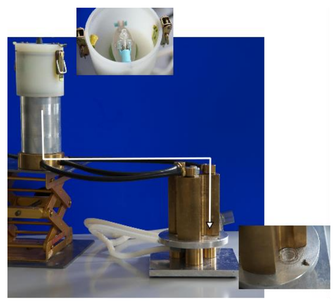
An improved aerosol deposition device to assess safety and efficacy of dry powder formulations at the air/liquid interface

M Hittinger[1], S Barthold[2], A Gress[3], B Wiegand[1], L Siebenbürger[1], C Börger[1], M Berger[4], T Krebs[4], CM Lehr[1, 2, 5], H Groß[1]

Introduction

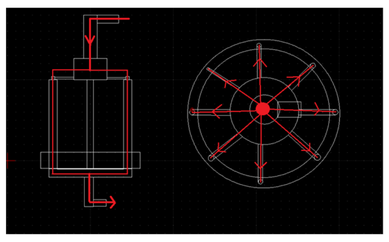
In order to replace animal testing in pulmonary drug delivery, the Pharmaceutical Aerosol Deposition Device on Cell Culture (PADDOCC), was originally designed by Hein *et al.* (Hein *et al.*, 2010, 2011) to enable deposition of dry powder formulations from commercial metered dose in halers (DPI's) on pulmonary cell cultures under physiological conditions. However, this prototype was still limited in several aspects which necessitated a complete redesign of such platform for aerosol testing. The newly developed instrument can be used with commercial dry powder inhaler devices and offers flexible adjustment of the flow rate and other process parameters. We investigated different dry powders and their performance in the system.



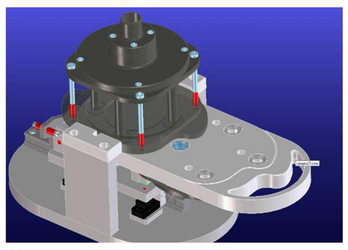
The Pharmaceutical Aerosol Deposition Device On Cell Cultures (PADDOCC)

Design of the device

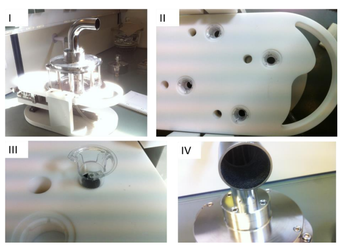
January 2015 — June 2015



Scheme of the basic idea of a flow – induced aerosol deposition device



3D - Sketch of the first prototype, Transwells™ can be shifted in deposition mode by moving the plate



The new device loaded with Transwell™-inserts including black SEM carbon disks. The movable plate contains 4 wells (II). The L-shaped throat part of the instrument (I, IV) can be connected to any inhaler.

Comparison of Pharmaceutical Aerosol Deposition Device On Cell Cultures (PADDOCC) and the new device

	PADDOCC	New device
Particle size	< 10µm	< 10µm
Inserts	Snapwells™	Transwells™
Time for 1 experiment	~40 minutes	~20 minutes
Number of wells	3	4
Dry powder release	Overpressure (leaks)	Flow
Compatibility	HandiHaler™	Flexible
Flowrate	Fixed	Flexible
Handling	Complex	Easy
Deposition	Sedimentation	Sedimentation

Deposition of dry powder aerosols *(proof of concept study)*

Deposition salbutamol sulfate

- A commercial salbutamol sulfate dry powder formulation was investigated in the device as it consists of large carrier particles (lactose) and small salbutamol crystalls (A)
- The flow duration was estimated by the powder release from the capsule (B)
- The time span after the flow and the change to the deposition mode (defined as waiting time) was estimated by electron microscopy (C)
- Deposition of salbutamol sulfate was quantified by HPLC-MS analysis (D)

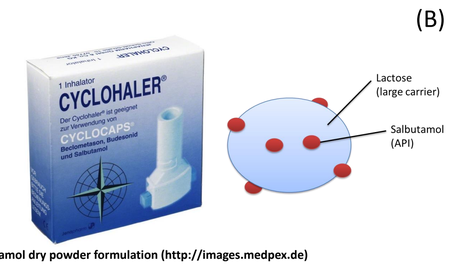
Device modifications

- The Teflon®-plate was replaced by a metallic plate to reduce charging effects and to reduce the standard deviation
- The tube length was modified to increase the amount of deposited particles
- Blendes can be used to modify the air-flow (can be placed as an insert after the L-shaped throat (E)

