AERx Essence® Pulmonary Delivery Device: AERx® system 'Unplugged'

Is getting your drug into clinical trials quickly important to you?
If so, a liquid formulation may be your best option.

Is limiting the cost of goods for your API important to you?
If so, a liquid formulation in a very efficient pulmonary delivery system may be your best option.

Is linearly scalable manufacturing important to you?
If so, we'd like to introduce you to the AERx Essence device.

The AERx® pulmonary delivery system combines precise control of aerosol particle size with regulation of the patient's inhalation flow rate to achieve maximal efficiency of drug delivery to the lungs. The AERx system consists of two components: the AERx Strip® dosage packet and one of the AERx system delivery devices. Previous device models emphasized multi-functionality. The AERx Essence pulmonary delivery device, the newest member of the AERx family of devices, maintains the emphasis on efficiency of delivery to the lung, but in a palm-sized, light-weight, inexpensive device. Essence is quick, easy and comfortable to use. For many drugs, an entire dose can be delivered in one breath.

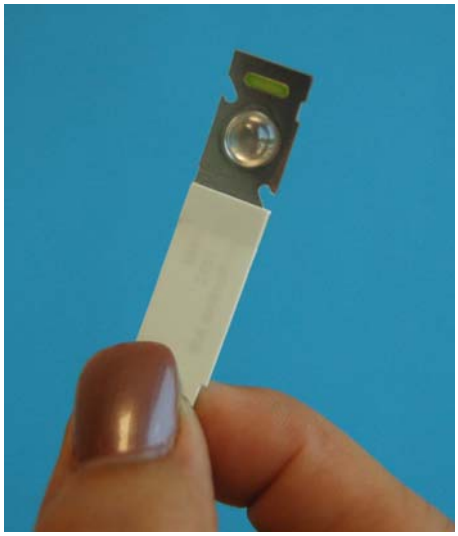
The AERx Strip technology uses the precision and speed of lasers to drill the aerosol nozzle arrays. Both the pattern of holes in the array as well as the size and geometric shape of each hole are tightly controlled. Every nozzle hole meets our quality standard. Such careful control of aerosol nozzle geometry results in the consistent production of aerosol particles in the range of 2 to 5 µm in diameter with low variability. This is the optimal particle size for deposition of drug into the lungs.

If a particular drug needs to reach the peripheral lung, the nozzle hole size can be adjusted to the lower end of the range. If a drug targets the airways, the nozzle hole size can be adjusted toward the larger end of the 2 to 5 µm range. Modifications in hole size are achieved through laser programming, and do not require any changes in the manufacturing process or the dosage form.

The AERx Essence device generates the aerosol and contributes to efficient aerosol delivery by a) initiating release of the aerosol early during the person's breath, and b) regulating his or her inhalation rate to ~ 30 LPM. This combination of precise particle size control and breath control minimizes aerosol deposition in the mouth and throat and maximizes the efficient delivery of drug to the lungs. In addition, the gentle aerosolization process does not degrade sensitive proteins.

Highly efficient delivery means that expensive API is not wasted, which translates into lower cost of goods. Studies have shown the AERx system to be 2 – 5 times more efficient than nebulizers at delivering proteins to the lung.

The patient needs only to load the AERx Strip dosage packet into the Essence device, press the activator button while inhaling through the mouthpiece at a normal rate, and remove the spent dosage packet. The dose is delivered to the lung as the patient finishes his or her
inhalation. It's that quick.



AERx Strip dosage packet

- Single use, disposable aerosol nozzle avoids clogging
- 300 – 450 µm sized nozzle holes per strip drilled with precision by laser
- Blister for 50 µL liquid dose
- Strip dimensions: 1.75" (44.37 mm) x 0.43" (11 mm) x 0.012" (0.3 mm); blister height 0.115" (2.92 mm)
- Efficient, scalable dosage packet manufacture and nozzle drilling processes

AERx Essence pulmonary delivery device

- Synchronizes aerosol delivery with start of inhalation
- Controls inhalation flow rate to less than 40 LPM
- Emitted Dose ≈ 57% of the dose loaded into the Strip
- Fine Particle Fraction (at or below 4.95 µm) ≈ 90%
- Fine Particle Dose (predictor of lung dose) ≥ 50%
- Simple to operate, palm-sized, portable
- Dimensions: 4.63" (11.8 cm) x 2.70" (6.8 cm) x 1.13" (2.9 cm)
- Weight: 6.5 oz (185 gm)
- Aerosol extrusion time: 2.5 seconds
- All-mechanical design means no charging of batteries
- Device life measured in years (proven effective after 12,000 actuations)
- Easy to clean: just hold device under running water
- No maintenance
- Low cost

The ability of the AERx Essence device to reliably deliver more of the drug into the lung with less oral deposition and waste makes it ideal for delivering proteins, peptides and other molecules that are difficult or expensive to produce. Efficient delivery to the lungs minimizes the cost of therapy without compromising the therapeutic benefits of expensive molecules. Figure 1 illustrates the efficiency of delivery by the AERx system with images from a gamma scintigraphy study of pulmonary delivery of interferon (IFN) gamma.

Figure 1. Lung Images: Inhalation of Interferon Gamma
Lung deposition after AERx delivery = 65%; after nebulizer delivery = 5%

The AERx pulmonary delivery system has demonstrated its value in over 50 clinical trials. Our partner, Novo Nordisk, is currently using the AERx system in multiple Phase 3 trials for the pulmonary administration of insulin for systemic delivery. Proteins such as EPO, hGH, IFN alpha, IFN gamma, rhDNase and the IL-4 receptor as well as small molecules, such as morphine, fentanyl, testosterone, and hydroxychloroquine have been successfully delivered to the lung by the AERx system. Figure 2 shows that fentanyl delivery to the lung via the AERx system has a plasma pharmacokinetic profile similar to that after intravenous administration. Figure 3 illustrates rapid onset of analgesia, similar to that after intravenous administration, for morphine delivered via the AERx system.

