

**Advancements in ease of dosing for nebulised drug products:  
Development of a closed, ampoule-based electronic nebulizer system**

**T. Gallem, M. Tservistas, M. Uhlig, A. Seidler, R. Waldner, S. Seemann, M. Keller, M. Knoch**

**PARI Pharma GmbH, Steinerstr. 15A, Munich, Germany**

**Summary**

An innovative medication specific nebuliser system for liquid aerosol therapies has been developed to address the need for easy and safe dosing. The system uses the eFlow® vibrating membrane technology to generate an aerosols with a distinct droplet size characteristic. The liquid medication is reproducibly supplied from an integrated, single dose blow-fill-seal ampoule which is required to operate the device. Therefore, potential misuse, particularly with respect to choosing the wrong medication or administering the wrong dose is minimized. Transferring the opening of the ampoule into the device will announce several advantages, such as simplifying the filling procedure as well as improving the dose uniformity and hygiene attributes. Preliminary performance data generated from an in-vitro characterisation of a real material prototype are presented and discussed.

**Introduction**

The eFlow technology platform provides a range of highly efficient nebuliser systems which have the benefit of short nebulisation times, silent operation and increased mobility for patients relying on frequent treatments with multiple medications. The devices combine the advantages of the eFlow vibrating membrane technology with those of traditional liquid inhalation therapy of jet nebulisers.

