AEROSOLTHERAPY: TECHNICAL ISSUES

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INTRODUCTION - BACKGROUND

- *Modeling & experiments of lung surfactant dynamics (PhD, Warsaw, 1997) - co-operation with MD*

- *Post-doc at Lovelace Respiratory Research Institute (Albuquerque, NM, 1999-2000)*

- *From 2000 - the research continued at WUT*

  - *budget sources (KBN): basic research*

  - *industry (pharmaceutical): engineering solutions and products*

OUTLINE

- DIVISION OF FUNDAMENTAL PROCESSES AND ENVIRONMENTAL PROTECTION
- AEROSOLTHERAPY
  - definition, aims, methods
  - technical issues

aerosol generation

- *devices (inhalers)*
- *drug formulation*

aerosol deposition in the lungs & interactions

- *modeling*
- *experiments (in vitro)*

aerosol measurement (quality tests)

- *standards (Pharmacopeia)*
- *alternative methods*

with selected examples from our research

- FUTURE STEPS

Division of Fundamental Processes and Environmental Protection

Head: prof. ***Leon Gradoń****, PhD DSc*

- *Laboratory of Dispersed Systems*
- *Laboratory of Engineering Methods in Medicine*

Areas of research:

- *aerosol and liquid filtration in fibrous filters*
  (A. Podgórski; A. Moskal; A. Bałazy, L. Gradoń)
- *aerosols in medicine: generation (inhalers), deposition and interaction with the lungs*
  (T. Sosnowski, A. Moskal, L. Gradoń, T. Ciach, K. Grzybowski)
- *lung surfactant dynamics and physiological effects*
  (T. Sosnowski, L. Gradoń, M. Pawelec)
- *biomedical materials and devices*
  (T. Ciach)

regular staff: 5 persons
+ 3 PhD students

EQUIPMENT: Aerosol generation, identification and filtration

MFP2000 system for testing of filter material (PALAS GmbH)

wide-range aerosol spectrometer XPS, 10-500 nm (MSP Inc., USA)

oil mist generator (PALAS GmbH)

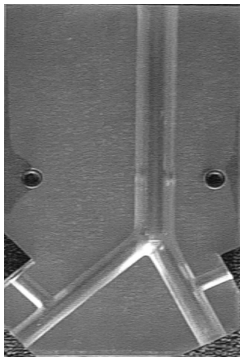
light-white aerosol spectrometer WELAS 2100, 0,2-40 μm (PALAS GmbH)

laser particle counter (A3 GmbH)

Electrospray monodisperse aerosol generator (TSI Inc.) 2-500 nm

EQUIPMENT: Medical aerosol testing and deposition studies

Artificial Lung Apparatus
(ALA)



Physical models
of lung geometry

Andersen-type
cascade impactor
(Copley Sci., UK)

Digital flowmeters
(TSI Inc., USA)

Flow calibrator
(BIOS Inc., USA)

EQUIPMENT: Lung surfactant properties and dynamic surface effects

Pulsating Bubble Surfactometer
(Electronetics Corp, USA)

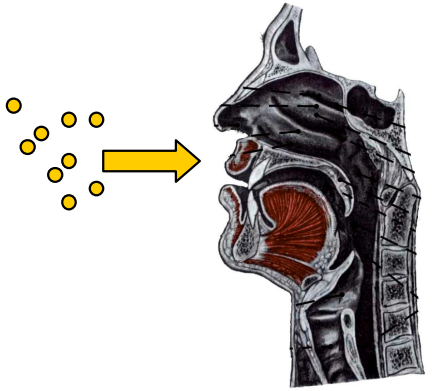
Langmuir-Wilhelmy balance
Minitrough (KSV, Finland)

Needle microtensiometer
(Kibron, Finland)

Bubble-pressure
DST tensiometer
(Krüss GmbH)

AEROSOLTHERAPY

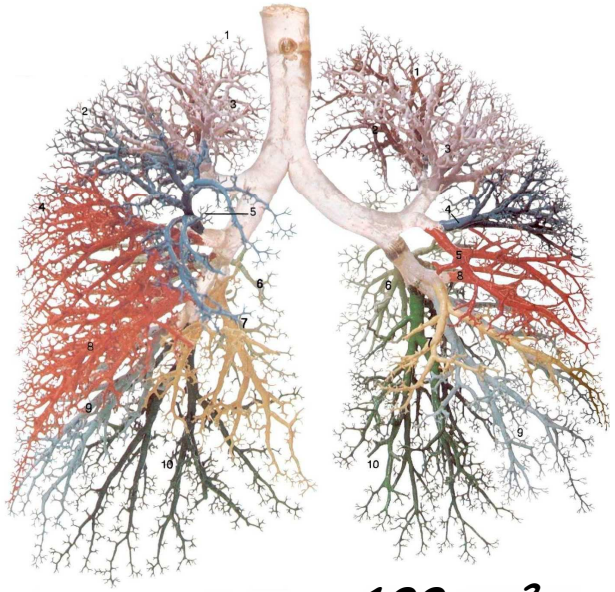
(drug delivery by inhalation)



Medical aerosols:

- drugs for pulmonary diseases (asthma & COPD)

- systemic drugs: insulin, vaccines, growth hormone



~ 100 m ^{2}

Advantages:

- ease of use

- maximization of the local dose (drug targeting)

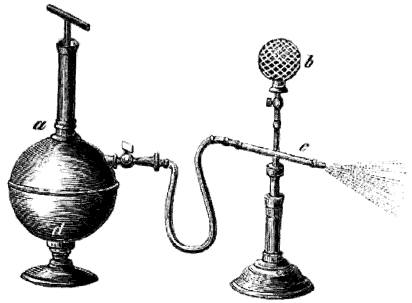
- minimization of side-effects

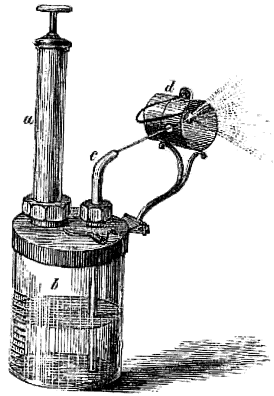
HISTORY

India 2000 b.c.: smoke inhalation (Datura stramonium, Atropa belladonna- alkaloids)
Hippocrates: hot vapor inhalation for throat and lung diseases

XIXth century:

- *first nebulizers (liquid atomizers)* →

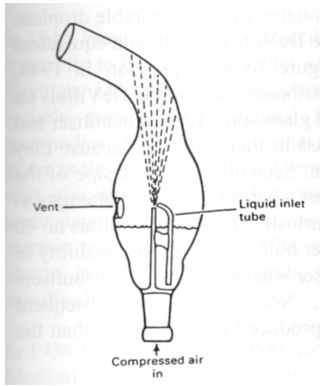




- *asthma cigarettes (bronchodilation)*

Vaporatorium

1930: De Vilbiss nebuliser



INHALERS TODAY

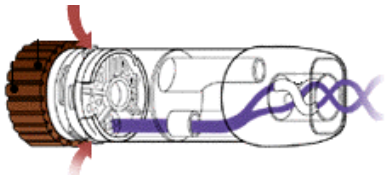
NEBULIZERS

PRESSURIZED METERED DOSE INHALERS (pMDI)

since1956

DRY POWDER INHALERS (DPI)

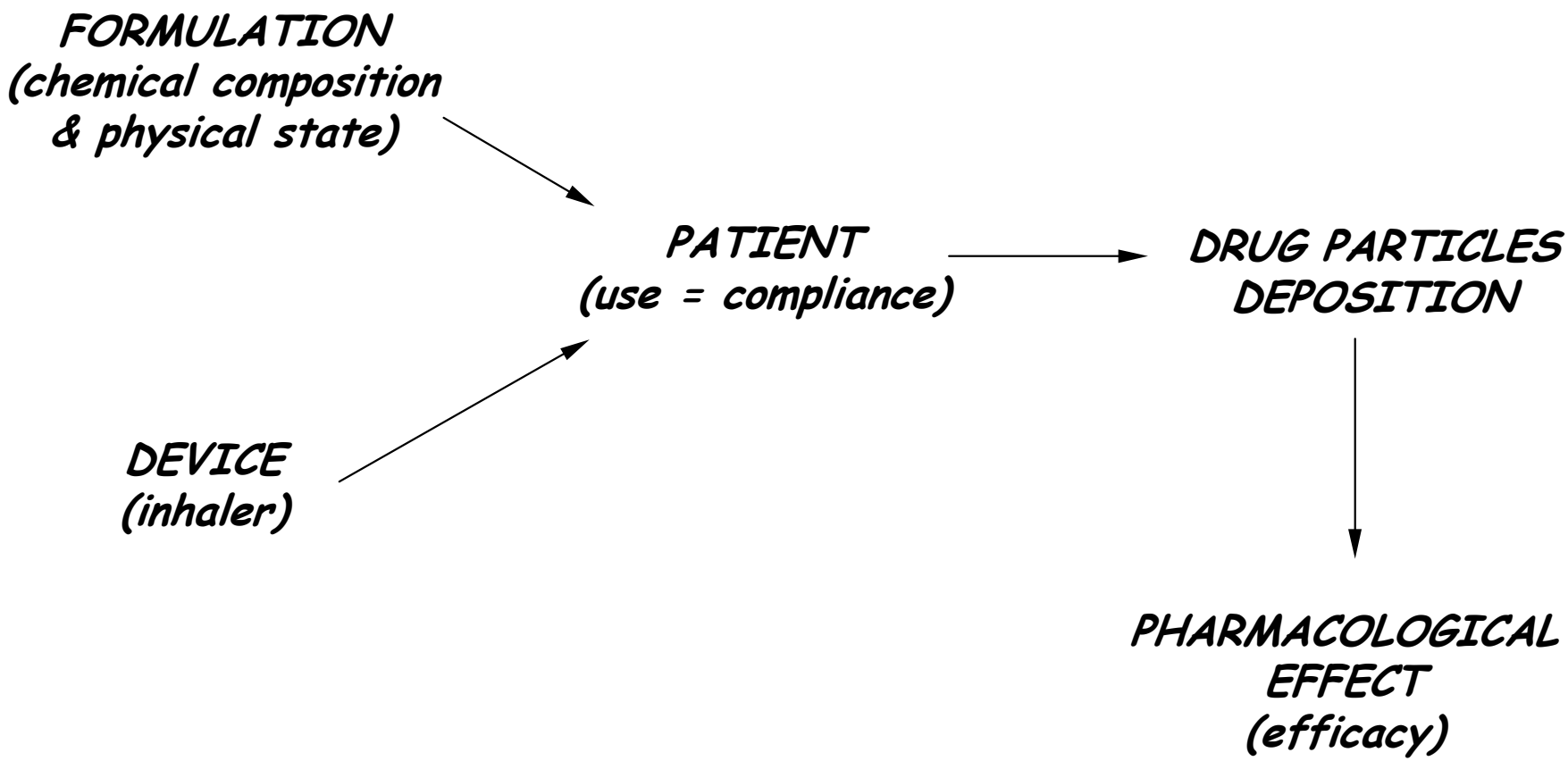
since 1971



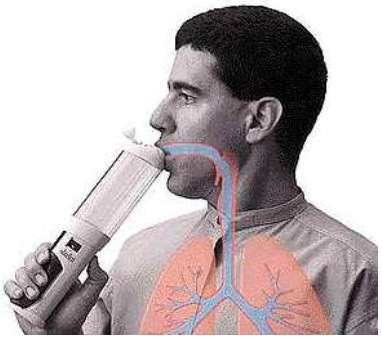
Now used by 40% of patients with COPD

Only up to 30% of the nominal drug dose is delivered to the lungs from inhalers currently available in the market

THERAPEUTIC EFFECT OF AEROSOLTHERAPY



TECHNICAL ISSUES:



- aerosol generation (liquid atomization / powder resuspension)
- aerosol flow and deposition in the respiratory system
- particle-lung interactions (via pulmonary surfactant)
- methods of testing of medical aerosol

Question #1 - what kind of particles is most suitable for inhalation drug delivery ?
(size, shape, density, morphology, surface properties, etc.)

Question #2 - how to characterize (measure) such particles ?

Question #3 - how to produce them in easy-to-use, cheap and portable devices ?

IMPORTANT REQUIREMENT: low dose-to-dose variation (= REPRODUCIBILITY)

Question #1

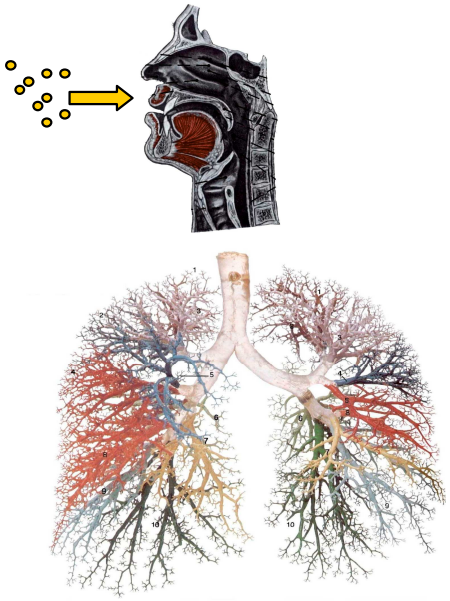
Which particles are most suitable for inhalation drug delivery ?

