

ENGINEERED MICROPARTICLES FOR DPI CONSTRUCTION AND POWDER ADMINISTRATION STRATEGY

Francesca Buttini

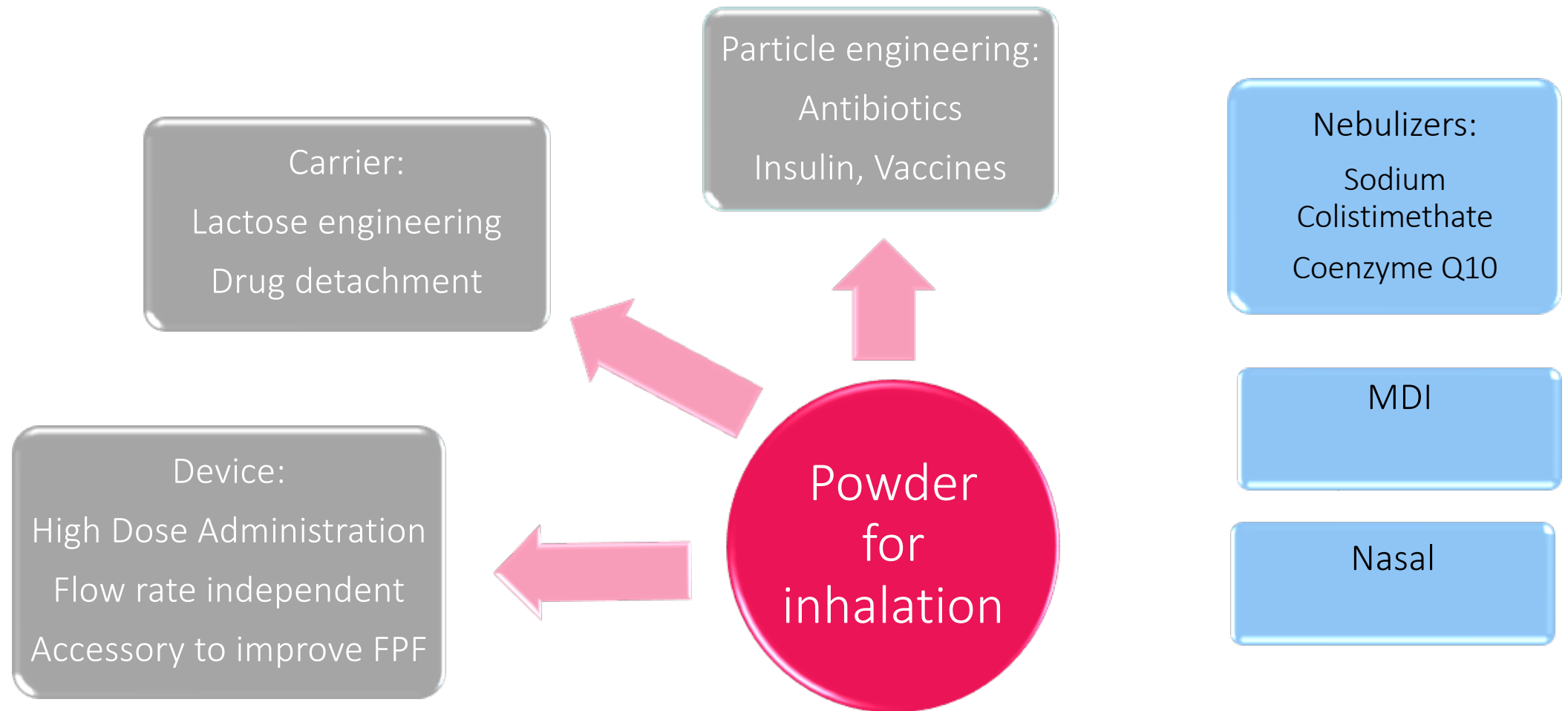


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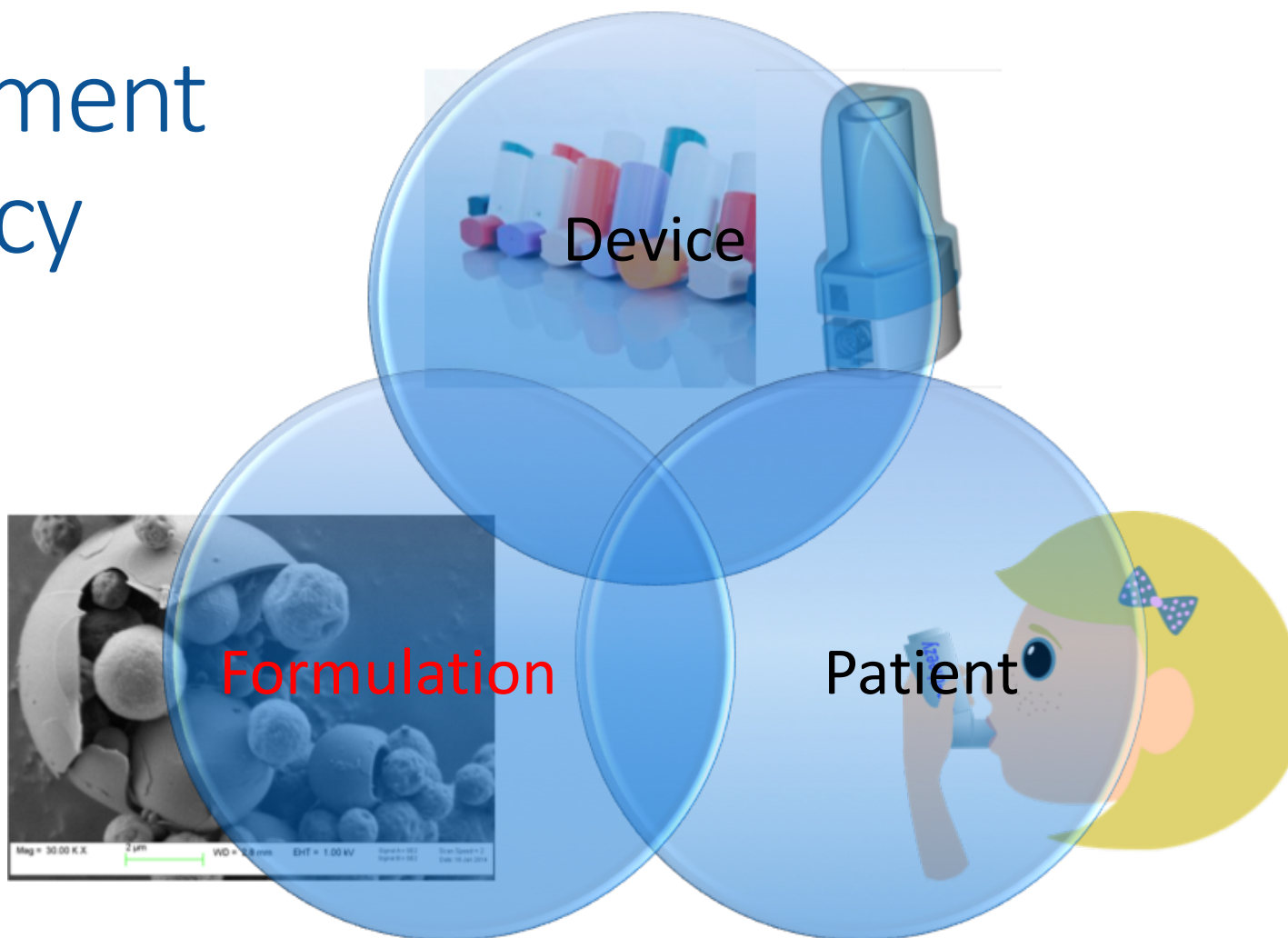
DIPARTIMENTO DI SCIENZE
DEGLI ALIMENTI E DEL FARMACO



Research in Inhalation Products



Treatment Efficacy



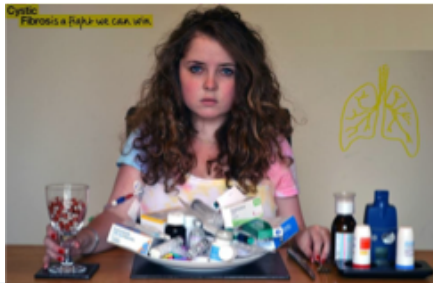
From Quality by Test to Quality by Design

“the only way to assure the quality of a product is by controlling its manufacturing process” (Shewhart, 1931)

“Product should be designed to meet patients’ needs and the intended product performance” (ICH Q8 R2 guideline)

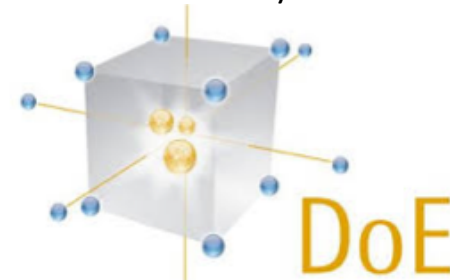
Relevant for patients are:

- Safety
- Efficacy
- Medication performances



Quality by Design Tools:

- Risk assessment (RA)
- Design of experiments (DoE)
- Process analytical technology (PAT)



The application of Quality by Design framework in the pharmaceutical development of dry powder inhalers

Francesca Buttini^a, Stavroula Rozou^b, Alessandra Rossi^a, Varvara Zoumpliou^b,
Dimitrios M. Rekkas^{c,*}






Why is Particularly Challenging the Development of Inhaled Drug Product?