Deposition of sodium fluorescein

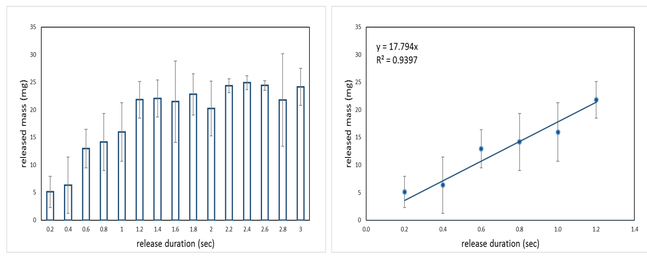
- The deposition of Sodium fluorescein (model for any dry powder chemical) was optimized in the device using different setups
- Best results were obtained for a tube length of 20 cm, Release duration: 0.8 sec, flow rate: 30 L/min, waiting time = 5 sec, settling time: 10 min, 15mm blende & 20 mg powder per capsule (F)

(A)



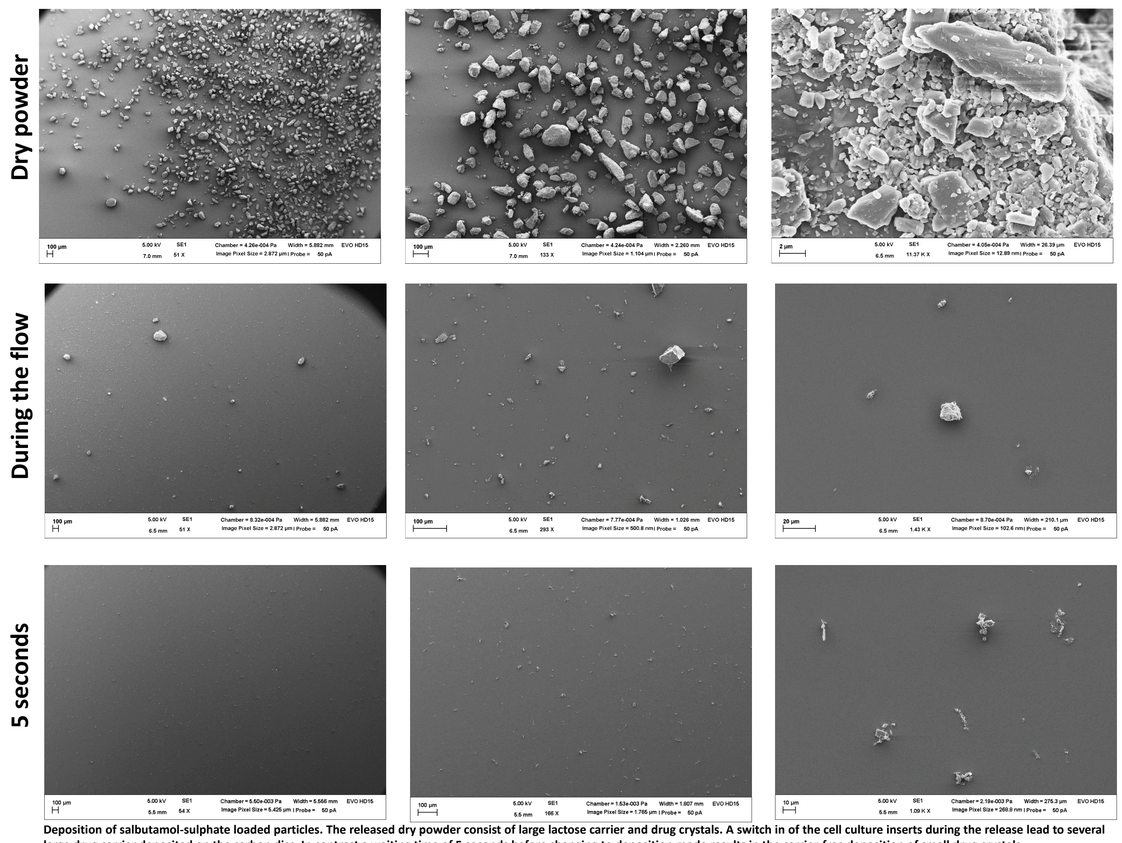
Salutamol dry powder formulation (http://images.medpex.de)

(B)



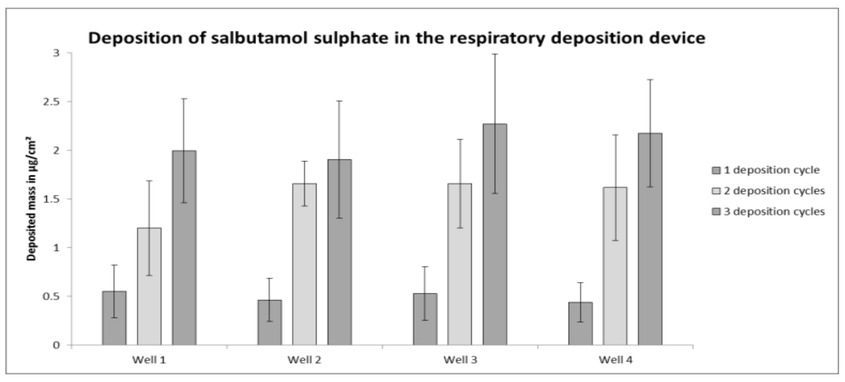
Dry powder release of Cyclocaps™ loaded with salbutamol sulphate. An increase up to 23 mg was observed within the first 1.2 seconds. In this time period, a continuous of 17.79 mg/s was observed (n=8 capsules per time point).