Knowledge on aerosol behavior in the respiratory tract and the local deposition efficiencies

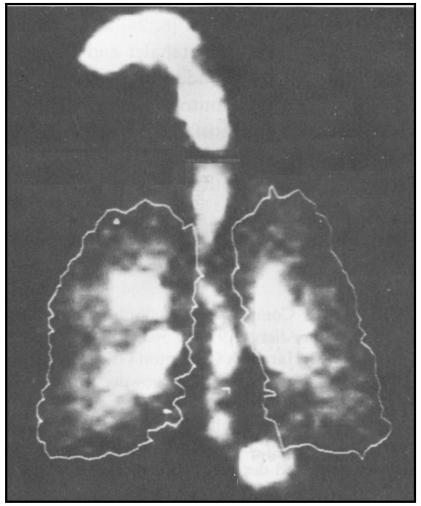
possible benefits

Better dose control
Safety
Targeted (dedicated) drug delivery to the lungs
Economical factors

PARTICLE DEPOSITION: state-of-the-art

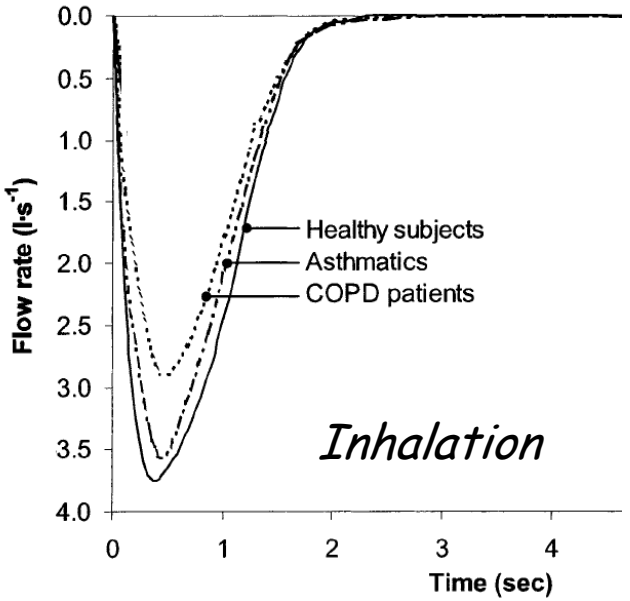


in vivo: radio-tracer techniques



Theoretical predictions (modeling):

- *very complicated geometrical structure*
- *non-steady flow pattern during breathing*
- *intersubject variability in both above factors (age, gender, health status)*

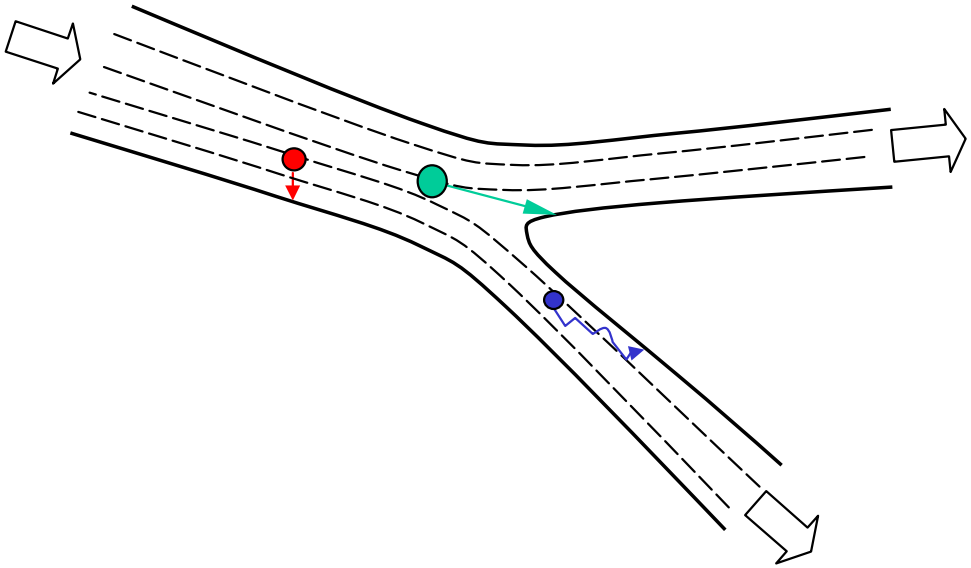


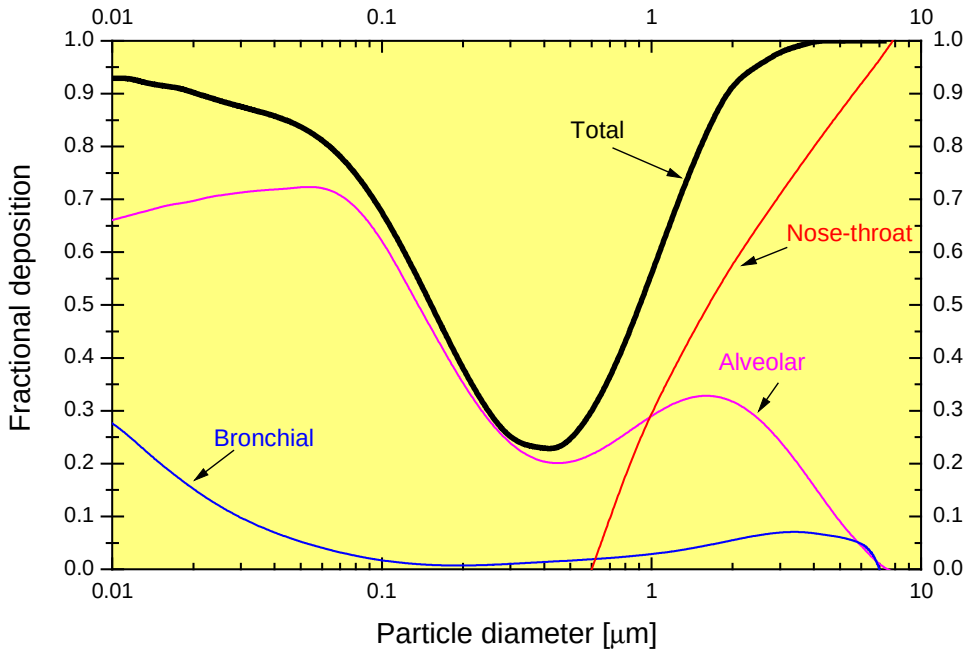
E.g., NCRP model (1997)

- *lung geometry (morphometry)*

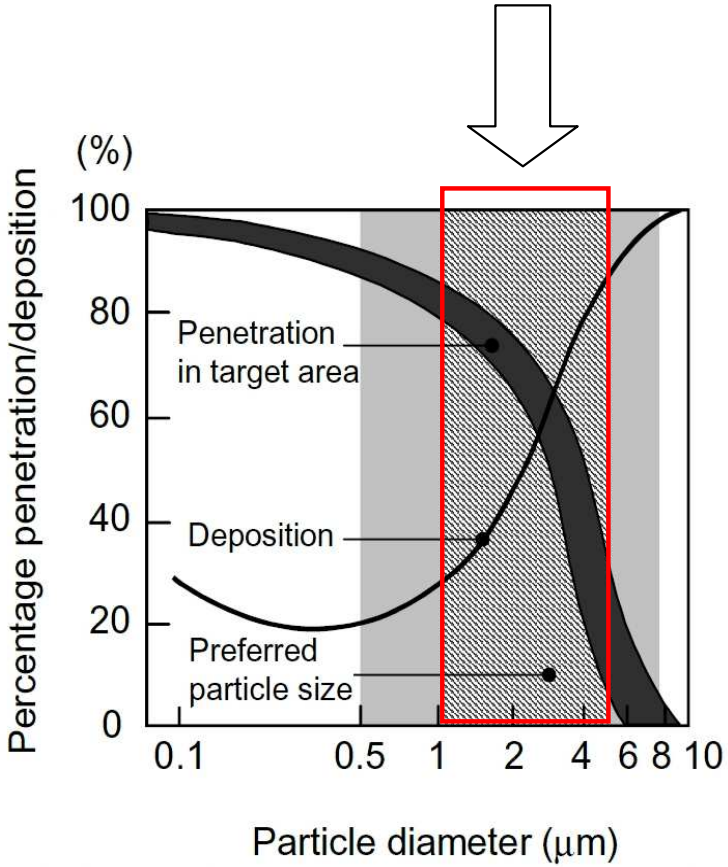
- *<u>average gas velocities</u> in different generations of tracheobronchial tree*

- *deposition mechanisms:*
  1. *impaction*
  2. *sedimentation*
  3. *diffusion*





General conclusions for aerosoltherapy



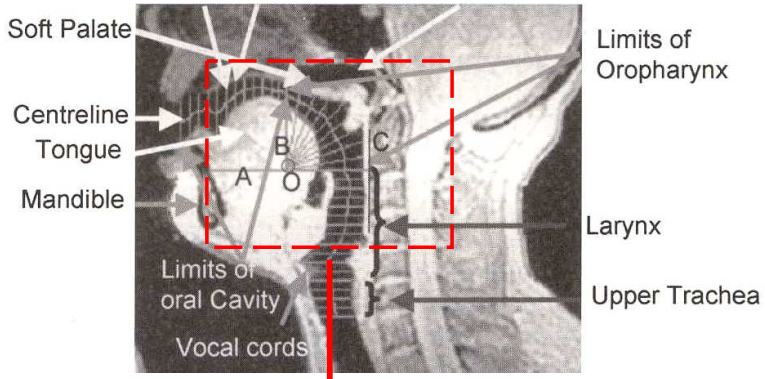
Possible further steps: *refinement of theoretical modeling techniques*
experimental studies in vitro (lung models)

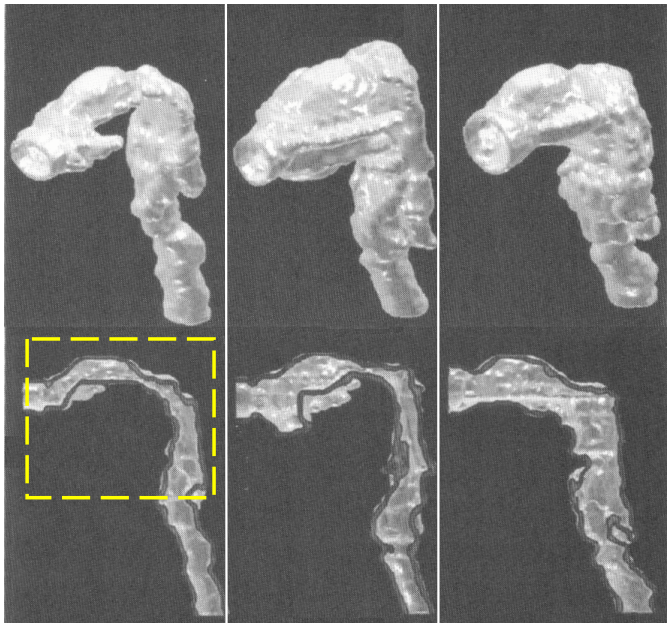
Common assumption in CFD modeling - constant flow rate

$V_E = f \times TV$ (= minute ventilation)