- Product is a formulation-device combination
- Product handling may affect the respirable dose
- Manufacturing process often exhibits low process capability
- Environmental conditions influence product manufacture and use
- Lack of clear *in vitro-in vivo* correlation



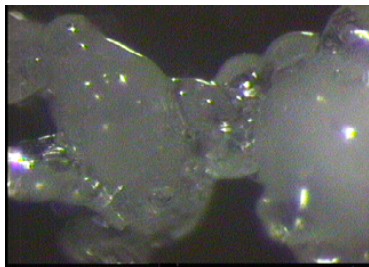
Constraints and Questions for DPI Design

- | | | |
|---------------------------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|
| 1. Microparticles manufacturing |  | Production process technique?
Pure API or plus excipient?
Excipient type? |
| 2. Formulation construction |  | How to transform sticky microparticles in a flowing and respirable powder? |
| 3. Device to identify |  | Single/multi dose inhaler? Disposable?
How to control of amount of powder to inhale?
How many maneuvers? |

Pulmonary Spray Dried Powders of Tobramycin Containing Sodium Stearate to Improve Aerosolization Efficiency

Chiara Parlati,¹ Paolo Colombo,^{1,4} Francesca Buttini,¹ Paul M. Young,² Handoko Adi,² Alaina J. Ammit,³ and Daniela Traini²

Antibiotic Microparticle Production



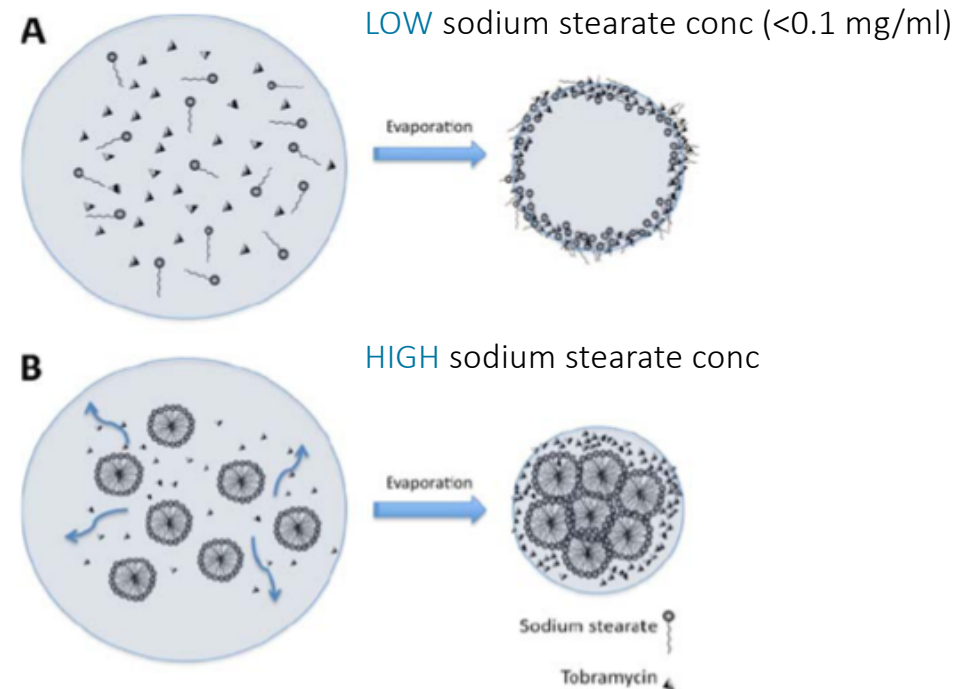
Optical microscope image of a pure tobramycin SD powder

Particle coating process for binary mixtures of tobramycin and sodium stearate during spray drying

Tobramycin
70% water

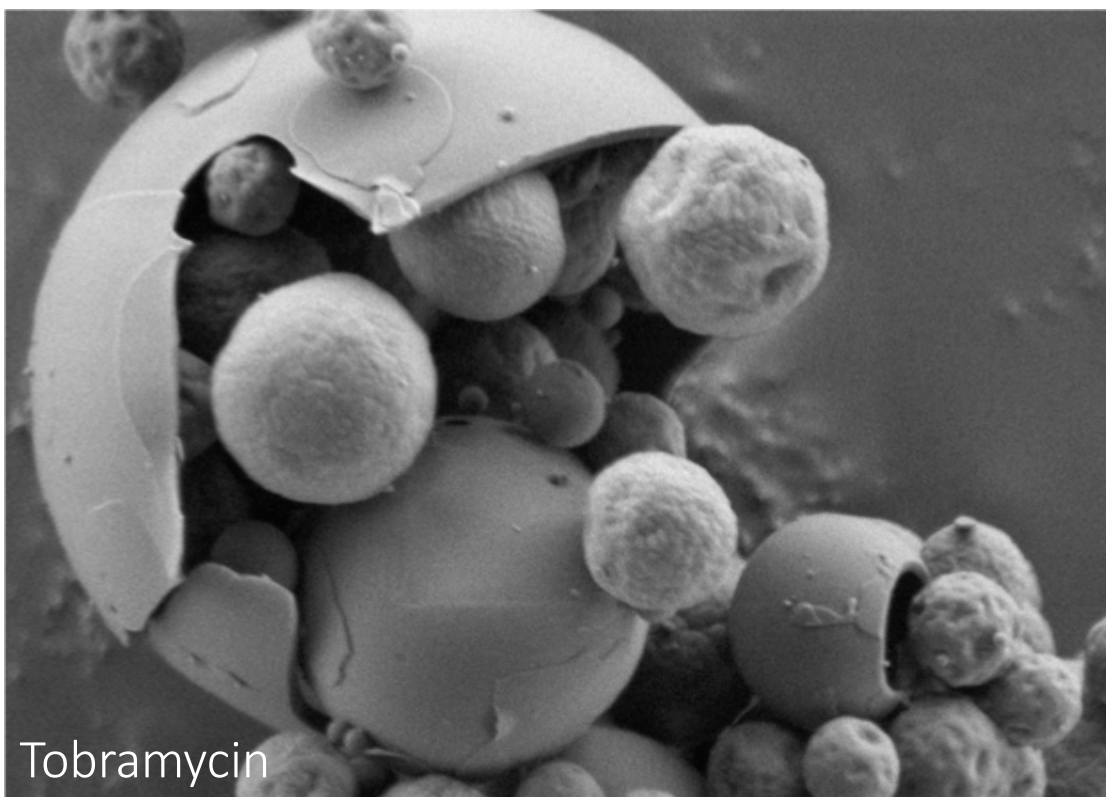
NaSt
30% ethanol

Mixing
@40°C





NaSt Technology



Tobramycin

Mag = 30.00 K X 2 μ m WD = 2.8 mm EHT = 1.00 kV
Signal A = SE2 Scan Spe
Signal B = SE2 Date :16 J



EUROPEAN COMMISSION
HEALTH & CONSUMERS DIRECTORATE-GENERAL
Directorate D - Health systems and products
D5 - Medicinal products - authorisations, EMA
Head of unit

Brussels, 16 December 2014

NOTE TO THE SPONSOR

Subject: Adoption of COMMISSION IMPLEMENTING DECISION relating to the designation of "Amikacin sulfate" as an orphan medicinal product under Regulation (EC) No 141/2000 of the European Parliament and of the Council

EU/3/14/1397 - EMA/OD/177/14

The Commission has adopted the abovementioned Decision on 16 December 2014.

The Decision will be notified forthwith to the addressee(s) of the Decision.

The Decision is going to be published for information in all official languages of the EU in the Community Register of Orphan Medicinal Products (<http://ec.europa.eu/health/documents/community-register/html/orphreg.htm>) after the Decision has been notified.

The attention has to be drawn to the fact that, under the general rules of the Treaty on the Functioning of the European Union, a Decision is a legal act whose publication is not obligatory in order to be binding.

Sabine Jülicher
pp. Gkioka Charalampia-Loukia



Amikacin SD using PEG_32 Stearate

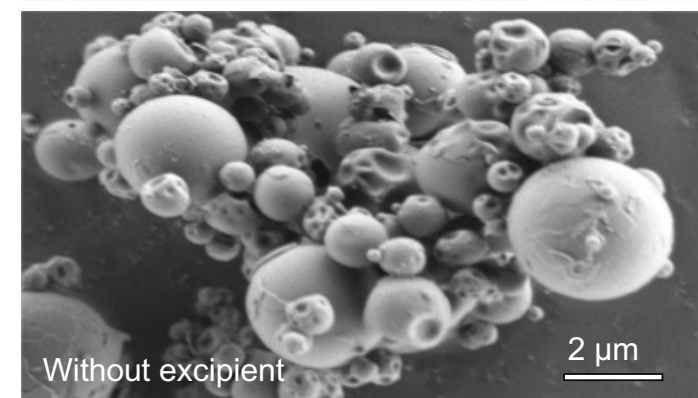
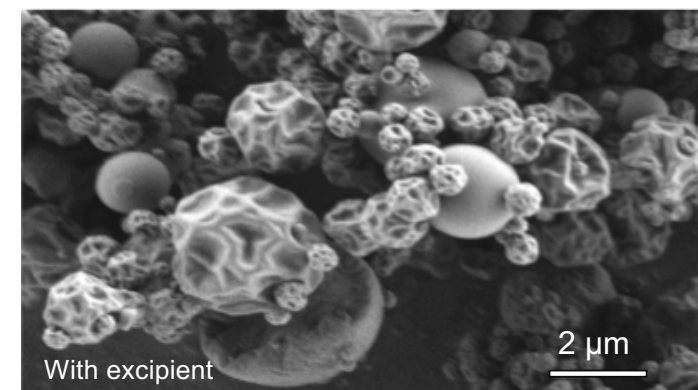
Half fractional factorial design (2^{n-1})
16 experiments

- Factor 1: Drying temp
- Factor 2: Feed rate
- Factor 3: Ethanol %
- Factor 4: PEG_32 stearate %
- Factor 5: Solid Conc

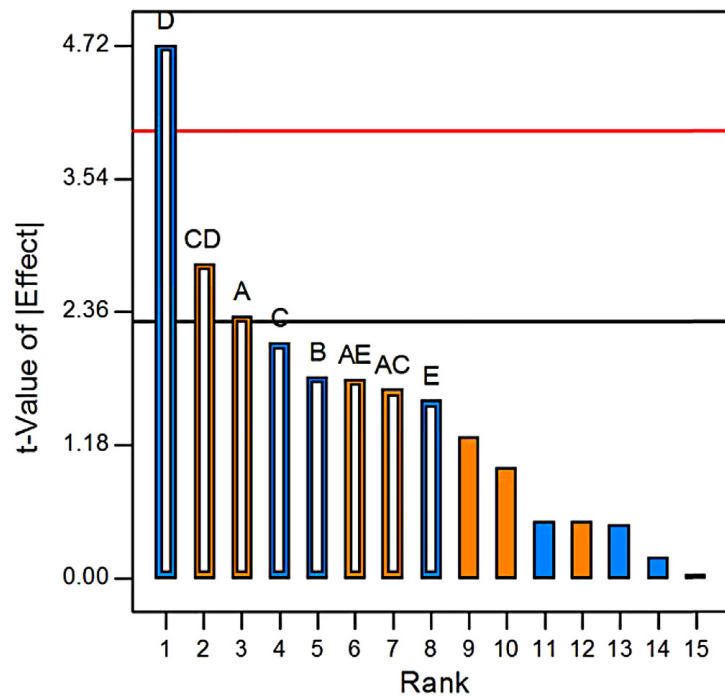
CQAs	Range Values	Negatively affected by	Positively affected by
SD yield (%)	67 - 88	Waxy excipient	High solid concentration
LOD (%)	7.6 - 9.7	Waxy excipient	Drying temperature
$D_{v(0.5)}$ (μm)	1.88 - 3.52	-	High solid concentration Feed rate
Bulk Density	Agglomeration had a positive effect	Waxy excipient High solid concentration Feed rate	Drying Temperature Ethanol (%)
ED (mg)	5.7 – 9.2	Waxy excipient	Feed rate Interaction between excipient and solid conc
FPD (mg)	3.5 – 6.1	Waxy excipient	Interaction between excipient and ethanol