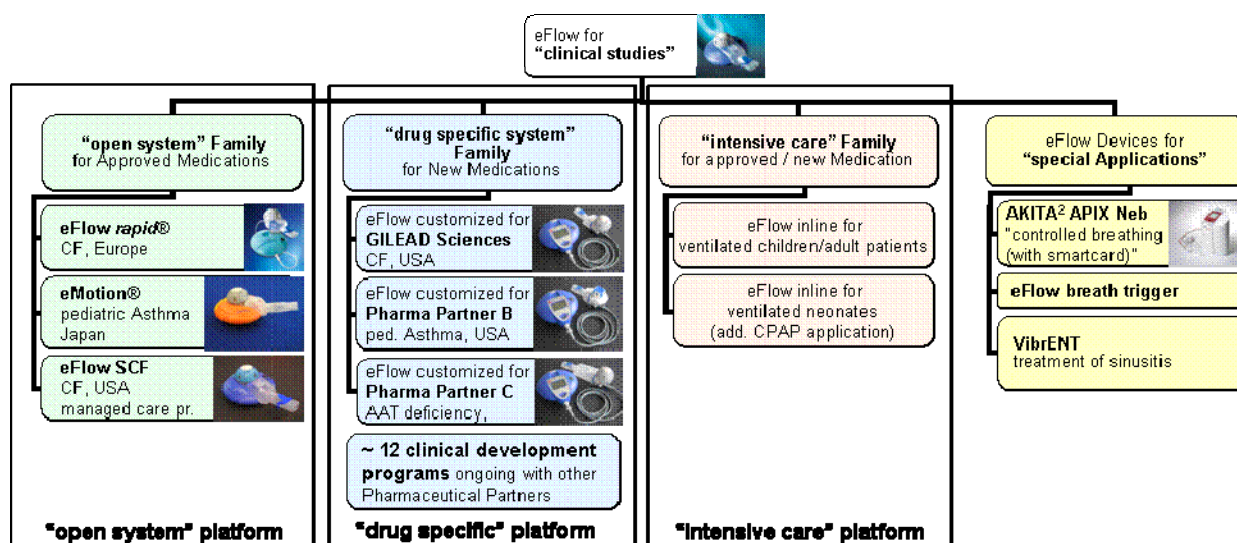


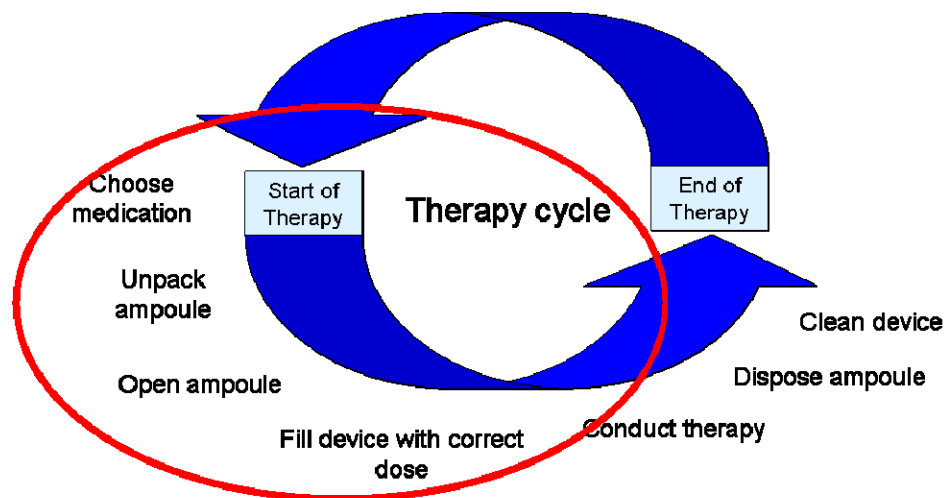
Figure 1: eFlow® Technology Platforms

Emerging from an investigational device configuration specified for use in clinical studies, a product portfolio was developed consisting of three product families / platforms and certain devices for special applications (Fig.1). (1) **Open system platform:** These devices are generally available nebuliser systems adjusted for use with currently approved drug formulations which offer the advantage of short nebulisation times and higher mobility compared to compressor driven jet nebulisers. (2) **Drug specific platform:** Within this platform, device and medication are engaged side by side by adjusting the physical properties of the drug formulation to the device characteristics and vice versa. Minimized fill volumes and dedicated aerosol characteristics allow targeted aerosol delivery within the shortest possible treatment time. (3) **Intensive care platform:** The devices of the intensive care platform will introduce the eFlow vibrating membrane technology in hospital intensive care units for the therapy of ventilated neonates, children and adults.

## Motivation

Nebulisers based on eFlow technology yield an up to three-fold higher delivery efficiency compared to standard jet and ultrasonic nebulisers. This bears the risk that patients, when using their standard medications not being approved with these new systems, would receive a much higher dose than the intended dose, potentially resulting in serious side effects. In order to minimize confusion, an approach may be taken to clearly label new medications for use with only one specific configuration of the higher efficiency nebuliser as customized for and used in the clinical trials.

While nebulisers with open medication reservoirs cannot prevent the patient from filling the wrong medication or dose into the device, the development of a forward looking device concept could address this challenge and in addition assure an accurate and repeatable filling process. Analysing the recurring handling procedures a patient needs to follow when taking an inhalation treatment brought to light that there are many steps that can impact the success of the therapy. Improving on these handling steps as depicted in Figure 2 was the main driver for the development of the eFlow “closed system”.



**Things can go wrong → Potential for optimization !**

Figure 2: Handling procedures of an inhalation treatment cycle

## Development

To assist the patient in filling the device with the adequate medication and the correct dose, a novel device concept for a closed, ampoule based electronic nebulizer system was developed that features three aspects: (1) A single dose ampoule becomes an integral part of the device, (2) the ampoule will be required to operate the device and (3) the opening of the ampoule is only enabled within the device.

The development program started with investigating the applicability of various commercially available primary packages such as blow-fill-seal (bfs) ampoules, blister packs and glass vials. All of the inspected packages meet the main requirement to provide for a robust container for the drug. However, a key function the ampoule has to fulfil in the eFlow “closed system” will be to afford a defined opening procedure. The blow-fill-seal ampoule was found to best fulfil this criteria and was finally chosen. Hence, a specific bfs ampoule (Fig. 3) containing a closure plate with a predetermined breaking line was developed. A protection rim will prevent the ampoule from unintended opening and the outside geometry forms a ring shaped groove to mount the ampoule inside an opening mechanism. When the ampoule is inserted into the nebulizer, a labelling tag remains visible for the patient to identify the medication.