PARTICLE DEPOSITION IN DIFFERENT REGIONS OF THE RESPIRATORY TRACT

ORO-PHARYNX



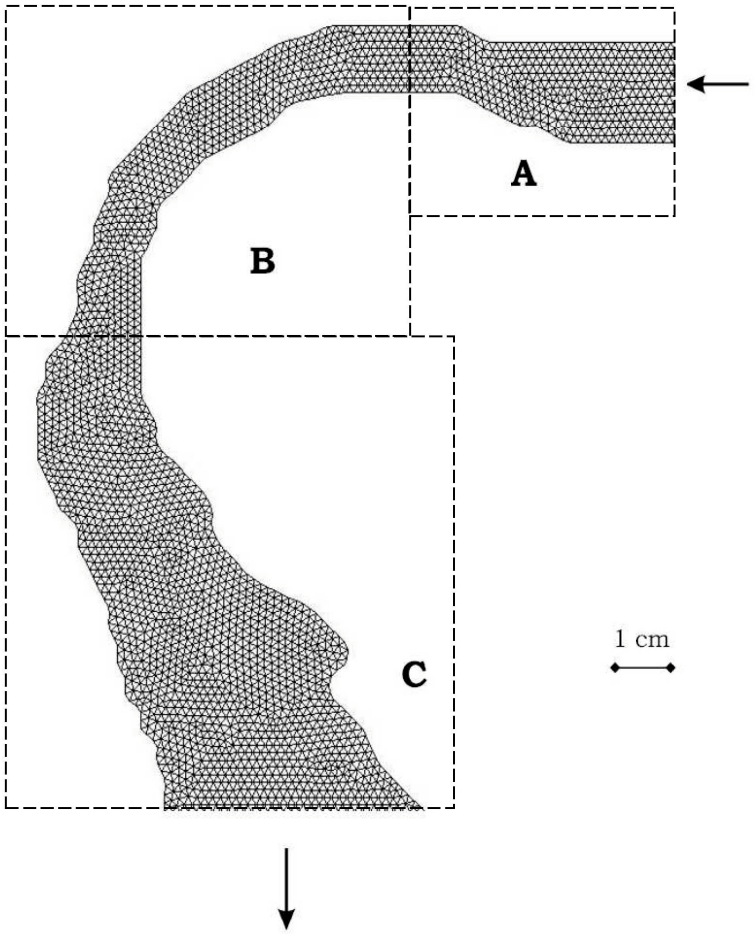


Ehtezazi et al., 2004 - MRI

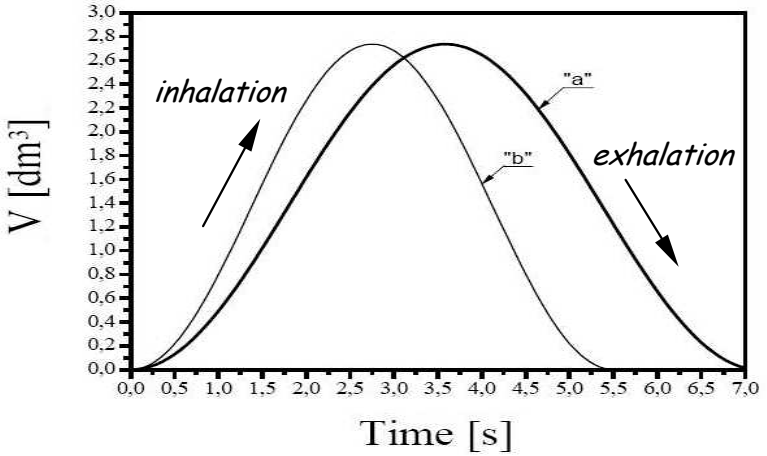
sillicone rubber replica cast

Correct representation !!!

CFD modeling - Fluent

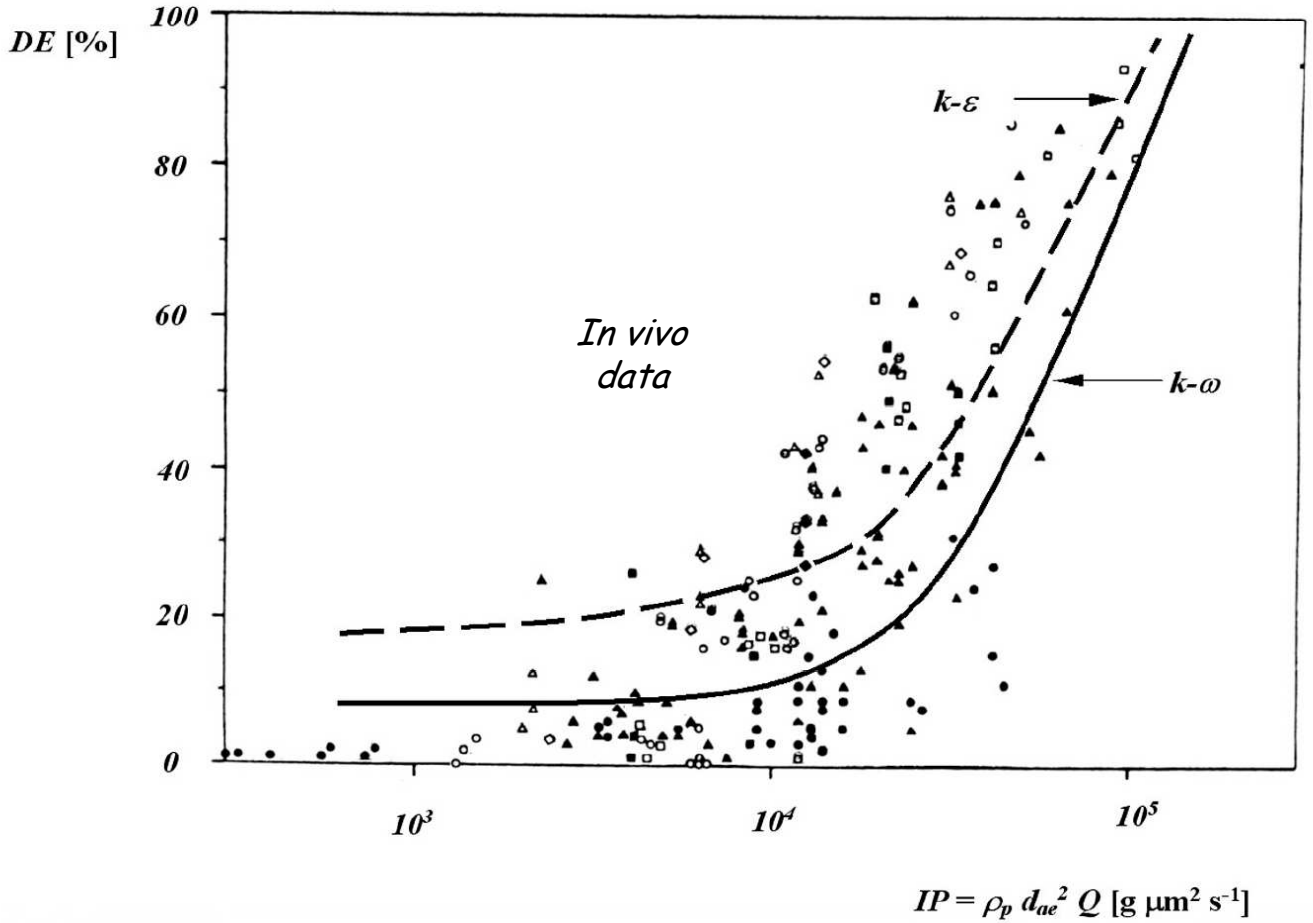


a - slow inhalation
b - fast inhalation



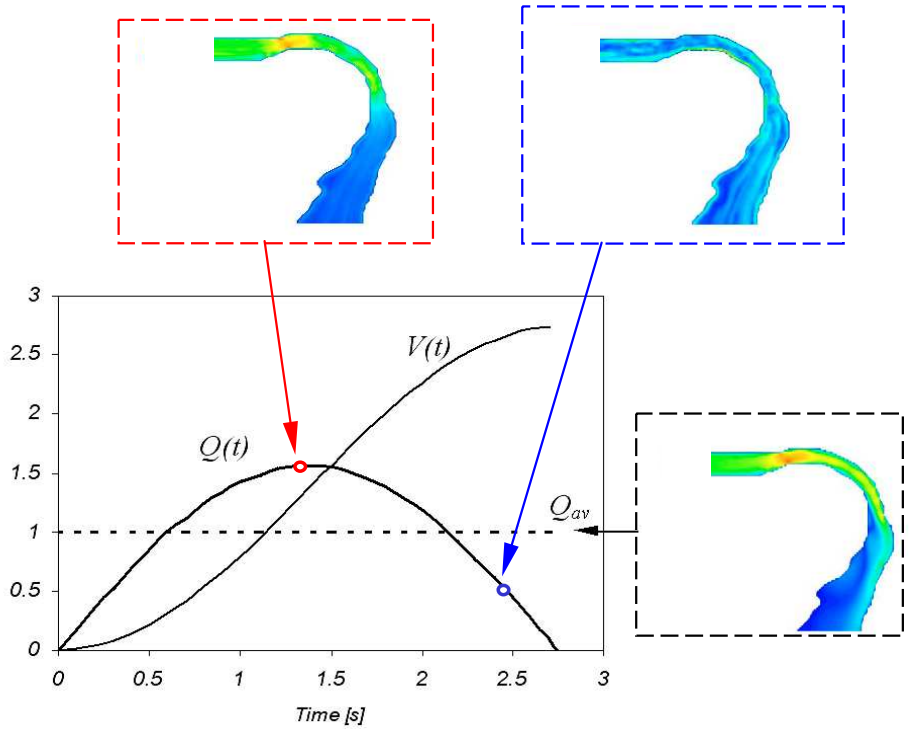
1. ***Calculation of temporal airflow field***
2. ***Lagrangian approach (particle tracking) for >1000 separate particles***
   d_p = 0.3; 1; 3 and 10 μm
3. ***Brownian diffusion included***
4. ***Neglected: inter-particle interactions, wall rebound, re-emission, electrostatic effects***

Problem:
selection of the appropriate
turbulence model (k-ε, k-ω, LES)

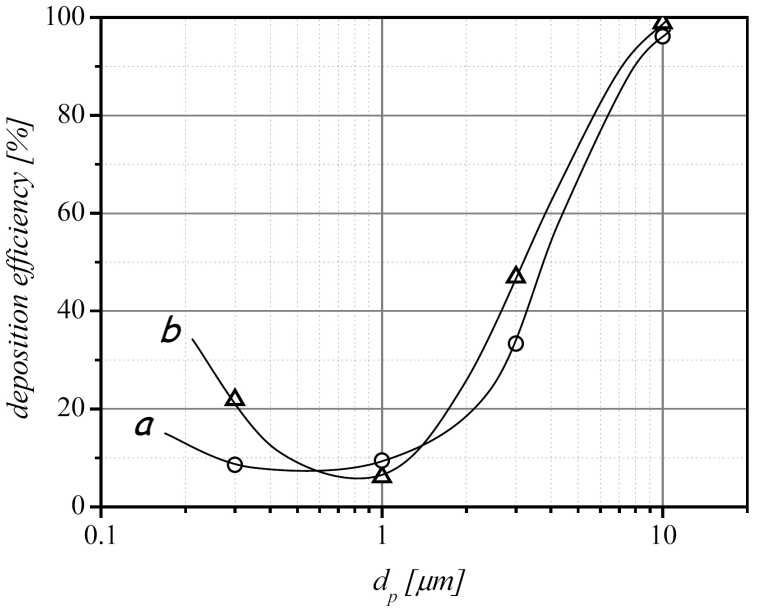


RESULTS

Comparison of airflow field for non-steady and constant flow conditions

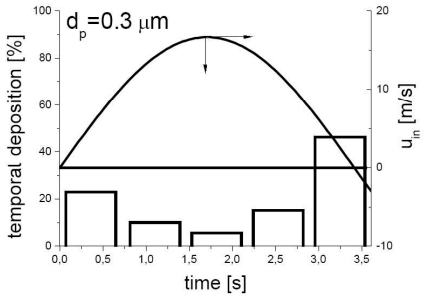


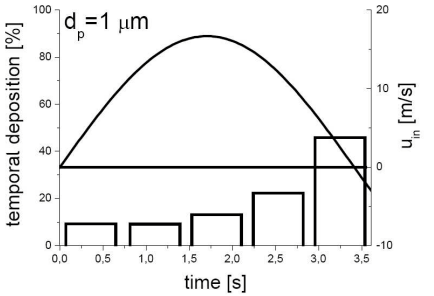
Overall deposition efficiency during inhalation