Spray dried amikacin powder for inhalation in cystic fibrosis patients: A quality by design approach for product construction

Silvia Belotti^{a,1}, Alessandra Rossi^{a,1}, Paolo Colombo^a, Ruggero Bettini^a, Dimitrios Rekkas^b, Stavros Politis^b, Gaia Colombo^c, Anna Giulia Balducci^d, Francesca Buttini^{a,*}

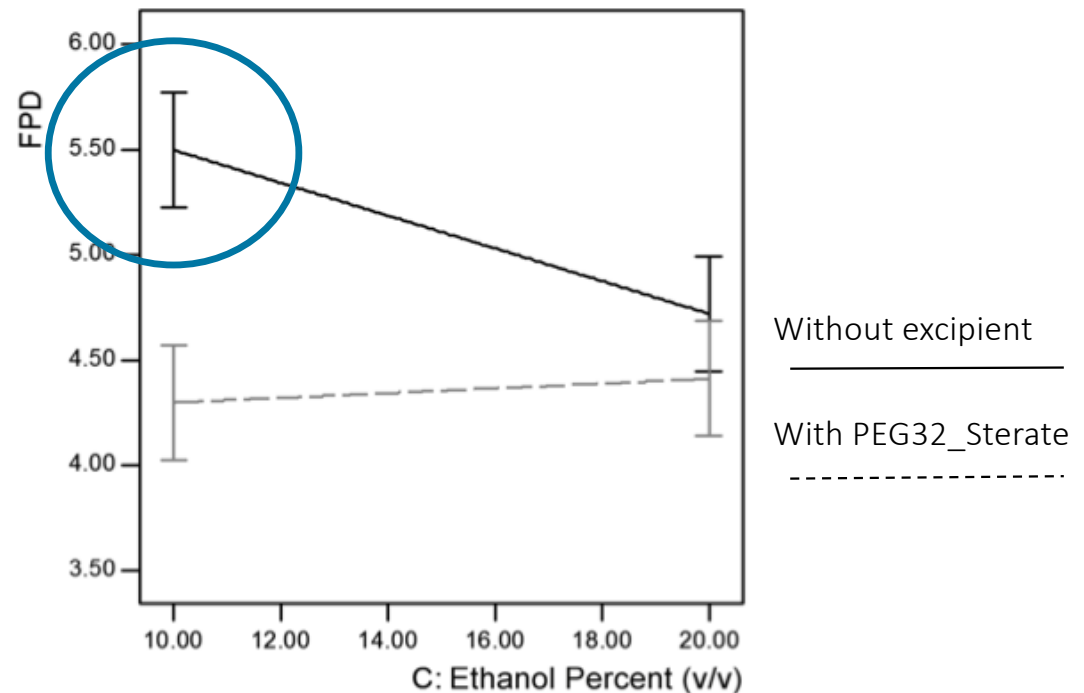


Rank of the t-values corresponding to the effect on the FPD of each factor and interactions



A: Drying temp.; B: feed rate; C: ethanol content; D: excipient presence; E: AMK conc

- Feed solution required the inclusion of 10% (v/v) ethanol
- Amikacin in the feed solution had to be kept at 1% w/v level
- Increase in drying temperature always led to an evident increase in emitted dose (ED) without affecting the fine particle dose (FPD) values



Ethanol Effect on Particle Morphology and Respirability

European Journal of Pharmaceutics and Biopharmaceutics 93 (2015) 165–172



Contents lists available at ScienceDirect
European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb



Research Paper

Spray-dried amikacin sulphate powder for inhalation in cystic fibrosis patients: The role of ethanol in particle formation



Silvia Belotti^a, Alessandra Rossi^a, Paolo Colombo^a, Ruggero Bettini^a, Dimitrios Rekkas^b, Stavros Politis^b, Gaia Colombo^c, Anna Giulia Balducci^d, Francesca Buttini^{a,e,*}

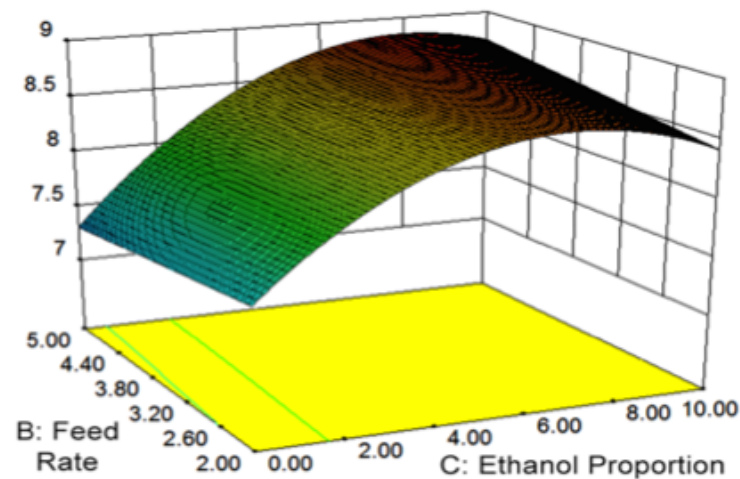
Central Composite Design

15 experiments

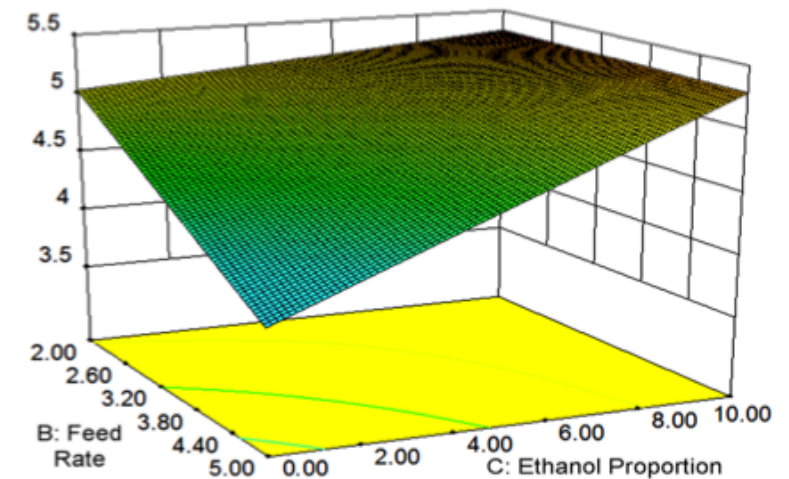
- Drying T (°C): 150-165-180
- Feed rate (mL/min): 2-3.5-5
- Ethanol presence (%): 0-5-10