The concept drawing in Figure 3 visualizes the main functional components of the eFlow “closed system” medication feeding, including the aerosol head (1), the ampoule–aerosol head interface (2), the ampoule (3) and the opening mechanism (4) to generate a defined relative movement between the ampoule and the opening collar.

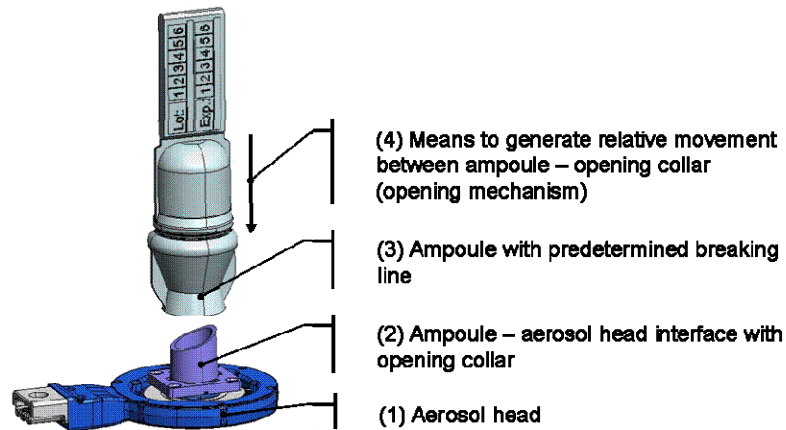


Figure 3: Functional components of the eFlow “closed system” medication feeding

The ampoule–aerosol head interface is containing the opening collar to punch and open the ampoule. The closure plate of the ampoule is designed to break off along the edge of the plate, flap aside and rest in a vertical end position when the opening collar and the ampoule are fully engaged. To ensure good handling and a simple and reproducible dispensing process, an opening mechanism integrates the ampoule into the nebulizer. This assembly comprises the ampoule adapter and the lid and enables drug loading and liquid feeding in two steps. First, the ampoule is inserted into the ampoule adapter and then the lid including the opening mechanism is attached to the nebulizer. While turning and closing the lid onto the nebulizer, a thread transfers the rotational movement into a linear movement of the ampoule relative to the opening collar. This function primes the system for starting nebulisation.



Figure 4: Real material prototype of the eFlow “closed system” nebulizer

To verify the performance of the concept, a real material prototype (Fig. 4) was built and tested in-vitro. To retain flexibility with respect of upcoming customization for clinical programs, a pre-production tool of the ampoule (nominal dose volumes 0.5 ml - 2.5 ml) has been built, allowing for an aseptic filling process for liquid medications. For improved delivery efficiency, the eFlow “closed system” nebulizer handset is additionally equipped with a valve-chamber-system to enhance aerosol delivery to the patient. [1, 2]

### **Representative data**

The results of the design verification test exceeded our expectations, derived from the fact that most conventional nebulisers achieve delivered doses in the range of 15 to 60% [3, 4]. The residual volume remaining in the ampoule at the end of a treatment is about 0.15 ml and virtually independent of the nebulizer orientation and the fill volume which is an important prerequisite for high dosing consistency. Quantitative assessment of the aerosol delivery performance was carried out by breath simulation using salbutamol solution (2.5 ml salbutamol sulphate, 600 µg/ml, GlaxoSmithKline) as test substance. Three different breathing patterns representing a normally breathing adult, an emphysema patient and a six years old child were investigated (Fig. 5). In addition to the delivered dose, the drug deposited on

the exhalation filter and the residue, i.e. the sum of the drug amounts remaining in the ampoule and the nebuliser handset, were measured using a HPLC method with UV detection.