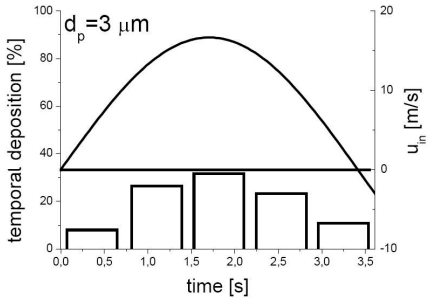


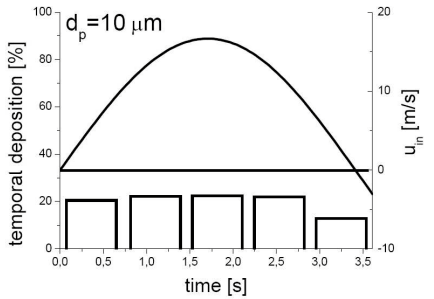
Temporal distribution of deposition

Curve *"a"*

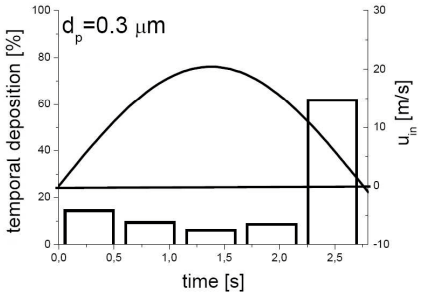


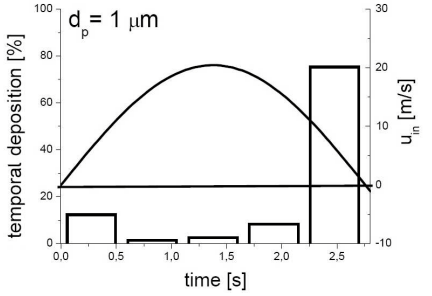


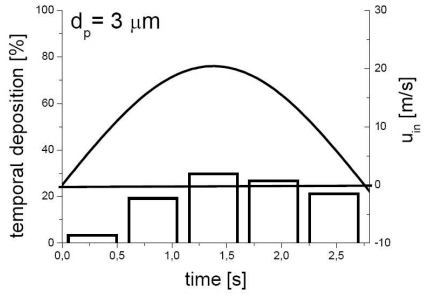


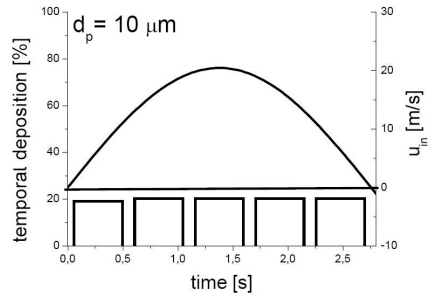


Curve *"b"*



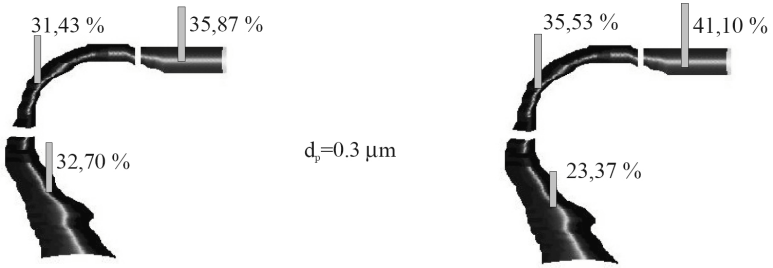


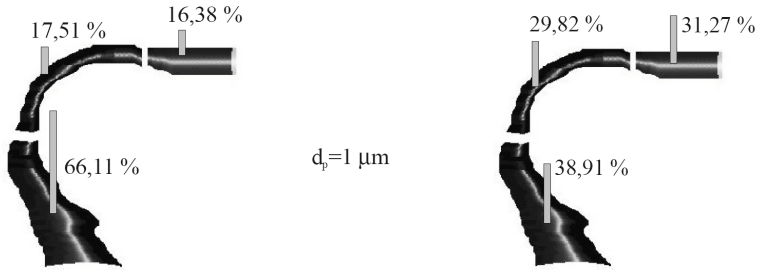


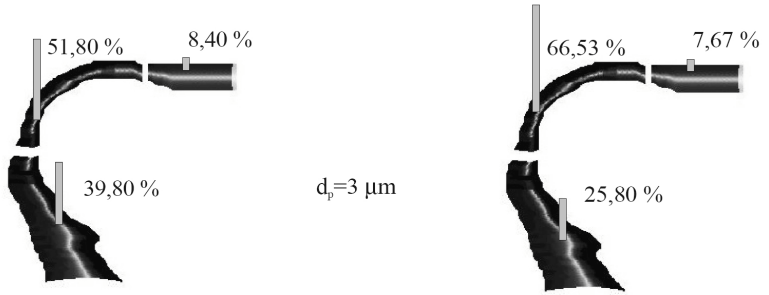


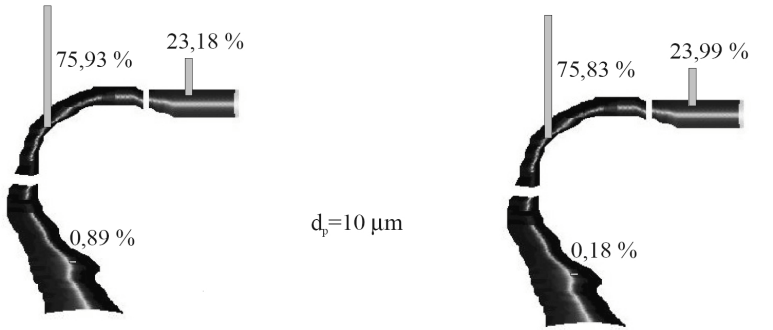
Spatial distribution of deposition

Curve *"a"* **Curve *"b"***

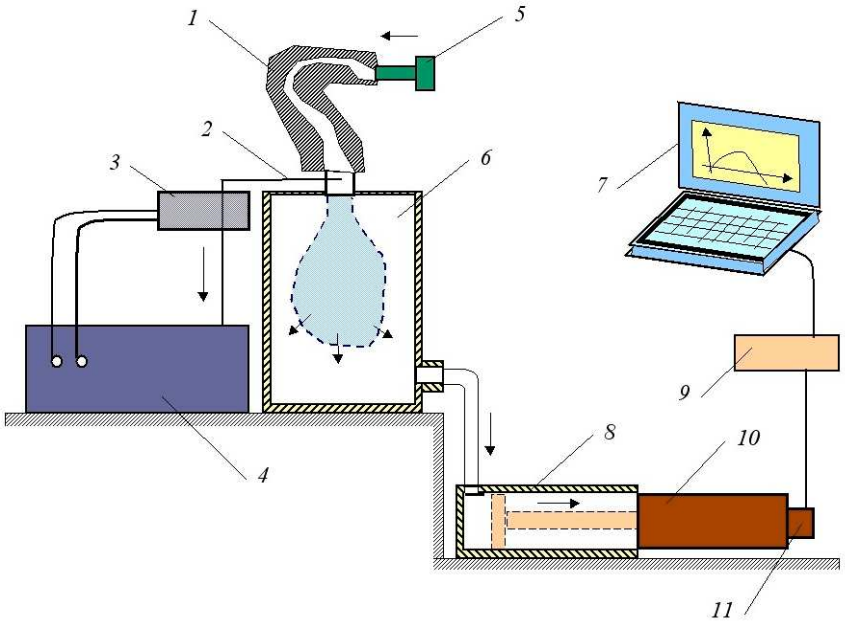






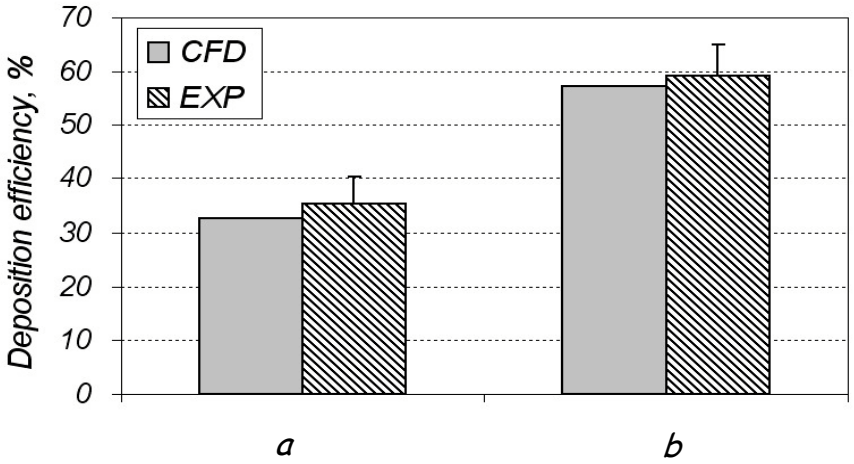


EXPERIMENTS

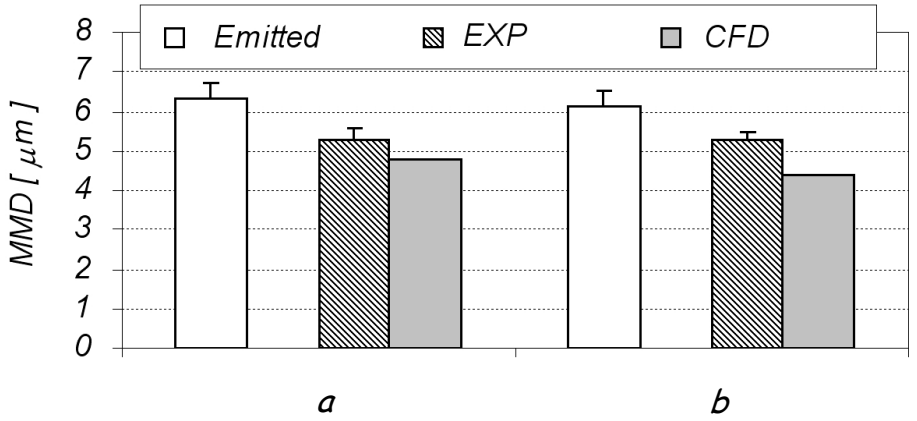


Artificial Lung Apparatus (ALA)

Total deposition of polydispersed aerosol



Change in particle size distribution of aerosol passing the cast



Modeling and experimental studies of particle deposition in the oro-pharynx

CONCLUSIONS:

CFD with realistic flow pattern reveals dynamic effects during aerosol flow and deposition in the airways, which are overlooked if constant flow is assumed

Influence of variations in breathing pattern on the local particle deposition in the mouth and throat is possible

Proper prediction of aerosol deposition in the oro-pharynx is important:

- local deposition in this region is responsible for several adverse effects of inhaled aerosol drug (irritation, mycosis)

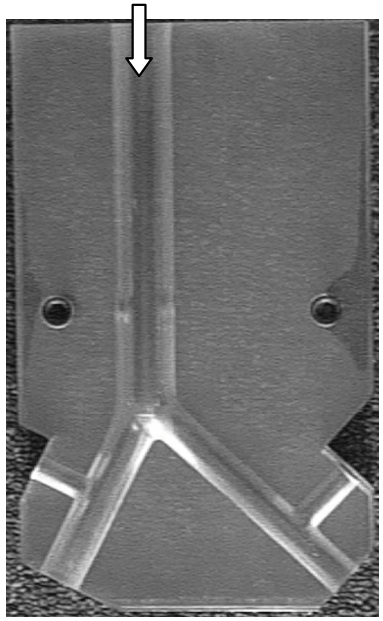
- total deposition determines the undesired systemic absorption (from drug ingestion), but also the bioavailability of the drug in the lungs

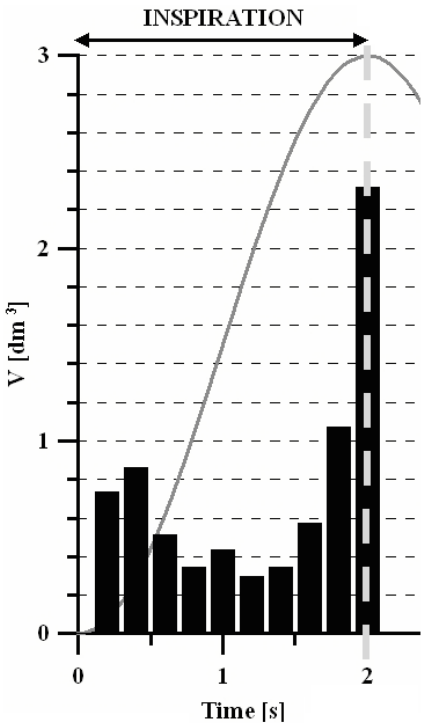
Broadening the knowledge of aerosol behavior in the respiratory system ⇒ better design of drug particles for inhalation

Sosnowski T.R., Moskal A., Gradoń L. Dynamics of oro-pharyngeal aerosol transport and deposition with the realistic flow pattern. *Inhal. Toxicol.*, 18, 773-780 (2006).

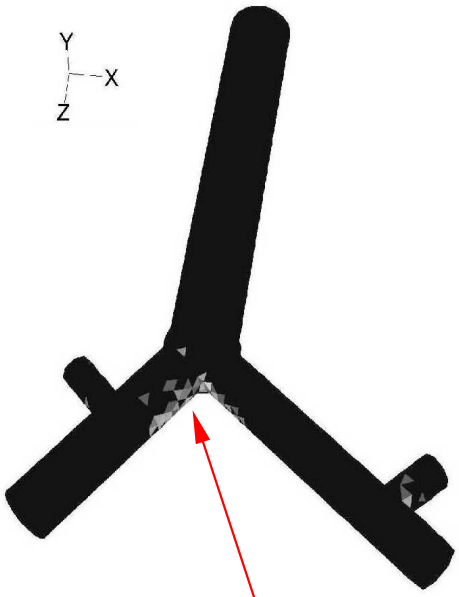
Sosnowski T.R., Moskal A., Gradoń L. Mechanims of aerosol particle deposition in the oro-pharynx under non-steady airflow. *Ann. Occup. Hyg.*, 51,19-25 (2007).