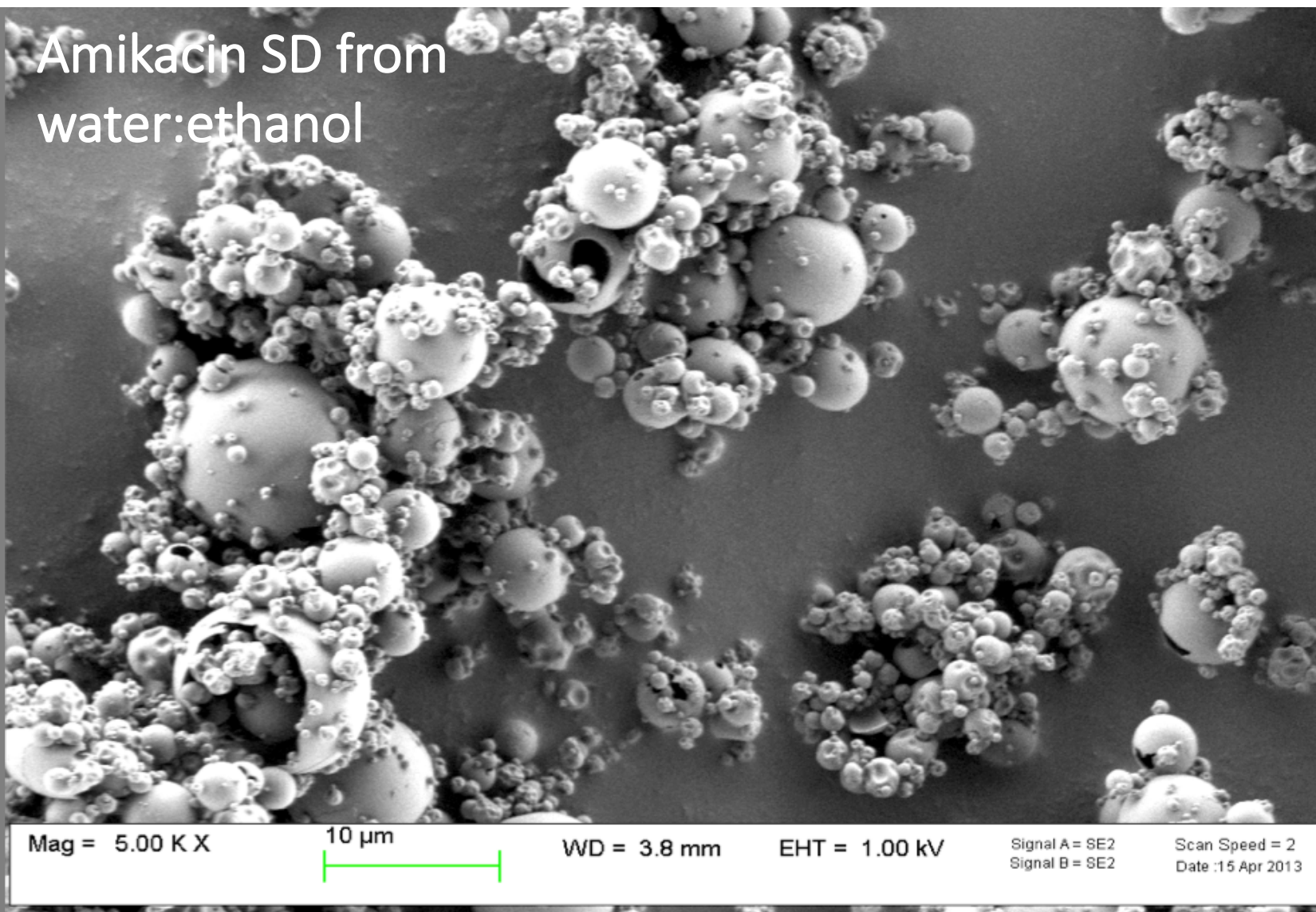
Emitted Dose



Fine Particle Dose



Amikacin SD from
water:ethanol

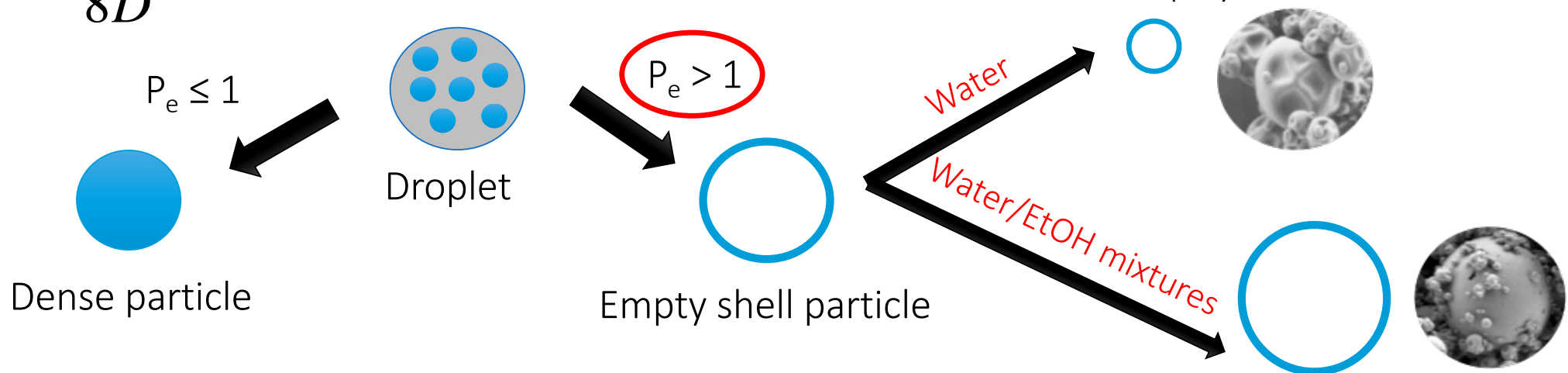


Solvent power and volatility influence texture and surface chemistry of spray-dried microparticles

The Peclet number (Pe) can predict the particle formation process and the resulting particle properties

$$Pe = \frac{K}{8D}$$

- Evaporation rate constant, κ = droplet surface area reduction in time (cm^2/s)
- D is the diffusion coefficient of dissolved substance in the sprayed solution



Chimeric Agglomerates / Soft Pellets

Primary microparticles held together by weak interactions.

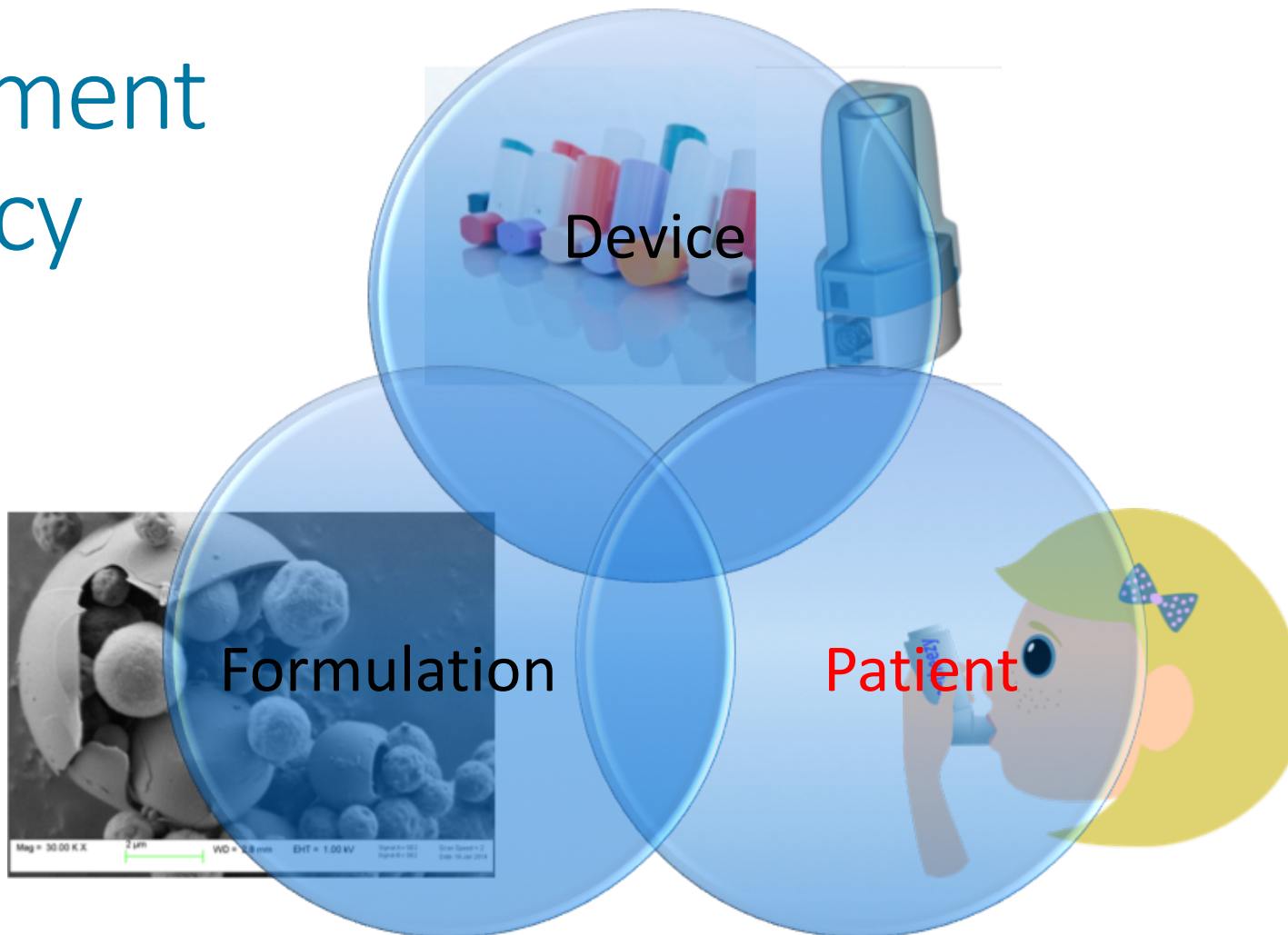
Strong enough for handling, but de-agglomerated by turbulent air flow during inhalation.





Belotti, et al. Eur J Pharm Biopharm (2015)

Treatment Efficacy

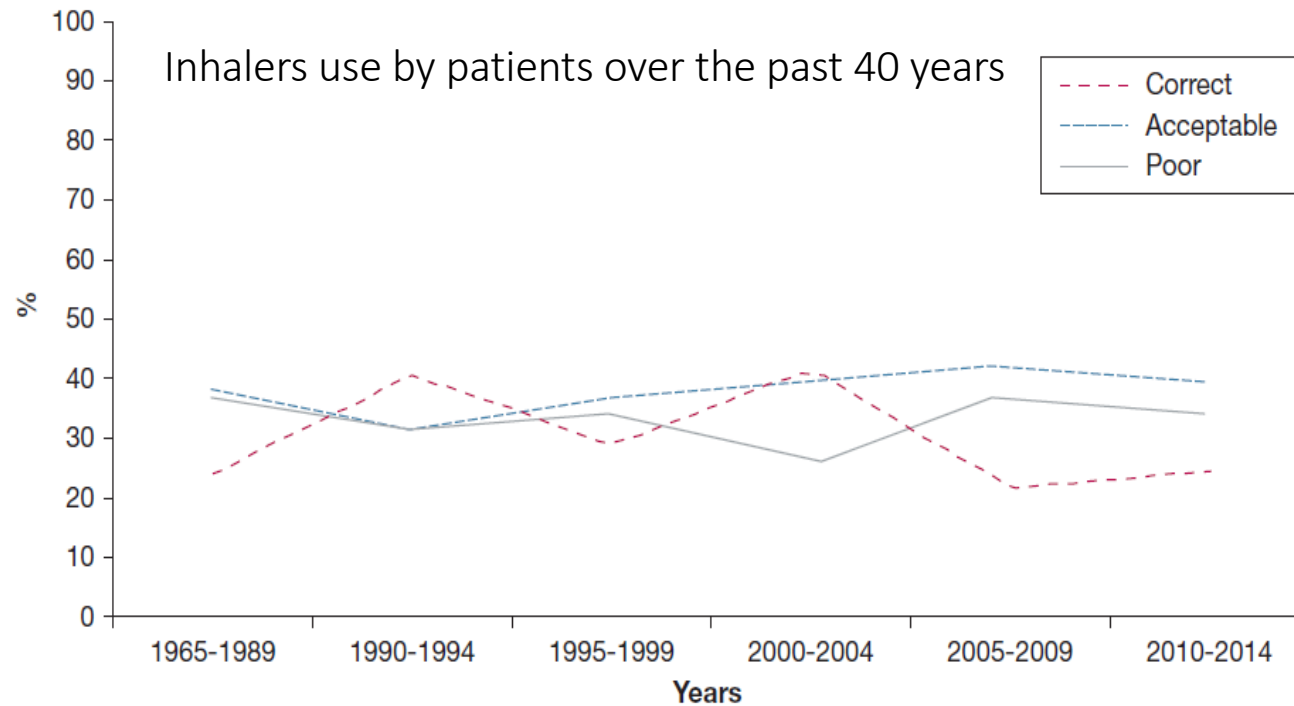


Systematic Review of Errors in Inhaler Use Has Patient Technique Improved Over Time?