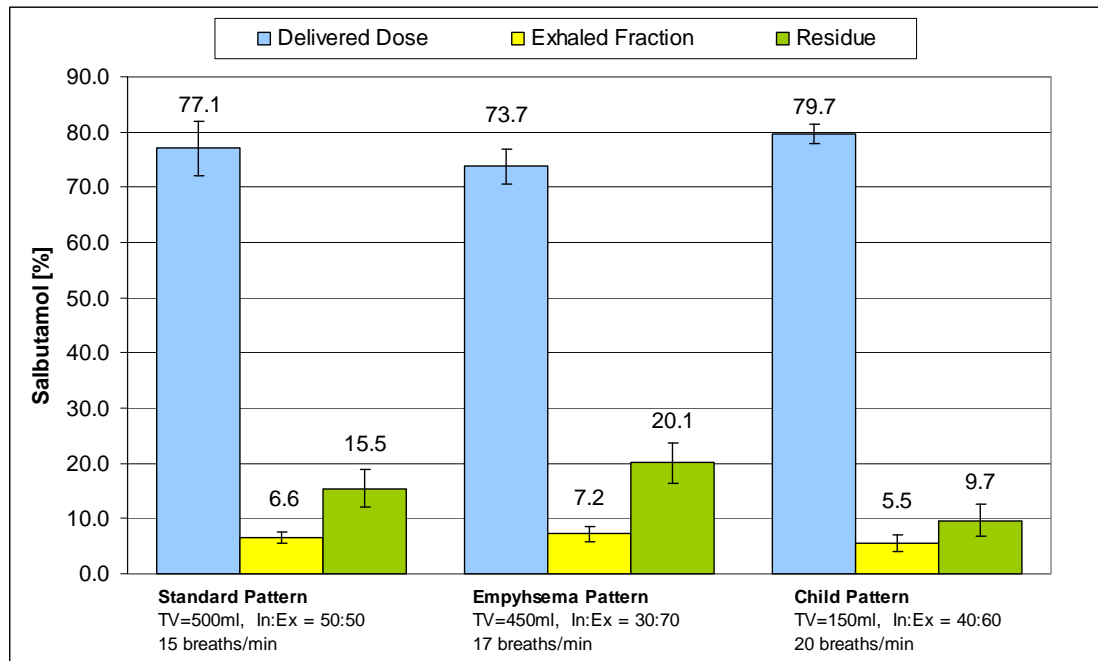


Figure 5: Drug distribution following nebulisation during simulated breathing conditions

Average delivered dose values between 70% and 80% of the dose contained in the ampoule were found for all breathing patterns, showing a high dosing efficiency and hardly any dependence on the applied breathing pattern. Exhalation losses were only about 6%, indicating a favourable aerodynamic design of the nebuliser chamber. Between 10% and 20% of the drug remained in the nebulizer (ampoule and handset) as drug residue.

### Discussion & Conclusions

The eFlow “closed system” may be ideal for expanding the device platforms to specific market segments where ease of handling, safe dosing and avoiding the use of unauthorized medications are key factors to the regulatory pathway and the success of an upcoming drug product. Indications like asthma or COPD are envisioned, but heading for applications which may afford a narrower therapeutic window or higher safety standards (opioids, cytostatics, etc.) is also an option. Irrespective of the exciting perspectives, there will be a number of challenges to be addressed. A large scale ampoule manufacturing process will require complex in-process quality tests to ensure reproducible ampoule geometry and filling. The acceptance of the eFlow “closed system” by patients, pharmaceutical partners and regulatory bodies will be critical to success. A planned usability study involving patients will help to demonstrate viability of the new device concept and show if demands of all stakeholders can be met.

### References

1. M. Borgschulte, M. Germer, M. Hug, M. Keller, M. Knoch, R. Stangl, (2004) “Means to Optimize Drug Delivery from a Novel Electronic Inhaler”, Respiratory Drug Delivery IX, Palm Desert, California.
2. Patent family based on German patent: DE 199 53 317, e.g. US 6,962,151
3. Balcke A. et. al. Effect of different nebulizer / compressor configurations on the nebulization efficiency of a salbutamol solution, Poster P1-22, ISAM Congress 2001, September 17th - 21st, Interlaken
4. Keller M. et. al., Reduced Treatment Time for Colistimethate Sodium Solutions (Colistin CF) Aerosolised by eFlow®rapid, a Novel Electronic Nebuliser, 29th European Cystic Fibrosis Conference, Copenhagen, Denmark, June 15th - 18th, 2006