TRACHEA AND MAIN BRONCHI

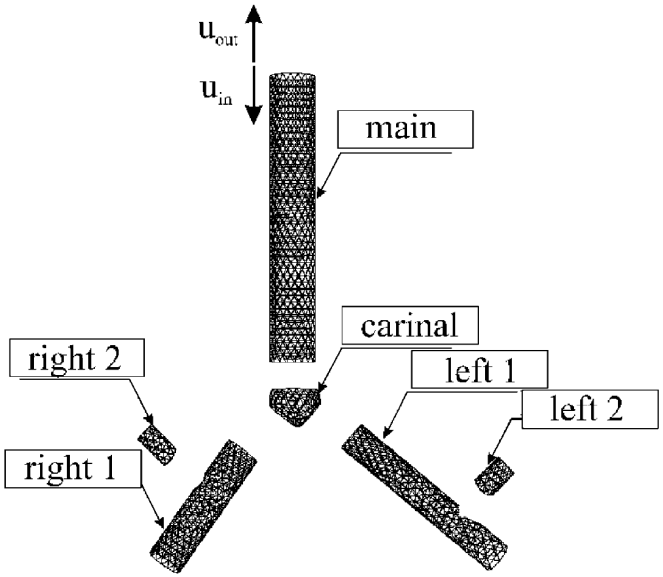




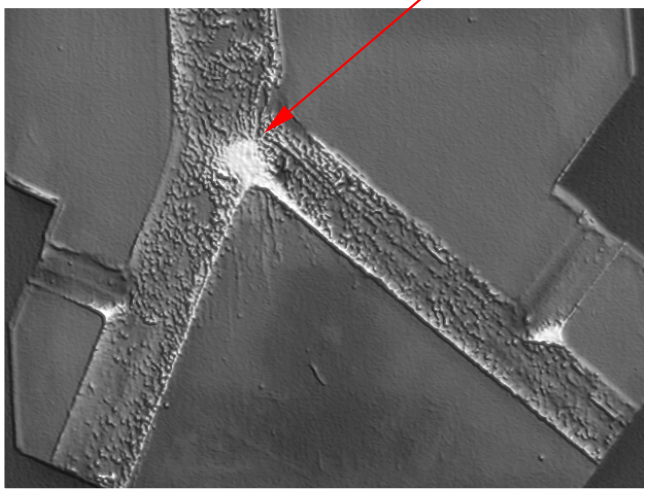
CFD



"Hot-spot"



Experiment



Moskal, A., Gradoń, L. 2002. Temporary and spatial deposition of aerosol particles in the upper human airways during breathing cycle *J. Aerosol Sci.* 33, 1525-1539

Question #2

how to characterize pharmaceutical aerosols ?

↓

European Pharmacopeia, United States Pharmacopeia (USP)

- *reproducibility of drug Metered Dose (MD) and Emitted Dose (ED)*

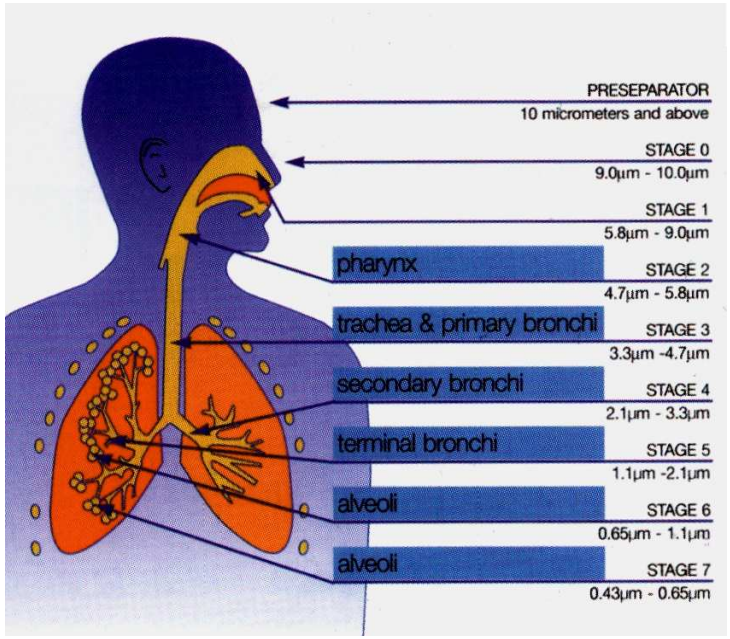
- *particle size distribution: Fine Particle Dose (FPD) and Fine Particle Fraction (FPF)*

ED = out-of-device dose of active substance [μg]
FPD = mass of particles < 5 μm
FPF = FPD/ED

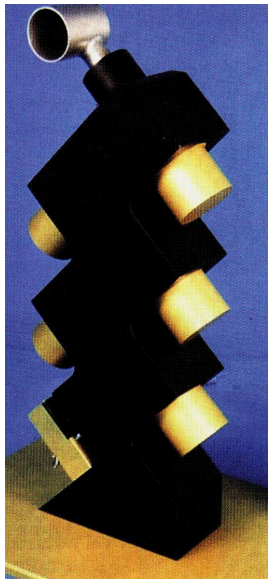
- *GLP (Good Laboratory Practice)*

- *Impactors @ Standard conditions: 28,3 LPM, for powder inhalers: 60 and 90 LPM*

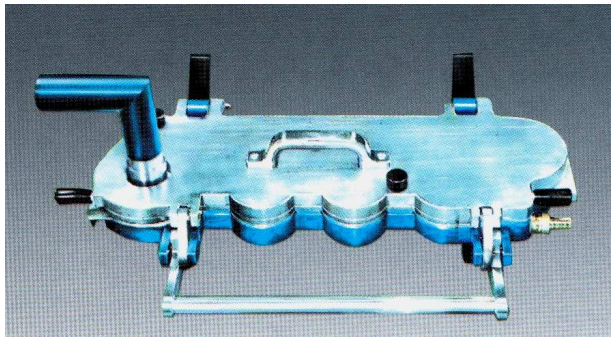
Andersen Cascade Impactor (8-stages)

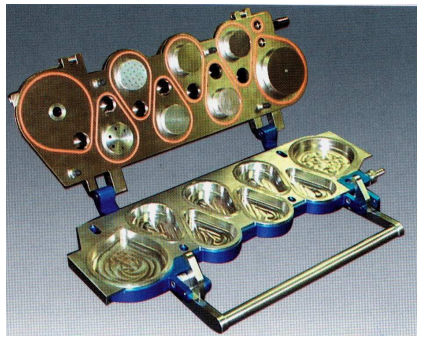


Marple-Miller Impactor (5-stages)



Next Generation Impactor (8-stages)





+ analytical assays (HPLC, spectrophotometry)

Question #3

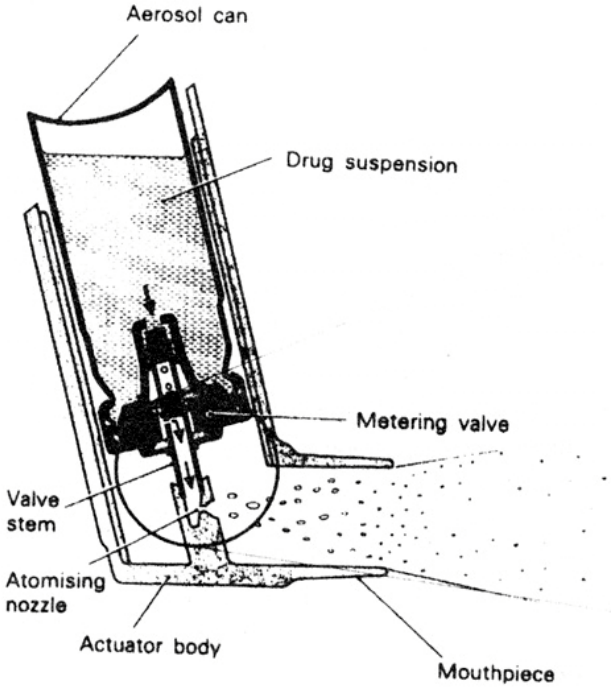
How to produce the required particles in <u>easy-to-use</u>, <u>cheap</u> and portable devices ?

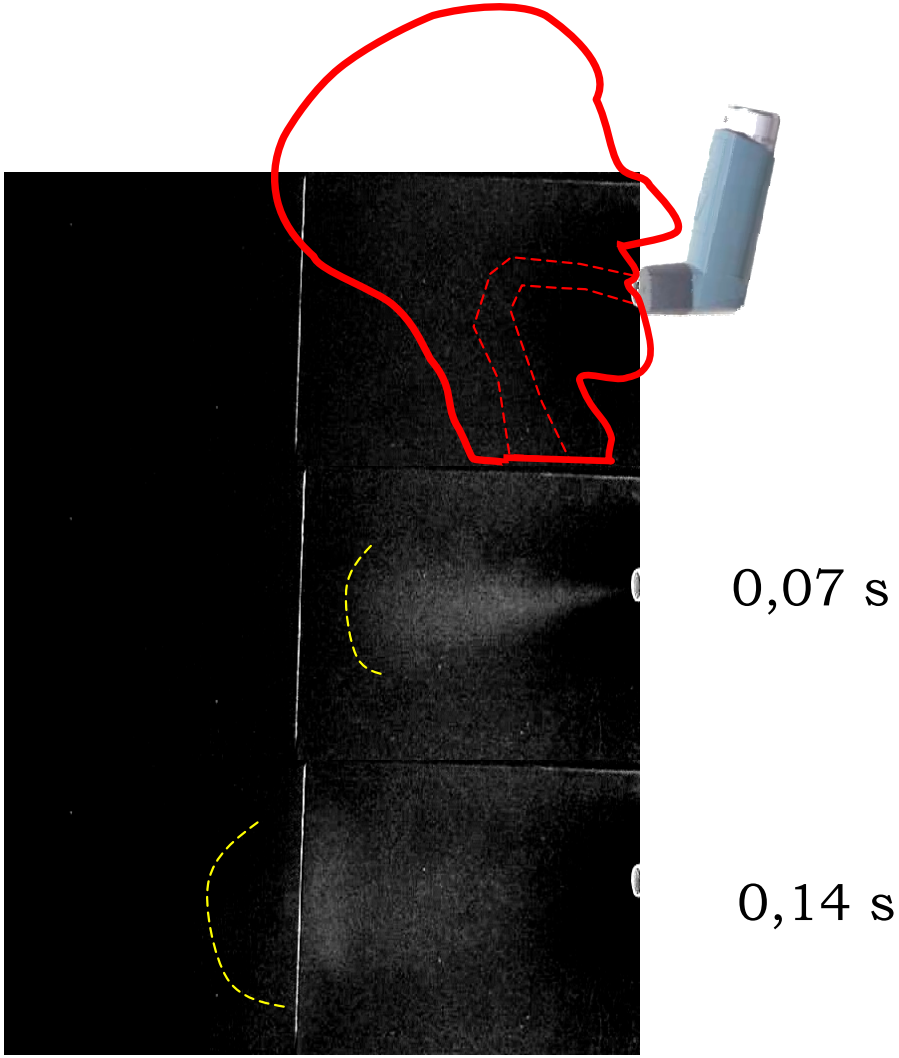
Knowledge on mechanisms of aerosol formation and size control

possible benefits

Better dose control
Safety
Targeted (dedicated) drug delivery to the lungs
Economical factors

PRESSURIZED METERED DOSE INHALERS (pMDI)





Benefits:

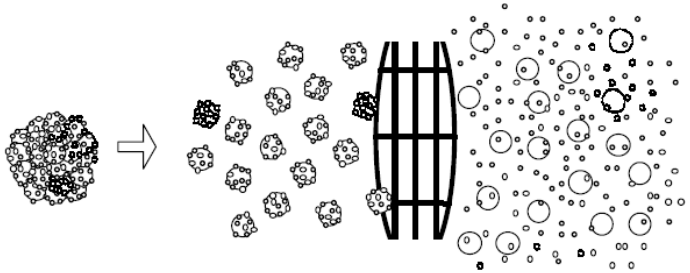
- portable
- easy to operate
- controlled dose

Drawbacks:

- high speed = high throat deposition
- need of coordination
- low lung deposition (<20%)

- CFC (now: HFA - need of reformulation)

DRY POWDER INHALERS (DPI)



resuspension

PATIENT'S BREATH-IN

Benefits:

- portable
- self-coordination

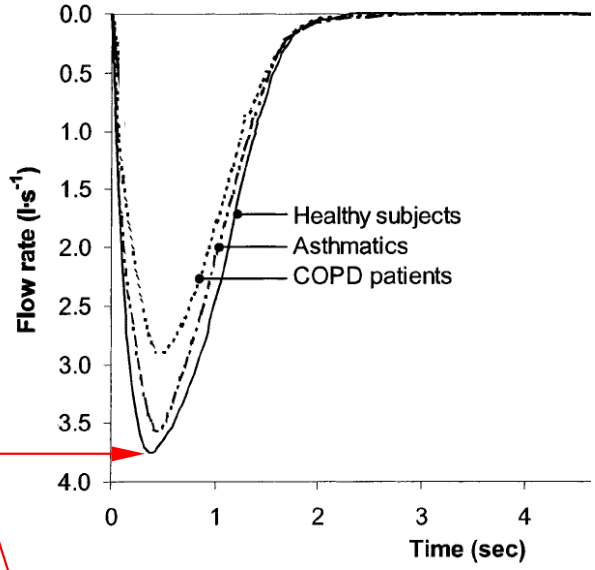
Drawbacks:

- airflow-dependent dose and PSD
- sensitivity to moisture

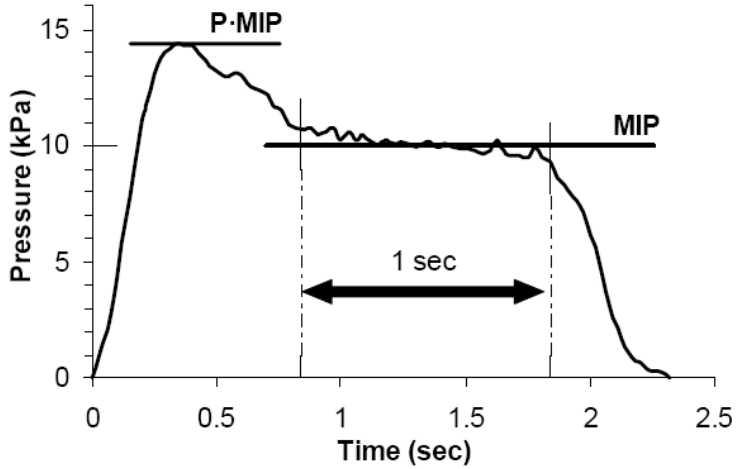
DPI

- single dose (capsule)
  - Aerolizer
  - Handihaler
  - Spinhaler
- multidose
  - blister
    - Diskus
  - metering
    - Turbuhaler
    - Novolizer

LIMITATIONS



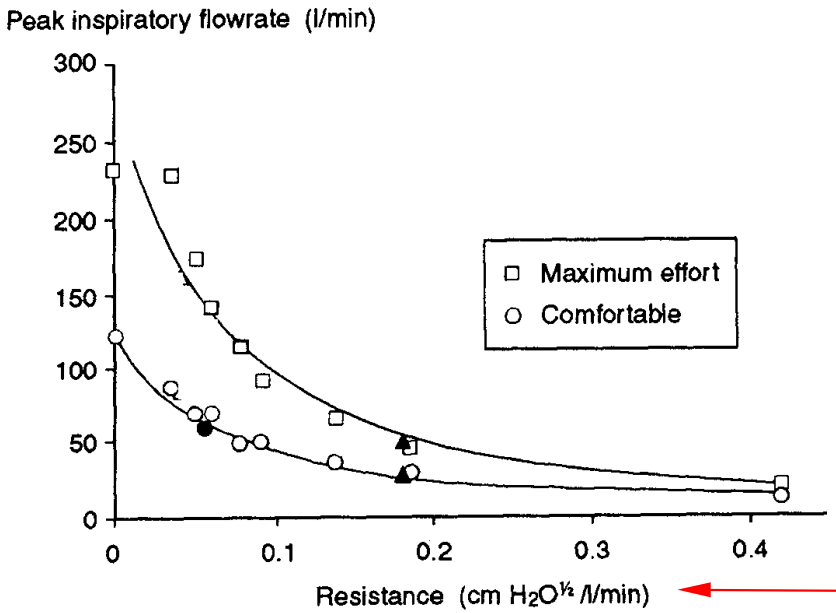
PIFR



Healthy:
MIP = 10 kPa
PMIP = 15 kPa

COPD:
MIP < 7 kPa
PMIP < 10 kPa

MIP - maximal inspiratory pressure (1 sec.)
PMIP - peak maximal inspiratory pressure
PIFR - peak inspiratory flow rate

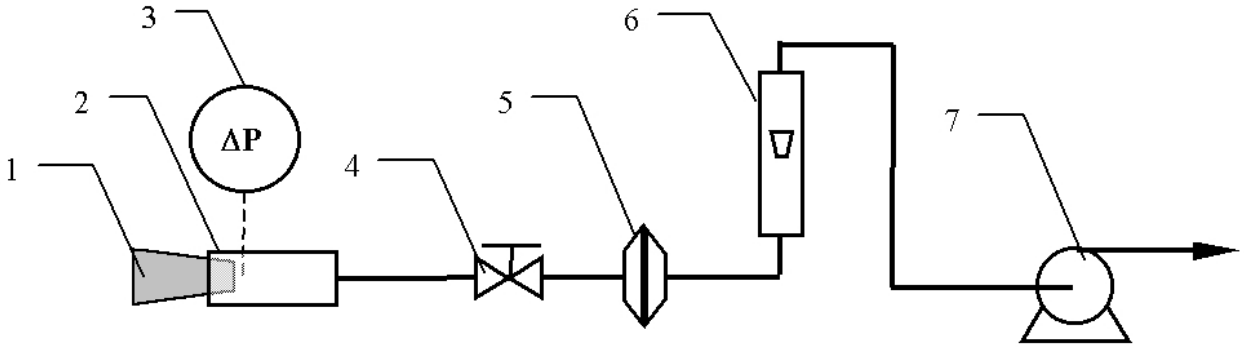


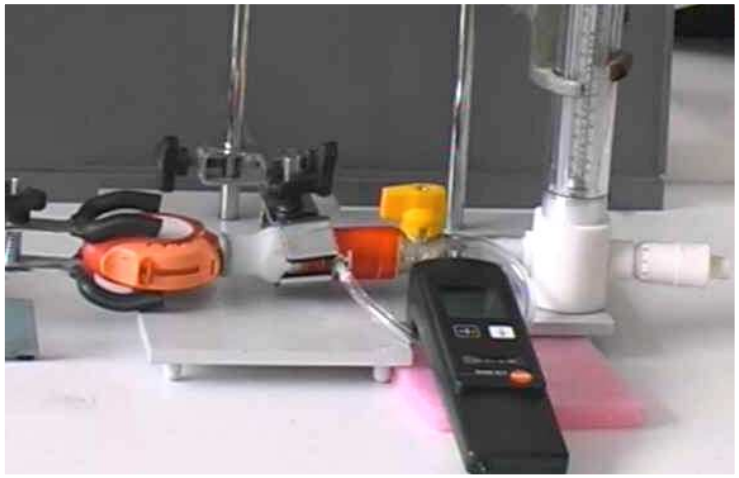
(inhaler) resistance to airflow

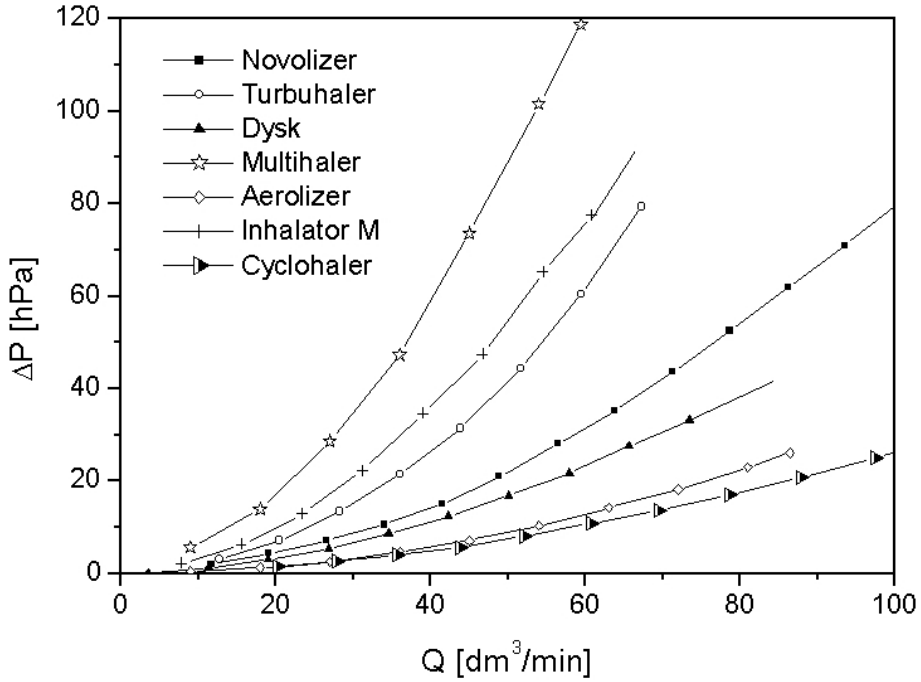
R_D *[hPa $^{1/2}$ dm^{-3} min]*

$$\sqrt{\Delta P} = R_D Q$$

R_D measurement







	Typ inhalatora	R_D [hPa$^{1/2}$ dm^{-3} min]
Low resistance	Cyclohaler	0,049
	Aerolizer	0,058
Medium resistance	Dysk	0,076
	Novolizer	0,086
Hogh resistance	Turbuhaler	0,130
	Inhalator M	0,140
	Multihaler	0,172

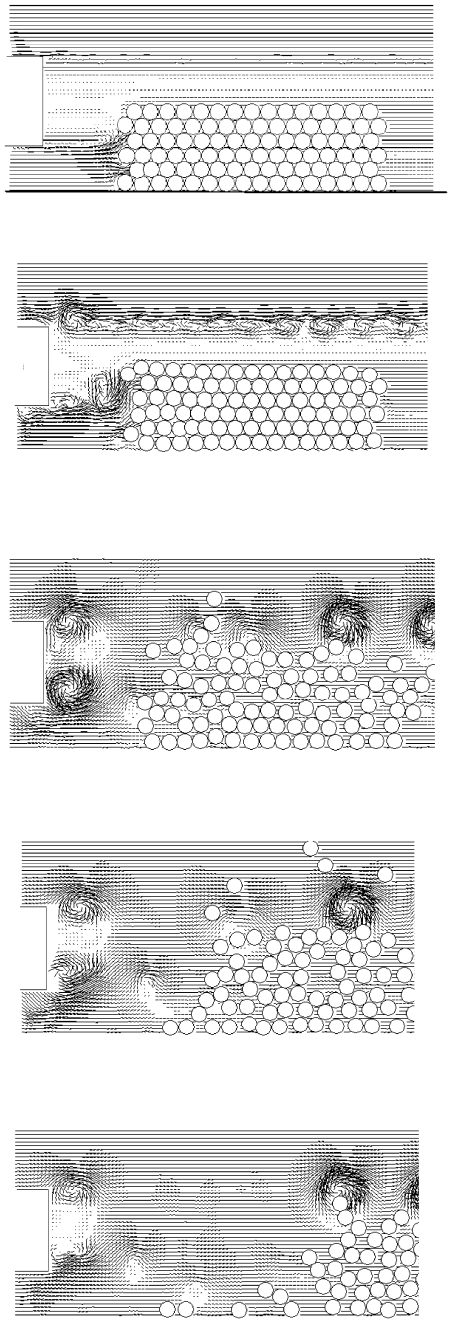
Sosnowski, Gradoń (2004)

Different resistance - appropriate selection of the inhaler for the given patient

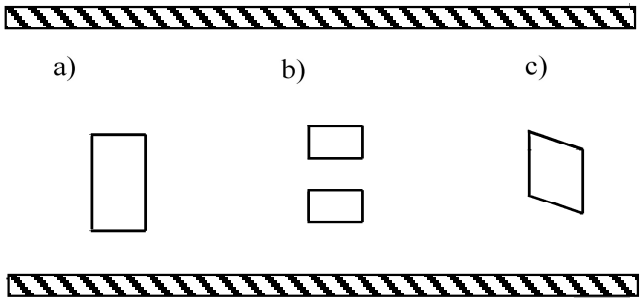
Research towards a low-resistant, effective design