Joaquin Sanchis, MD, PhD; Ignasi Gich, MD, PhD; and Soren Pedersen, MD, PhD, Dr Med Sci;

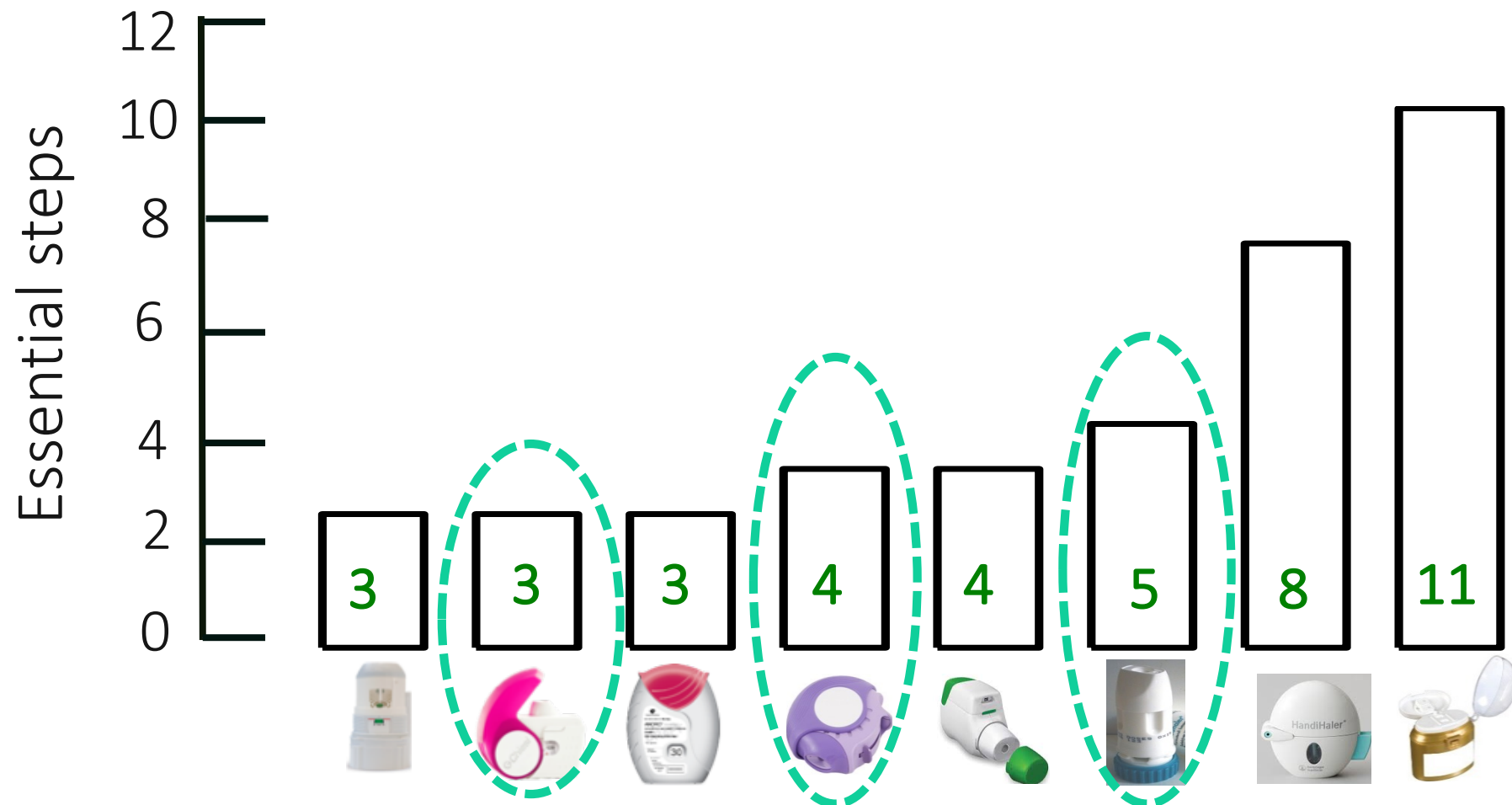


2016; 150(2):394-406



Despite considerable attention by researchers to develop new inhalers = there has been no sustained improvement over the past 50 years in patients' ability to use inhalers

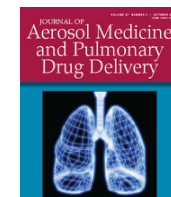
DPIs: essential steps for drug inhalation



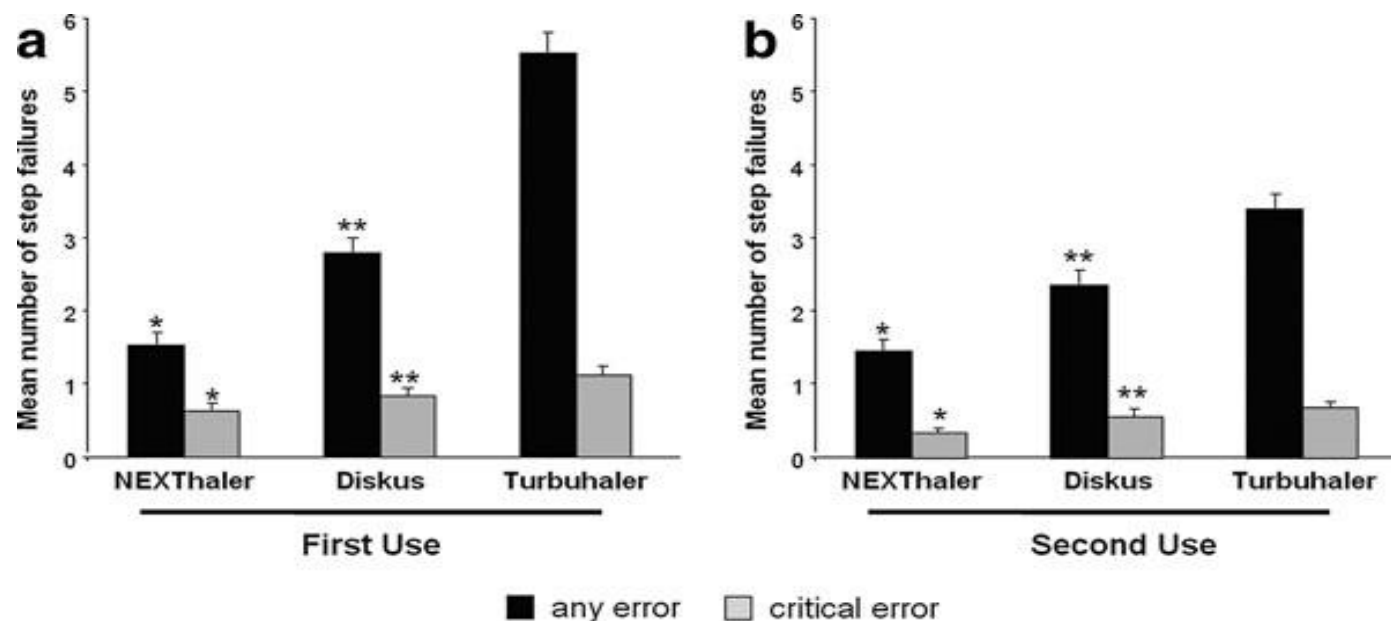
Device Number of Operation Steps

Comparing Usability of NEXThaler[®] with Other Inhaled Corticosteroid/Long-Acting β_2 -Agonist Fixed Combination Dry Powder Inhalers in Asthma Patients

Thomas Voshaar, MD,¹ Monica Spinola, PhD,² Patrick Linnane, BEng,² Alice Campanini, BSc,² Daniel Lock, MIEHF,³ Anthony Lafratta, MIEHF,³ Mario Scuri, MD,² Barbara Ronca, PharmD,² and Andrea S. Melani, MD⁴



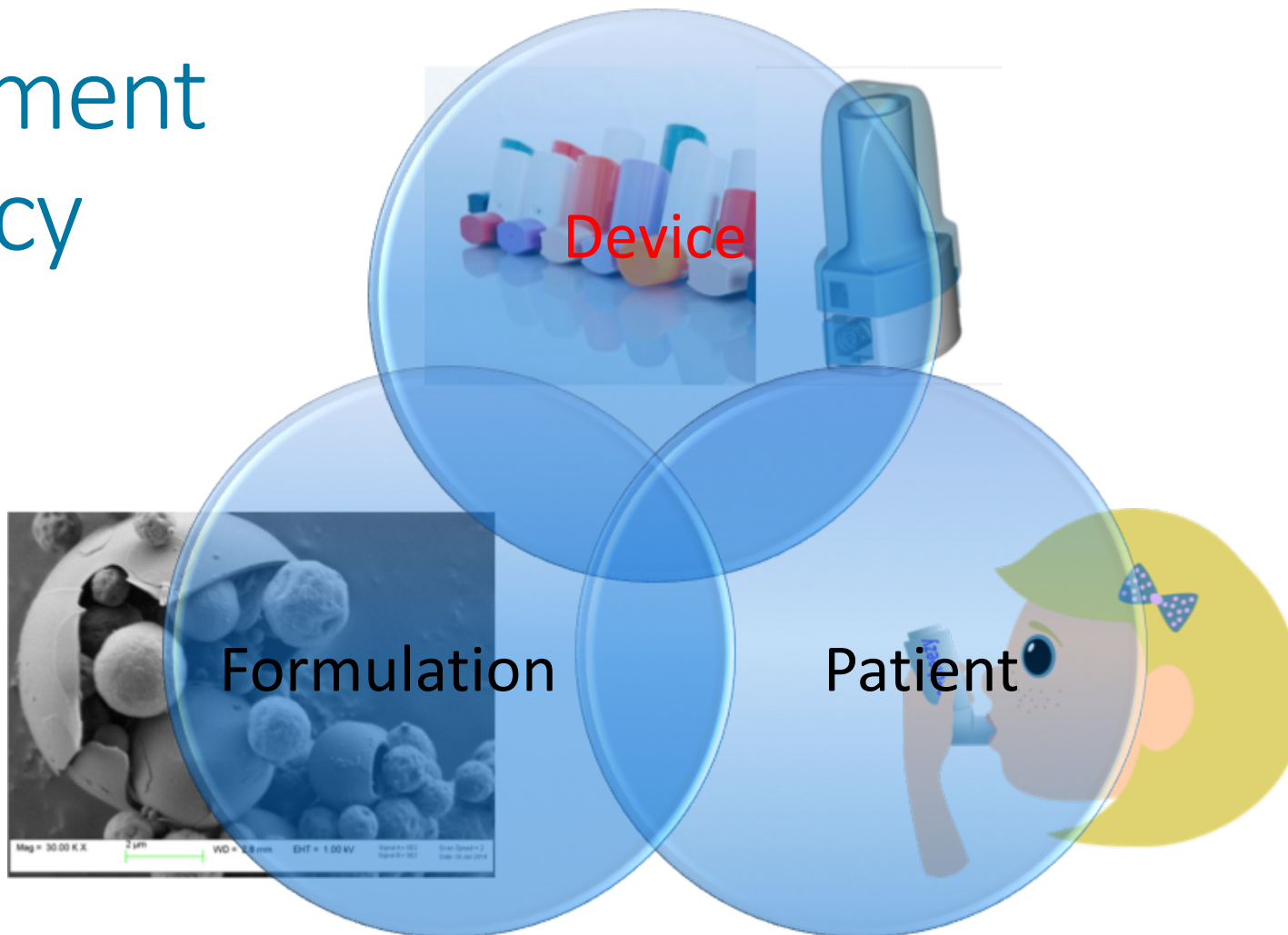
Volume 27, Number 0, 2014
© Mary Ann Liebert, Inc.
Pp. 1–8



Reducing the number of operation steps decreases the probability of serious errors with DPIs



Treatment Efficacy



Patient compliance vs number of capsules

TOBI® PodHaler®

200 mg powder (eq 112 mg of tobramycin)

