009), *RDD*, Lisbon, 189-200
- Donovan MJ, et al., (2010), *DDL*, Edinburgh, Scotland
- Chodosh S, et al., (2001), *Journal of Aerosol Medicine* 14, 309-315
- Brand P, et al., (2007), *The Journal of Clinical Pharmacology* 47(10), 1335 -1341