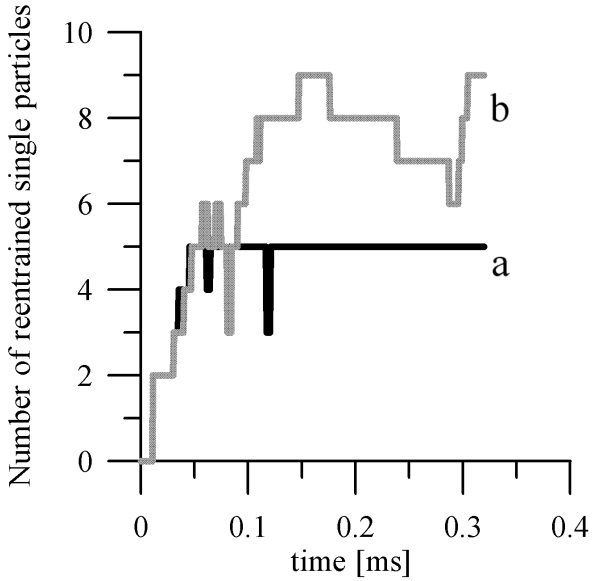
POWDER RESUSPENSION STUDIES → inhaler design

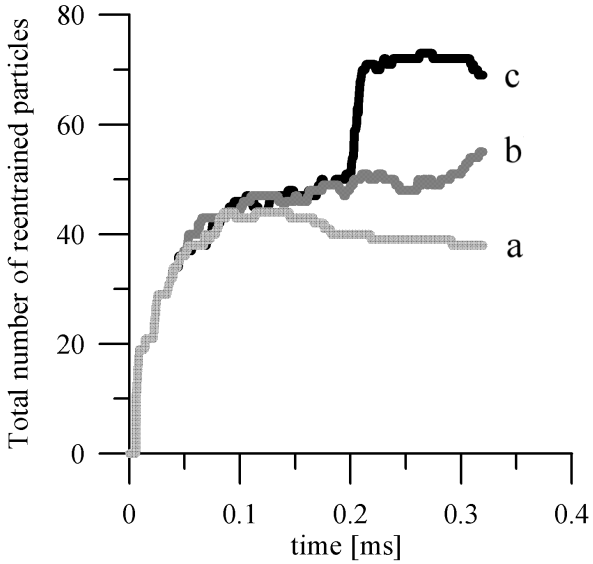
TURBULENCE PROMOTERS - basic analysis



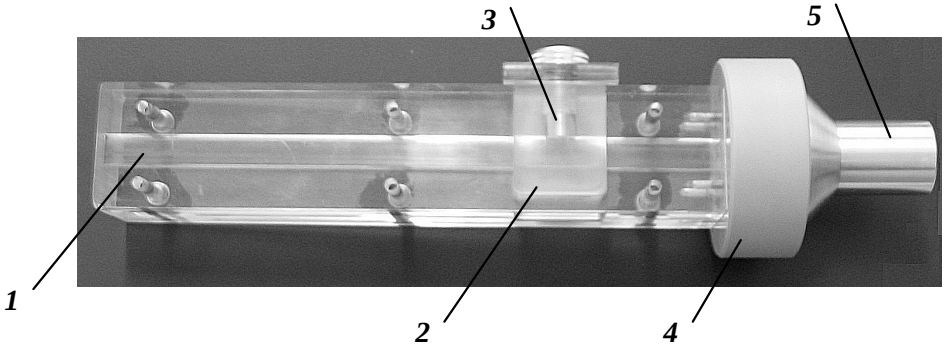
Influence of the promoters' shape

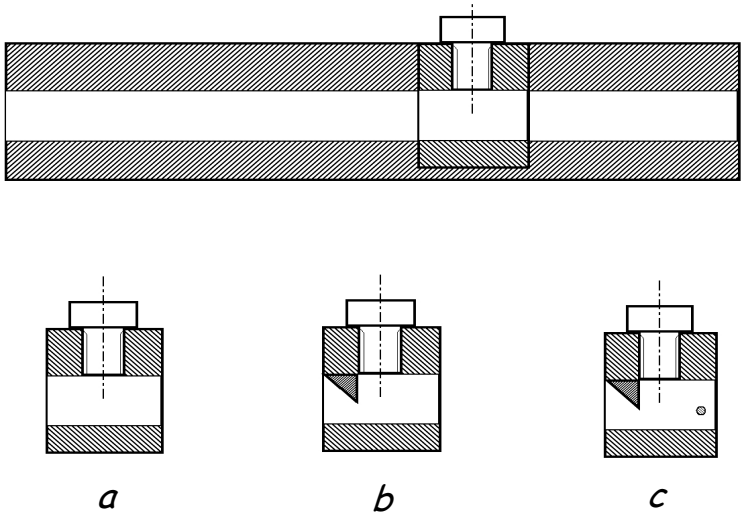




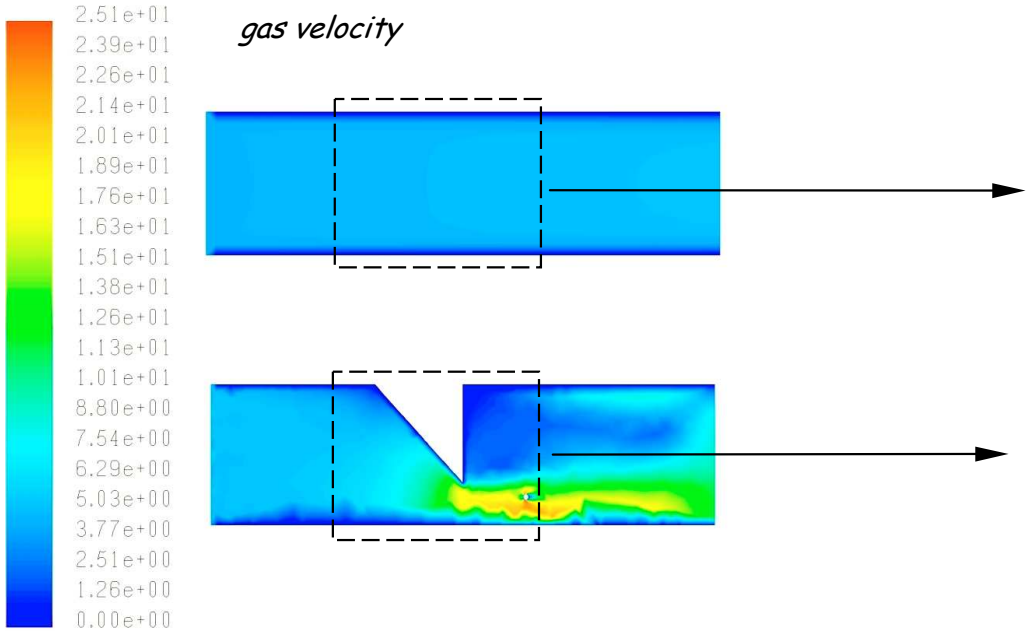


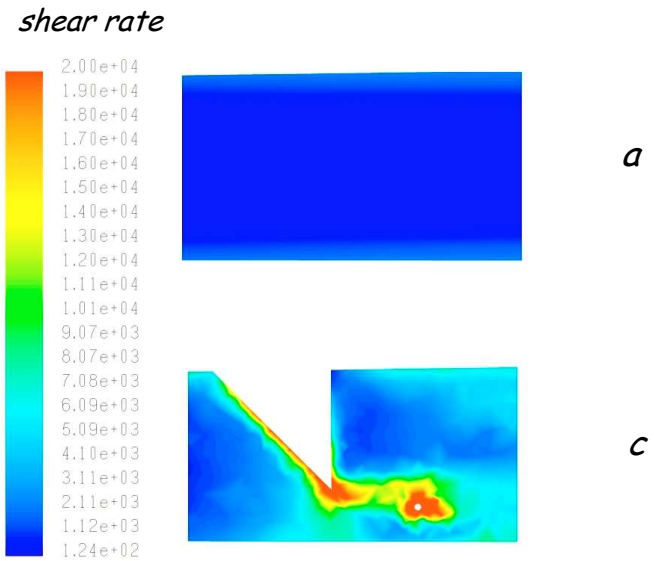
Real macroscopic system



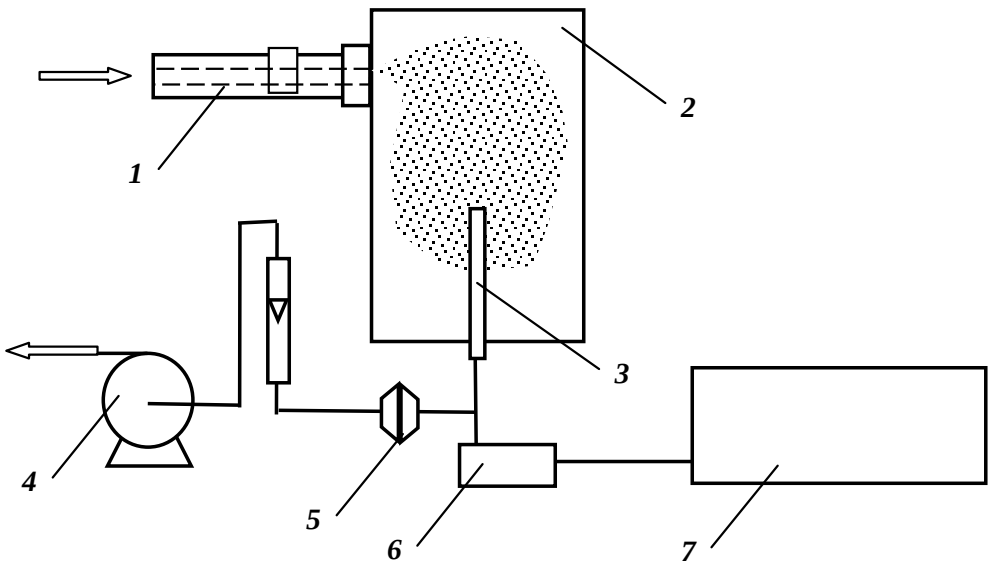


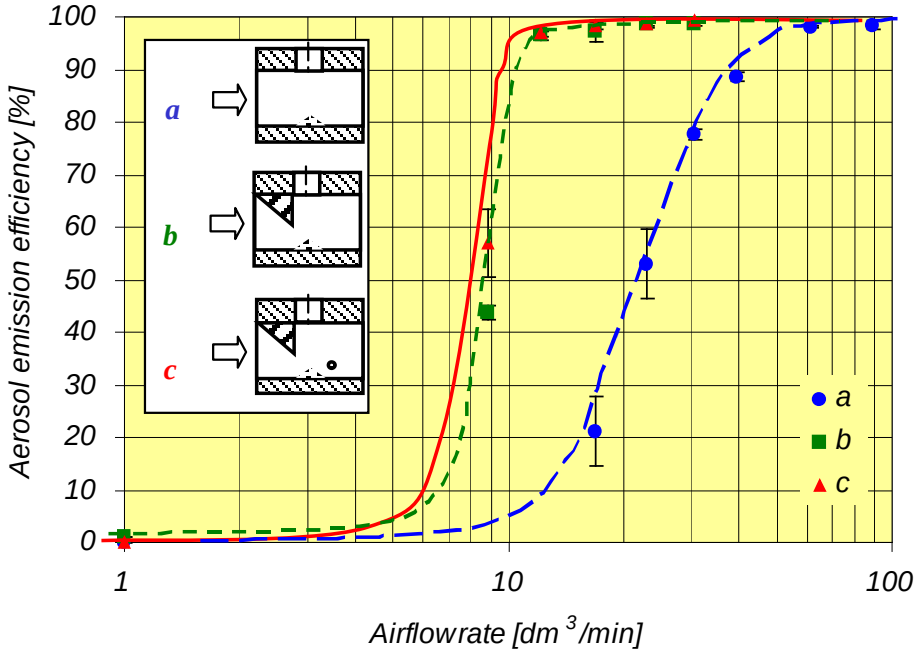
CFD modeling

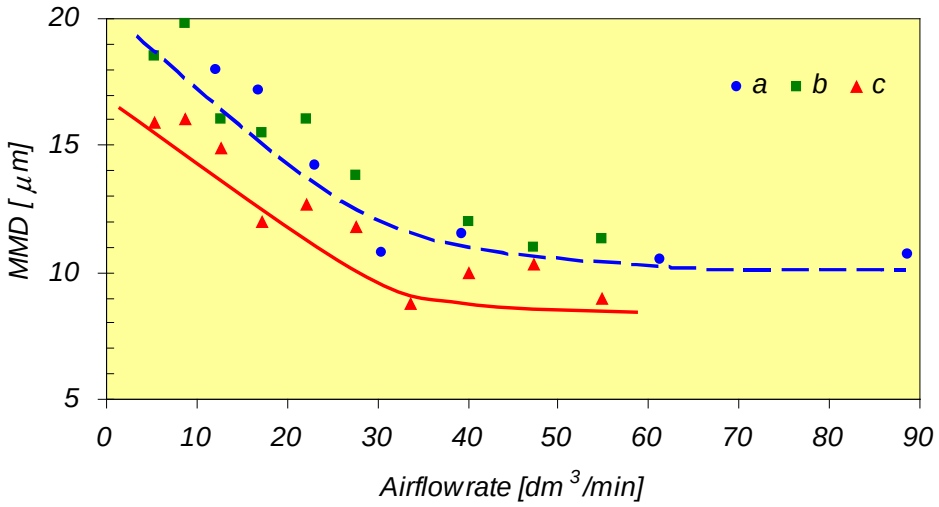


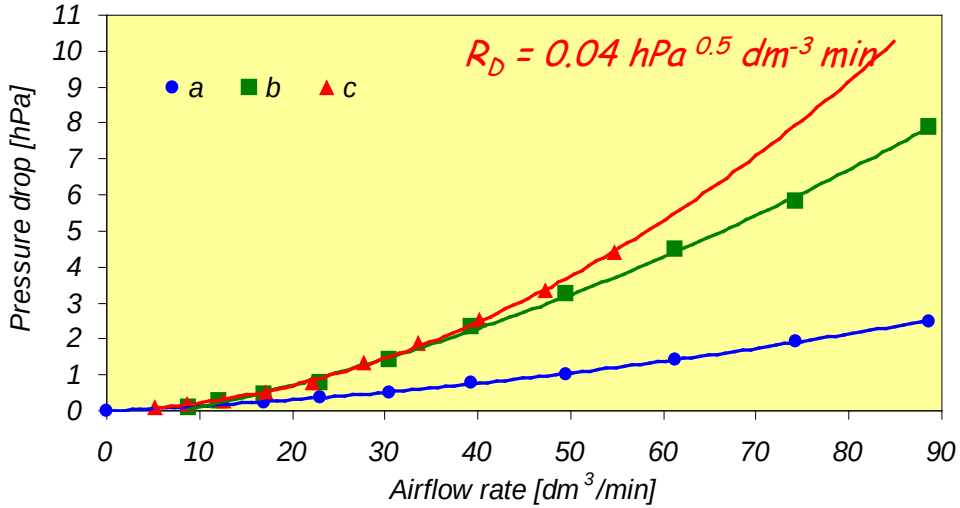


Experiments









Low-resistant DPI: 0.05 hPa $^{0.5}$ dm^{-3} min

Modeling and experiments on particle resuspension from a powder layer

CONCLUSIONS:

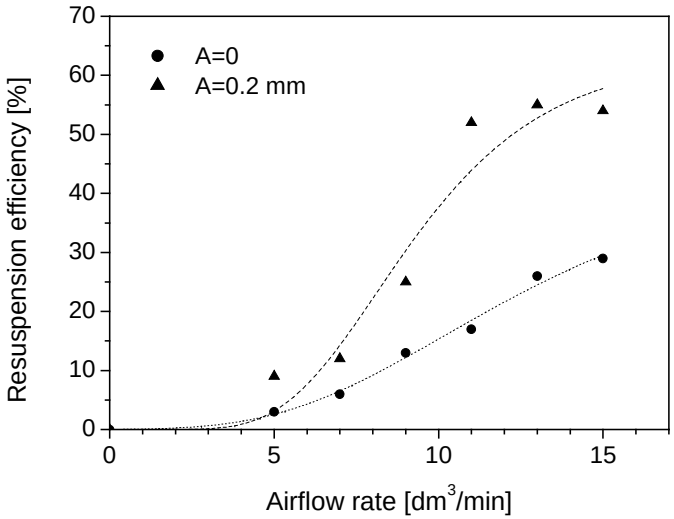
Flow arrangement around the powder layer is important for particles' re-entrainment (lifting-up) and de-aggregation (break-up of clusters), which may occur in two separate steps

Turbulence promoters improve powder resuspension, but simultaneously lead to increased flow resistance

Optimization is required to make the design applicable in real DPIs.

Other concepts to improve powder resuspension and lung deposition:

- vibrations



Grzybowski, K.,Gradoń, L. *Inż. Chem Proc.* (2004)

- multidirectional air streams

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

PCT

(43) International Publication Date
30 March 2006 (30.03.2006)

(10) International Publication Number
WO 2006/033584 A1

(51) International Patent Classification:
A61M 15/00 (2006.01)

(21) International Application Number:
PCT/PL2005/000059

(22) International Filing Date:
8 September 2005 (08.09.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
P.370285 23 September 2004 (23.09.2004) PL

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(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **GRADON, Leon** [PL/PL]; Bronikowskiego 1/45, PL-02-796 Warszawa (PL). **SOSNOWSKI, Tomasz** [PL/PL]; Petofiego 2a /14, PL-01-917 Warszawa (PL). **MOSKAL, Arkadiusz** [PL/PL]; Opaczewska 32/6, PL-02-372 Warszawa (PL).

(74) Agent: **LISIECKI, Wojciech**; Grunwaldzka 189, PL-60-322 Poznan (PL).

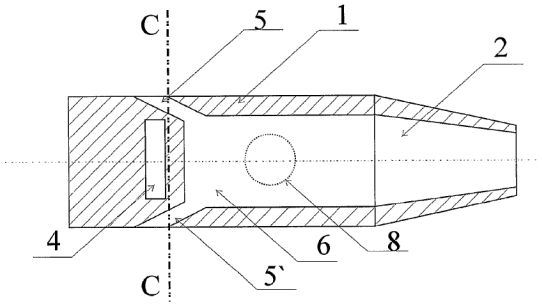
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *with amended claims*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: POWDER INHALER

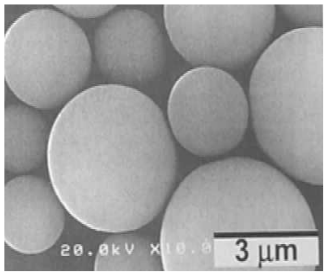


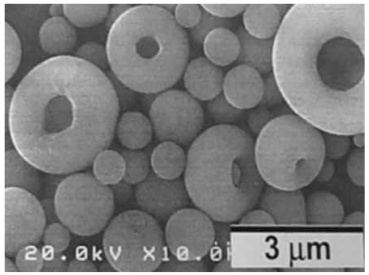