4 capsules

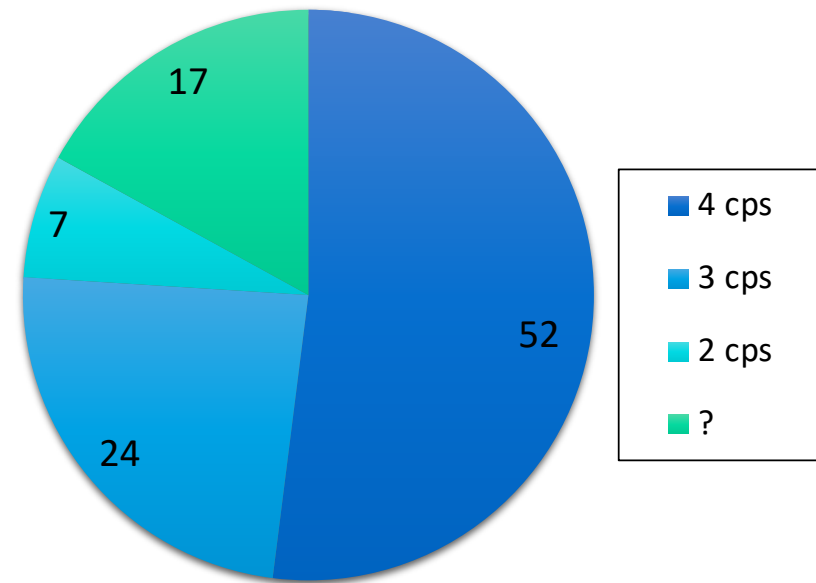
2 inhalation acts

Twice daily



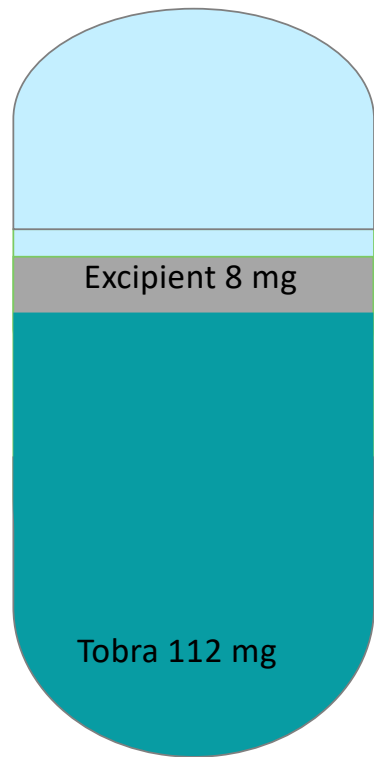
Number of capsules to inhale in
one week of therapy

Patients vs Capsule Number (%)



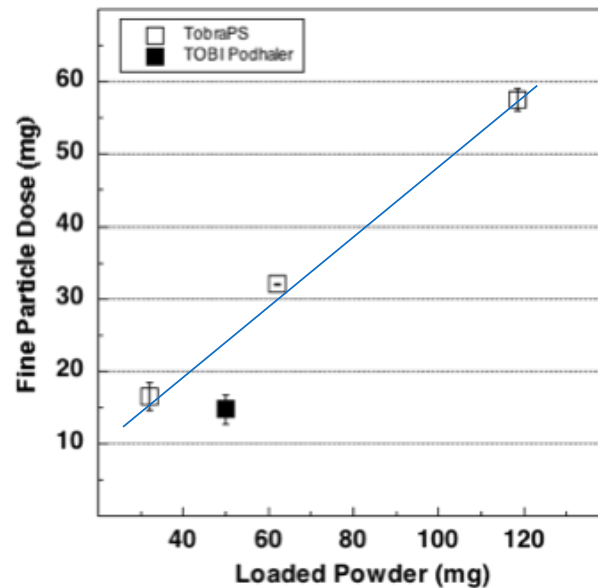
Boerner et al., 37th European CF Conference, 2014, Gothenburg

Administration Strategy of TobraPS

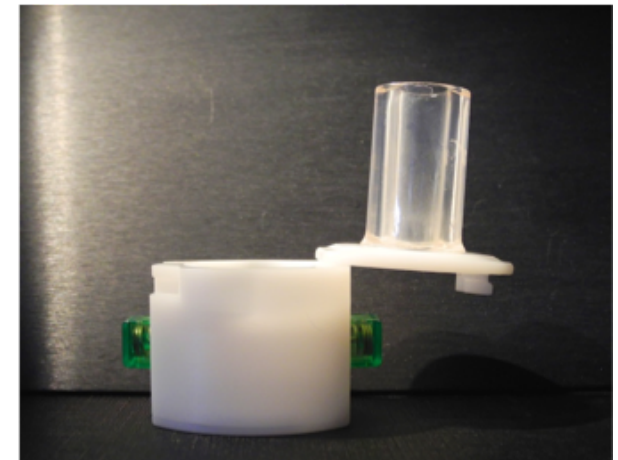


TobraPS
1 cps x 120 mg

The linear relationship validates the capsule number reduction by increasing the strength



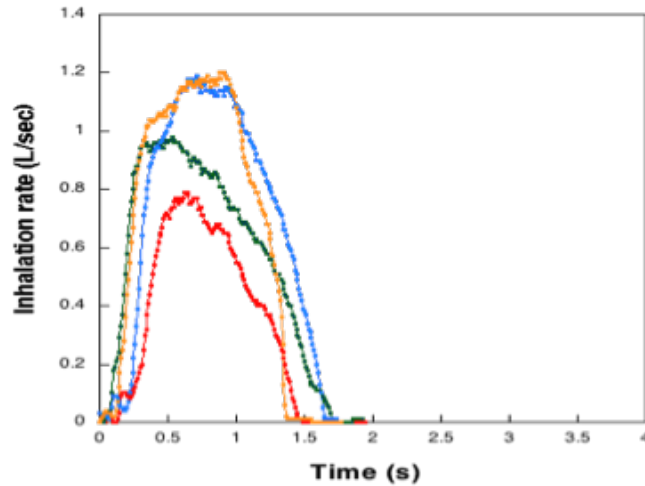
RS01 inhaler
housing cps size #0



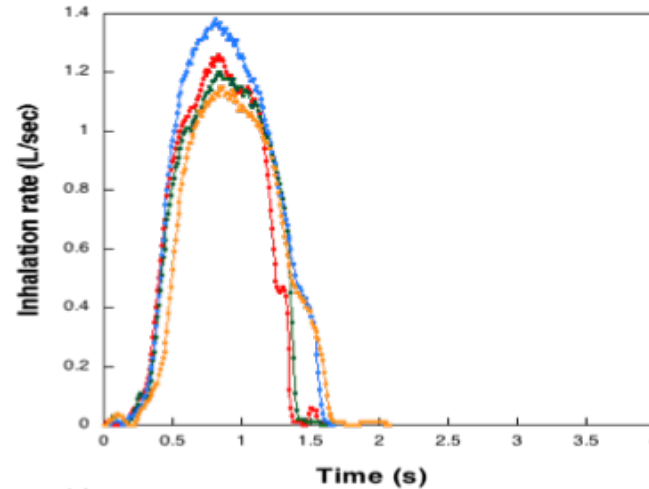
	Preparation Steps #	Inhalation Acts #	Time
TobraPS	6	?	?