(C)



Deposition of salbutamol-sulphate loaded particles. The released dry powder consist of large lactose carrier and drug crystals. A switch in of the cell culture inserts during the release lead to several large drug carrier deposited on the carbon disc. In contrast a waiting time of 5 seconds before changing to deposition mode results in the carrier-free deposition of small drug crystals.

(D)

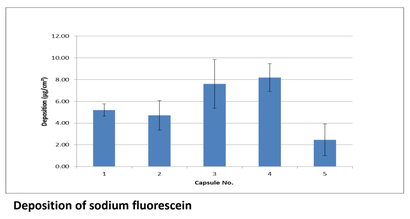


Deposition of salbutamol sulfate applied in 1-3 cycles (n=14 for 1 cycle ; n=3 for 2 & 3 cycles). Release duration: 0.8 sec, flow rate: 30 L/min, waiting time = 5 sec, settling time: 10 min

(E)

Blendes – size: 20-, 15-,10-, 7- & 4 mm

(F)

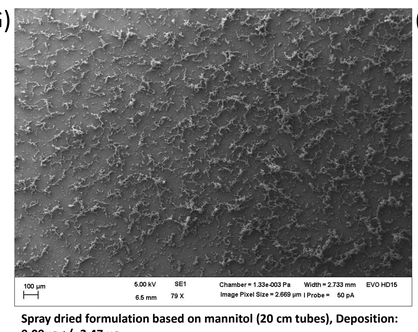


Deposition of sodium fluorescein

Deposition spray dried particles based on mannitol (G) or trehalose (H)

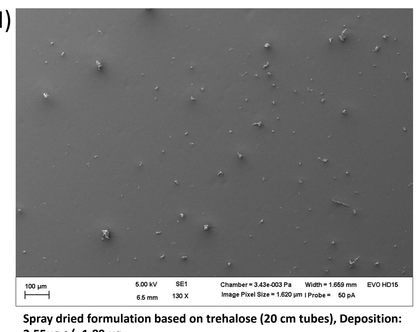
- Deposition depends on aerosol formulation
- Process parameter have to be optimized for each aerosol
- Measurement of deposited mass during the experiment could be helpful

(G)



Spray dried formulation based on mannitol (20 cm tubes), Deposition: 9.09µg +/- 2.47 µg

(H)



Spray dried formulation based on trehalose (20 cm tubes), Deposition: 2.55µg +/- 1.89 µg

Outlook

- Controller for individual settings (I)
- Implementation of micro-balances to measure the mass depositon (J) during the experiment in the deposition system (K)
- Full controlled movement of the plate
- First experiments using Calu-3 with focus on transport and cytoxicity

(I)

Individual flow controller

(J)

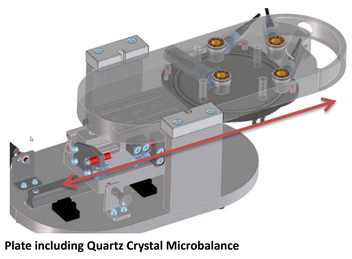
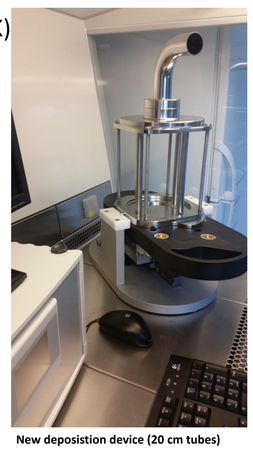


Plate including Quartz Crystal Microbalance

(K)



New deposistion device (20 cm tubes)

Affiliation

[1]PharmBioTec GmbH, Saarbrücken, Germany
[2]Saarland University, Department of Pharmacy, Saarbrücken, Germany
[3]Max Planck Institute for Informatics, Saarbrücken, Germany
[4]Vitrocell Systems GmbH, Waldkirch, Germany
[5]Helmholtz Institute for Pharmaceutical Research Saarland (HIPS), HZI, Saarbrücken, Germany

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