(57) Abstract: The invention consists of a powder inhalator for administrating medications. The inhalator, according to the invention, has a chamber with a mechanism for opening the medication capsule and an aerodynamic chamber in which the medication particles are separated from the carrier capsules. In the aerodynamic chamber, on the opposite side to the mouthpiece opening, there are air inlet ducts which form a multidirectional system of air ducts. The air ducts are shaped in a way which makes the air that flows through them create at least three streams. Due to the intersecting of the air streams the air flow is strongly turbulent even if low speeds are involved. Consequently the separation of the active substance particles form the carrier surface is very effective.

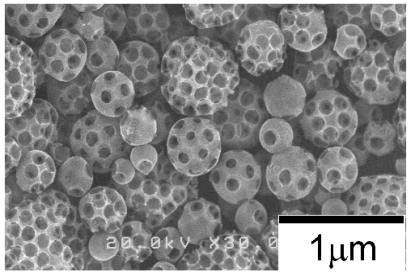
WO 2006/033584 A1

Gradoń, L., Sosnowski, T.R., Moskal, A., Powder inhaler. *European Patent Application PCT/PL2005/000059* (2006)

- change of particle morphology and surface properties (particle engineering)

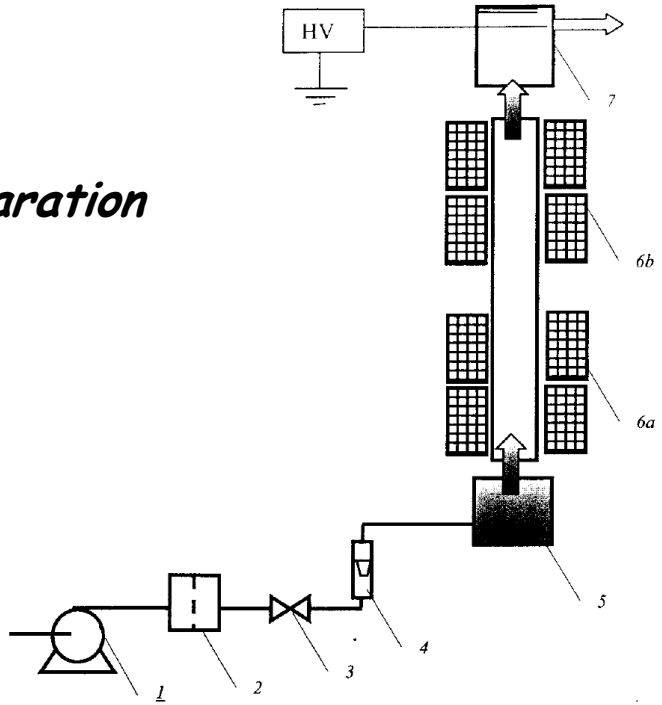




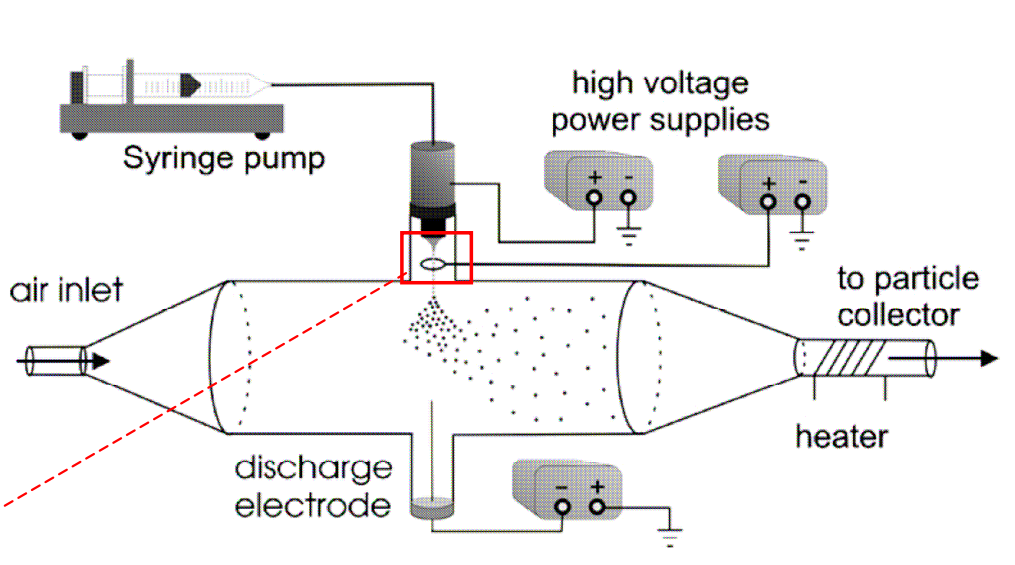


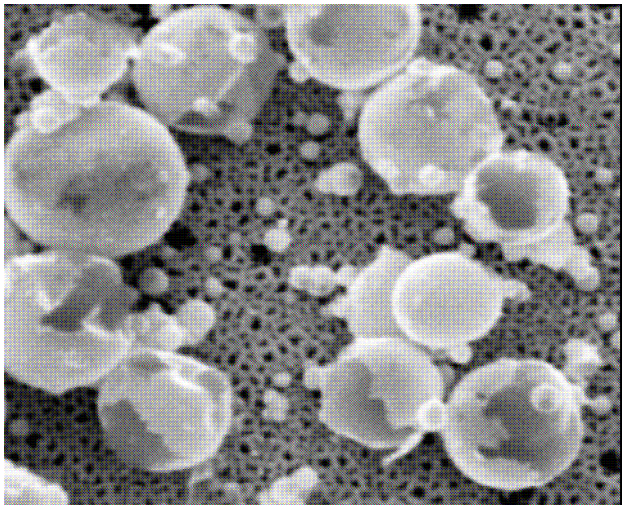
Sosnowski T.R., Gradoń L., Iskandar F., Okuyama K.
In: Optimization of aerosol drug delivery.
Kluwer Academic Publishers, Dordrecht, 2003

Novel techniques of particle preparation are required:



Electro-HydroDynamic Atomization (EHDA)





Hollow particles (~1 µm)

Ciach, T. Microencapsulation of drugs by electro-hydro-dynamic atomization. *Int. J. Pharmaceutics*, 324, 51-55 (2006)

CONCLUSIONS

- *Several technical issues of aerosoltherapy need to be solved to improve the therapeutic effect of inhaled particles by proper adjustment of quality of aerosol emitted from inhalers*
- *A better understanding of particles dynamics is the essential factor in designing and effective application of inhalers in targeted drug delivery with minimized side-effects*

} *ENGINEERING PROBLEMS*

FUTURE STEPS

- *Deposition modeling for different breathing pattern (asthmatic,restrictive diseases, children of different age, ventilation-supported patients, etc.)*
- *Particle-particle interactions during aerosol flow in the inhaler and in the airways (coagulation & break-up)*
- *Novel solutions of inhalers (active devices, adaptive delivery, etc.)*
- *Novel particle types (e.g., structural) and their generation techniques -PARTICLE ENGINEERING*