Inhalation Profile through RS01 size #0 during powder inhalation

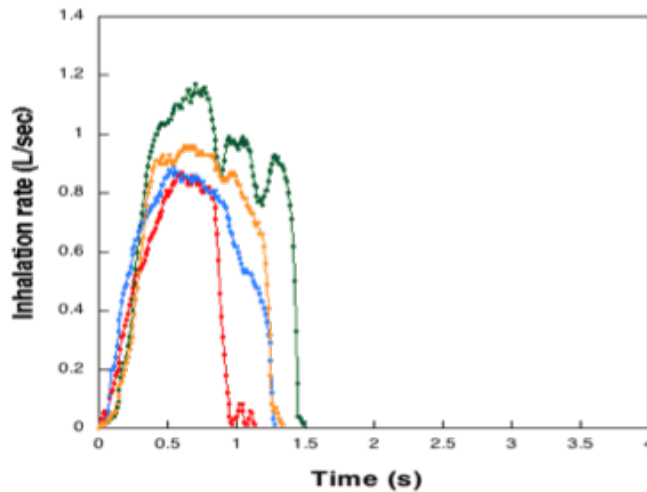
Subj 1



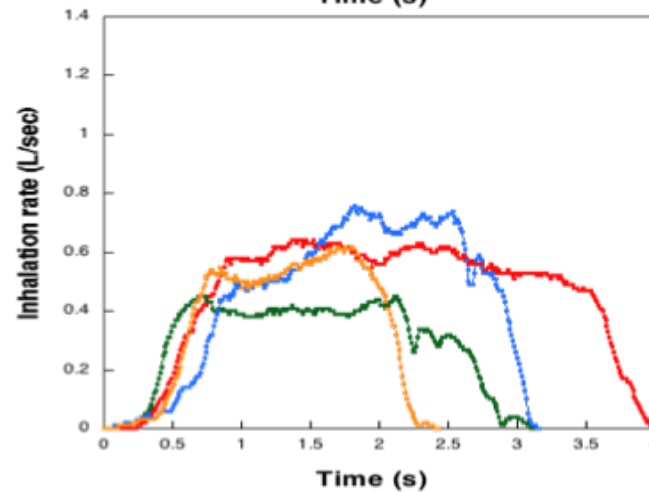
Subj 1



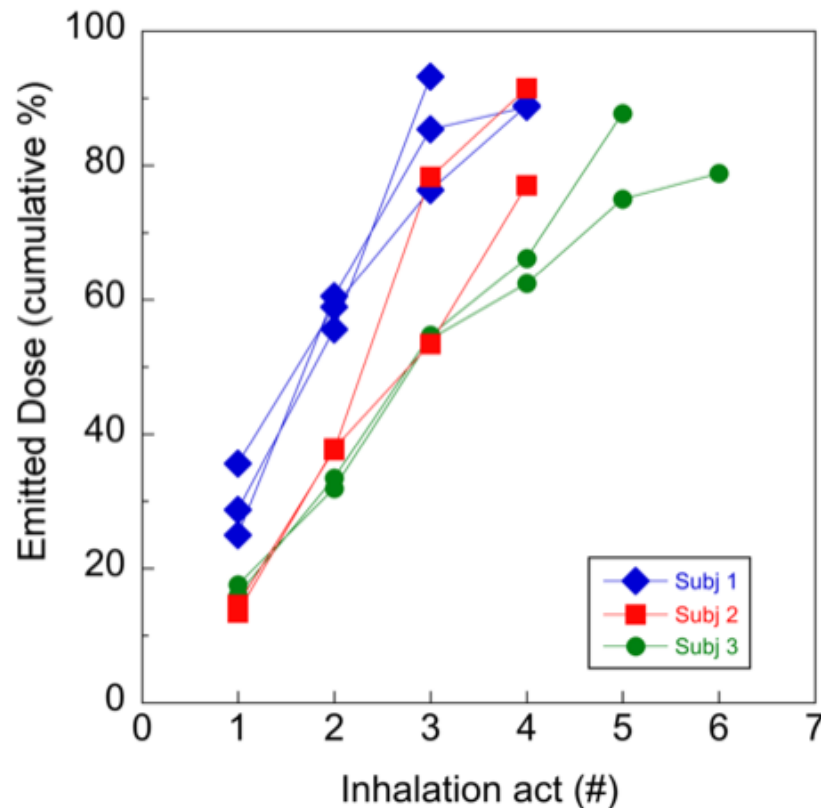
Subj 2



Subj 3



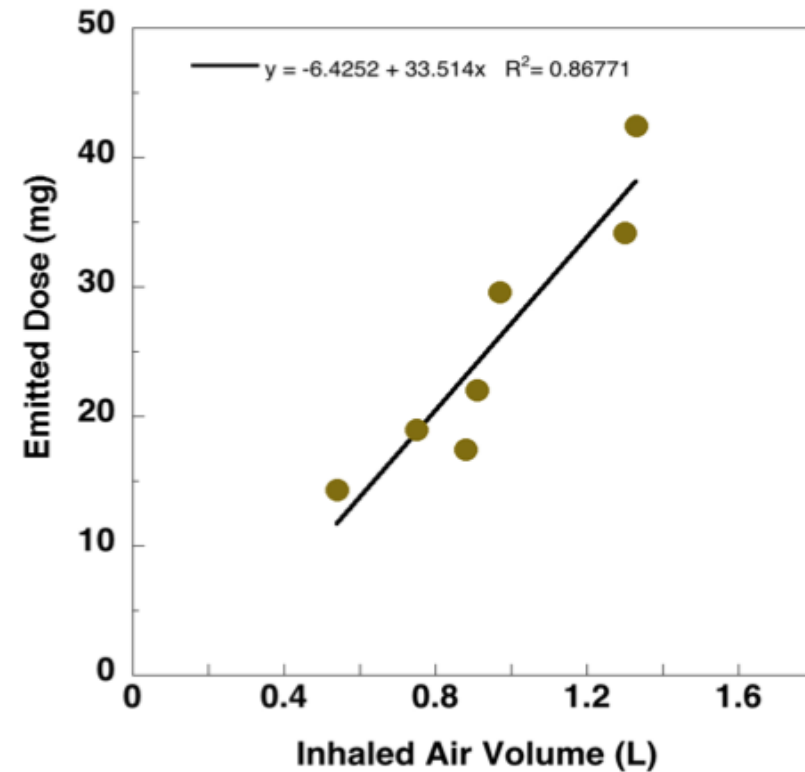
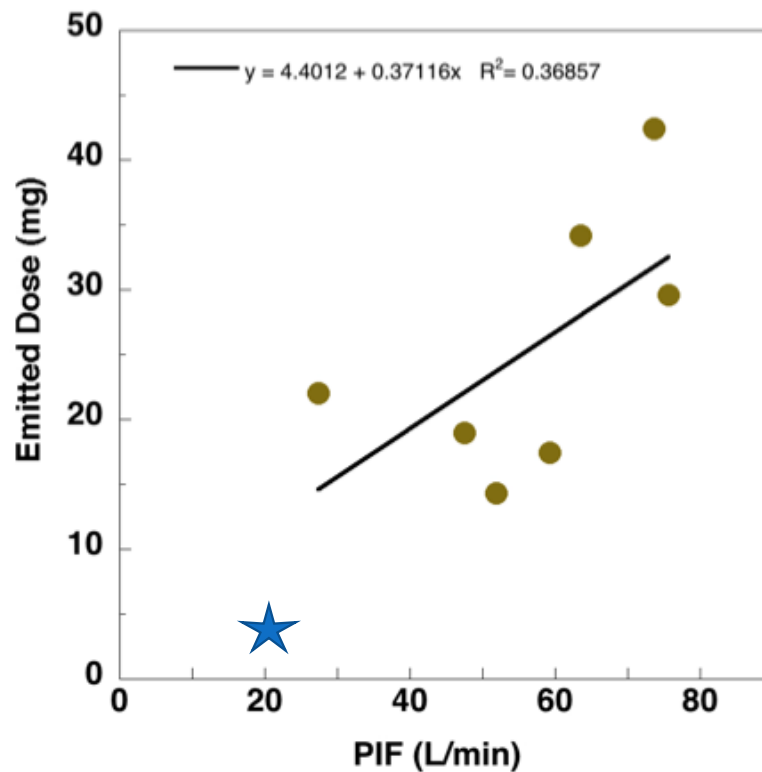
Emitted Dose & Sequence of Inhalation Acts



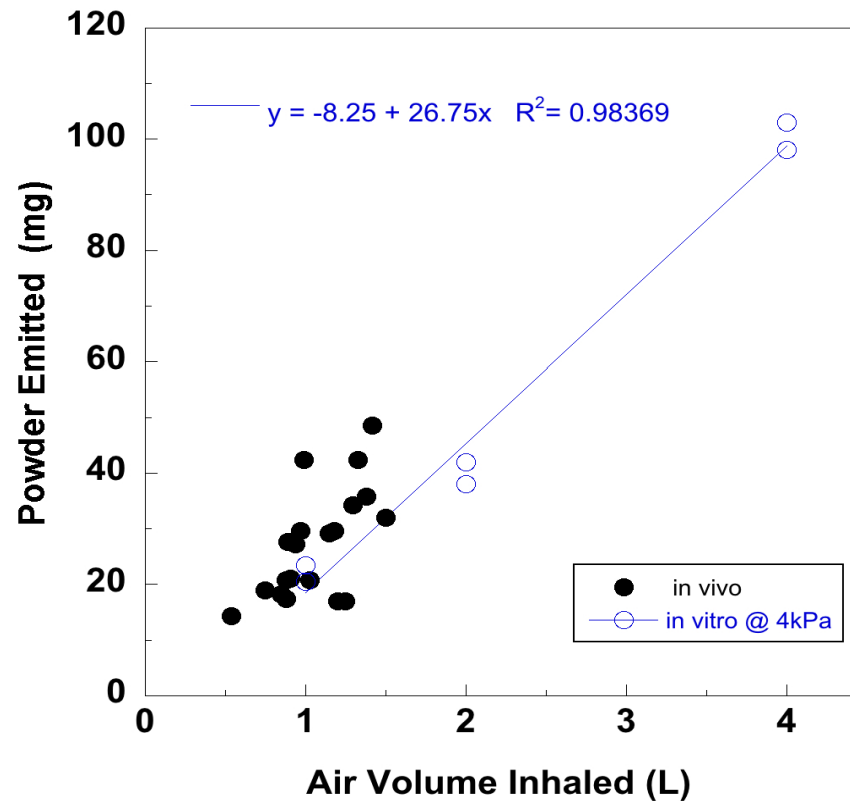
- 3 healthy volunteers (1F, 2M; age 31-71)
- TobraPS Dose: 120 mg (equivalent to 112 mg of drug)
- RS01 device size cps size #0
- Time to complete the administration: 2-3 min

Relation between Emitted Dose Peak Inhalation Flow - Inspiratory Volume

(first inhalation act)



Powder Emitted & Air Volume: *in vitro/in vivo* all inhalation acts



TobraPS Dose: 120 mg
(equivalent to 112 mg of drug)
Cps size #0

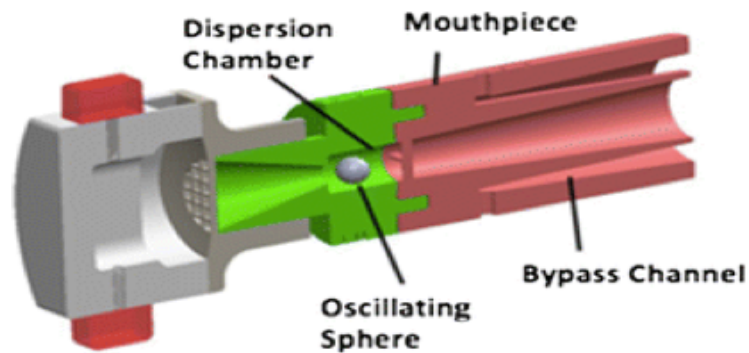
In vitro:
Flow rate: 60 L/min



How Can We Improve the Respirable Dose?

AOS (Axial Oscillating Sphere)

Respira Therapeutics Inc.



AOS accessory to add or incorporate within the mouthpiece of existing DPI; Device resistance slightly raises; the sphere oscillation during inhalation flow promotes the formation of extra-fine aerosol particles.

Pharm Res
DOI 10.1007/s11095-016-2023-0



RESEARCH PAPER

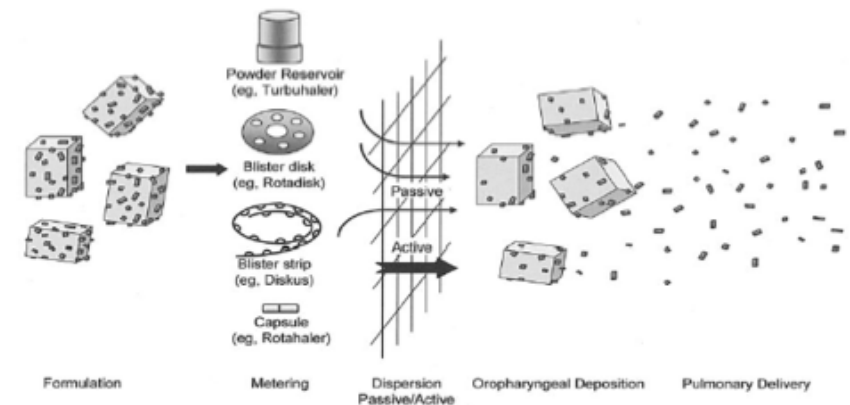
Accessorized DPI: a Shortcut towards Flexibility and Patient Adaptability in Dry Powder Inhalation

Francesca Buttini^{1,2} • James Hannon³ • Kristi Saavedra³ • Irene Rossi¹ • Anna Giulia Balducci^{1,4} • Hugh Smyth^{3,5} • Andy Clark^{3,6} • Paolo Colombo¹

Foradil® Aerolizer® (Novartis)

Formoterol fumarate lactose blend:

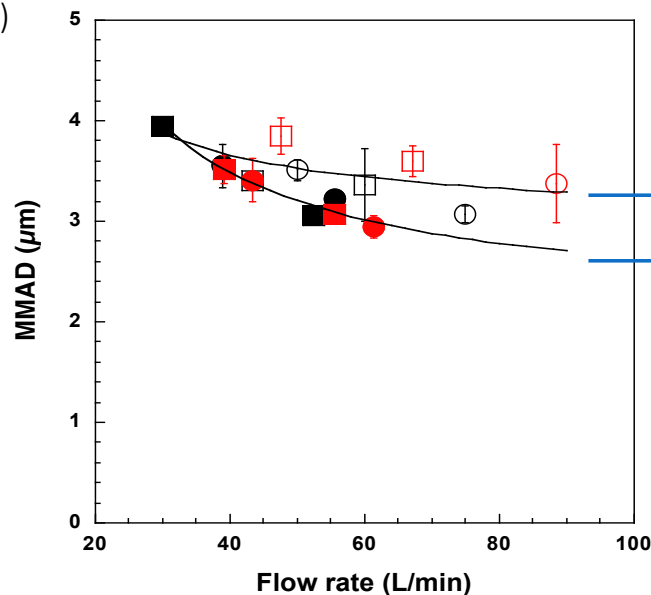
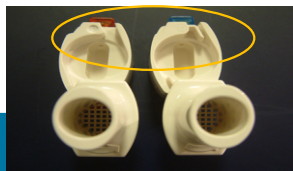
12 µg / 25 mg of lactose



Relationship between MMAD and flow rate for the RS01 devices with and without AOS

Full Factorial Design

- Altitude (m): 55 (Parma), 1560 (Albuquerque)
- Device type: RS01_MR, RS01_LR
- Device configuration: No-AOS, With-AOS
- Pressure Drop (kPa): 4, 2



Inverse relationship driving to an asymptote

No-AOS, the asymptote = 2.99 μm

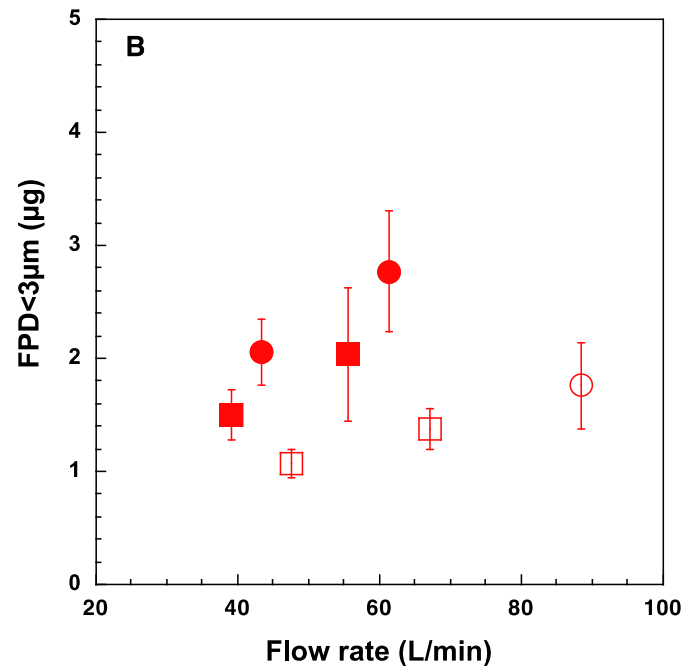
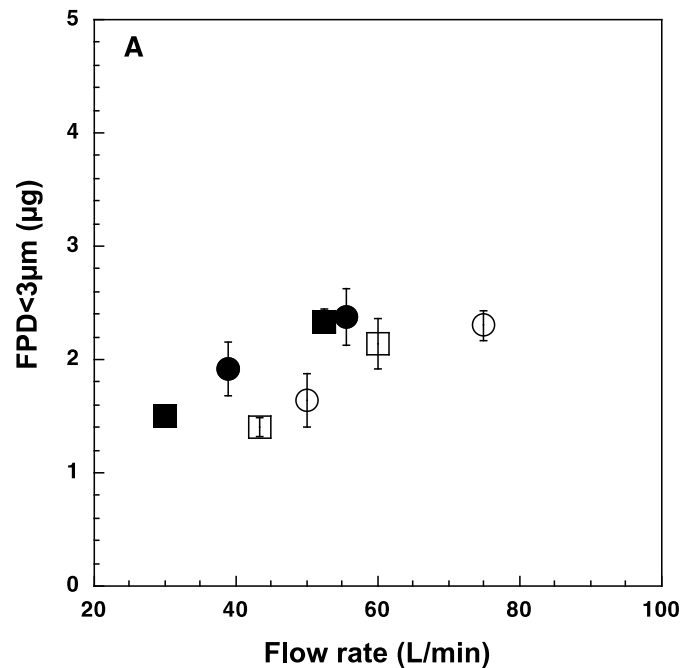
With AOS, the asymptote = 2.07 μm

Estimated formoterol fumarate

$$MMAD = 1.7 \cdot \sqrt{1.2} \approx 1.9 \mu\text{m}$$

Fine Particle Dose of formoterol fumarate vs flow rate

Circle: RS01-LR; square: RS01-MR
Empty symbols: without AOS;
Full symbols: with AOS



- AOS Improved API deaggregation
- Device performance less dependent on the inspiratory effort
- DPI dependence on atmospheric pressure was almost completely eliminated

Independent flow rate Device: Investigation by DoE

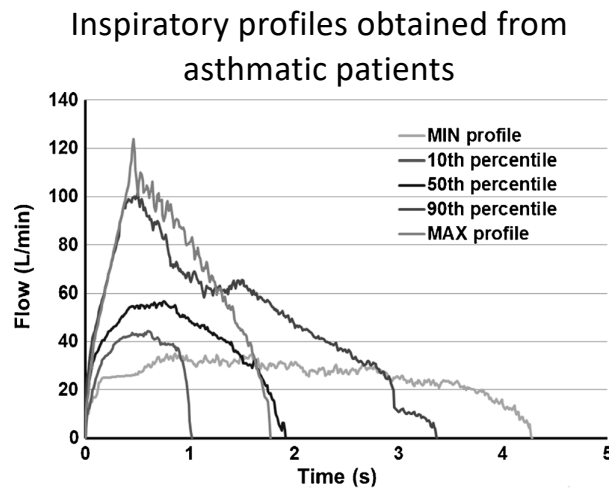
Pharm Res
DOI 10.1007/s11095-015-1820-1



RESEARCH PAPER

Multivariate Analysis of Effects of Asthmatic Patient Respiratory Profiles on the *In Vitro* Performance of a Reservoir Multidose and a Capsule-Based Dry Powder Inhaler

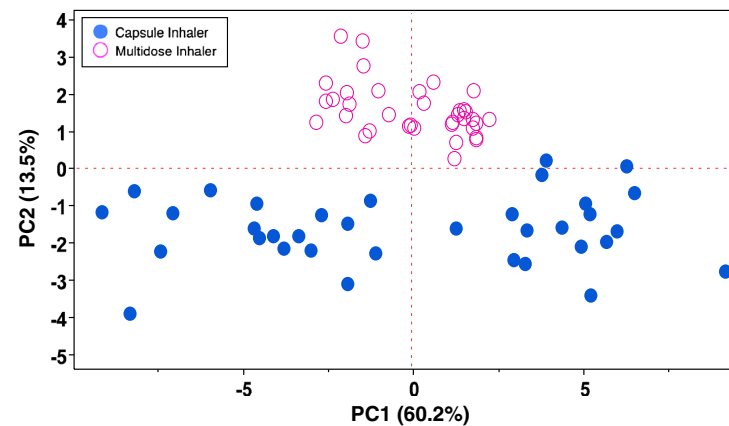
Francesca Buttini^{1,2} • Irene Pasquali³ • Gaetano Brambilla³ • Diego Copelli³ • Massimiliano Dagli Alberi³ • Anna Giulia Balducci⁴ • Ruggero Bettini¹ • Viviana Sisti³



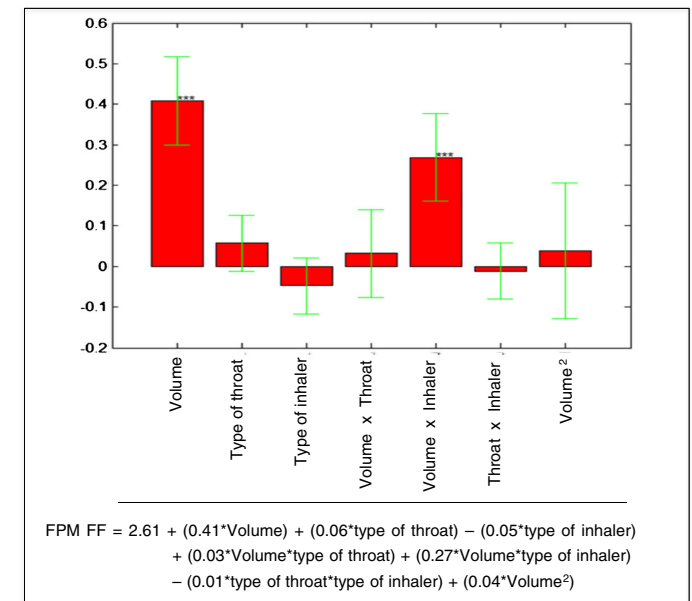
Multidose-breath
activated device

Single dose capsule
device

Scores plot: the effect of the type of inhaler on aerodynamic performance



Exp plan: 24 exp in triplicate (n=72)



The coefficients of the model and the equation of the model for the formoterol fumarate fine particle mass

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Acknowledgments

University of Parma (IT)

Prof. Paolo Colombo
Prof. Ruggero Bettini
Prof. Fabio Sonvico
Dr. Alessandra Rossi
Dr. Anna Giulia Balducci (present at Chiesi Ltd. UK)

King's College London (UK)

Prof. Ben Forbes
Prof. Christopher Marriott

Chiesi Farmaceutici (IT)

Dr. Paolo Chiesi
Dr. Gaetano Brambilla
Dr. Andrea Casazza
Dr. David Lewis

RCPE (Graz, AT)

Prof. Johannes Khinast
Massimo Bresciani

CF Centre – Parma Hospital

Dr. Giovanna Pisi
Dr. Antonio Chetta

Pulmonary Dept - Careggi Hospital

Prof. Federico Lavorini

University of Athens (GR)

Prof. Dimitrios Rekkas

Respira Therapeutics Inc (US)

Prof Hugh Smyth
Dr. Andy Clark

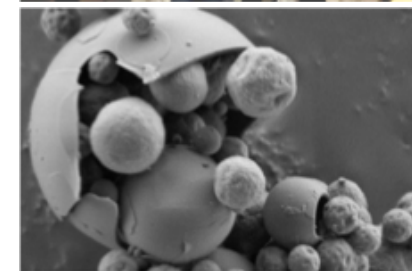
Plastiape Spa (IT)

Eng. Mauro Citterio



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