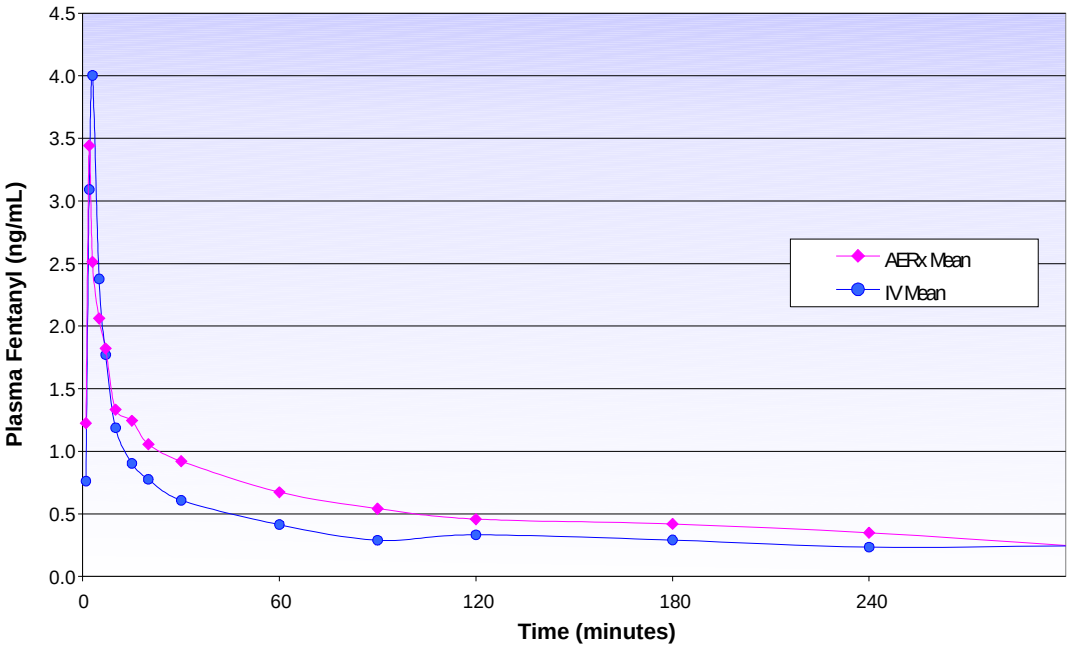


Figure 2. Fentanyl Pharmacokinetics after AERx Delivery and IV Administration. AERx delivery produced 67% Bioavailability relative to IV administration in 10 healthy volunteers

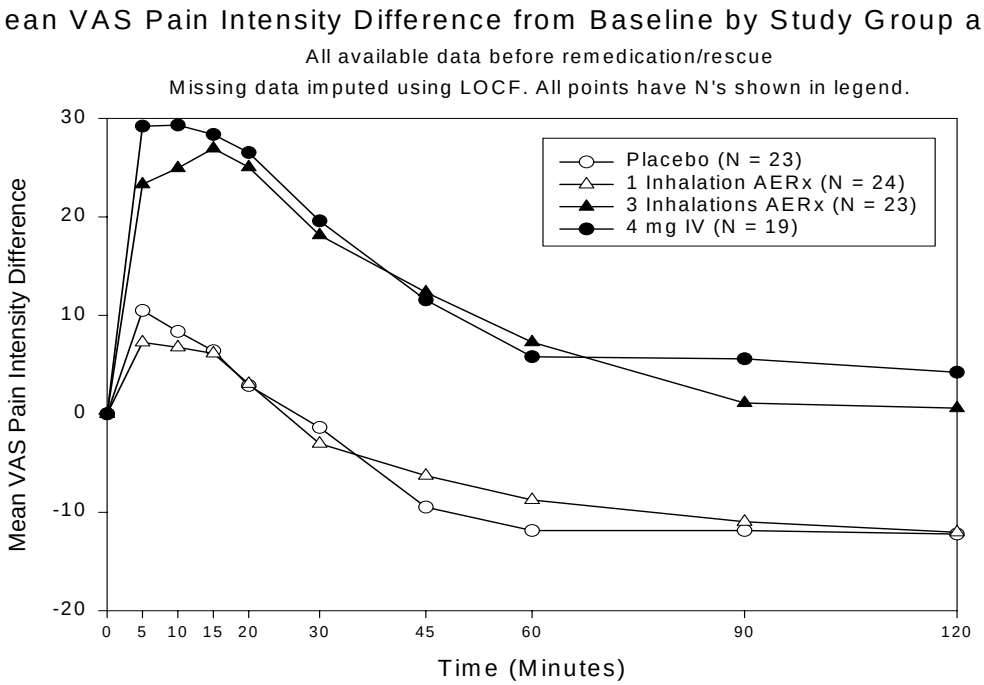


Figure 3. Post-Operative Pain Relief Resulting from Administration of Morphine via the AERx system or IV administration. Dose-response is indicated by number of inhalations.

Millions of AERx Strip dosage forms have been produced to support the many clinical trials concluded and underway. The manufacturing process has proven to be both efficient and scalable. The use of liquid formulations for the AERx system allows for standard formulation scale-up processes to be used as products move from early feasibility through commercialization.

Aradigm is interested in forming partnerships with pharmaceutical companies for the use of the AERx system with the company's proprietary molecules. For further information, contact Aradigm business development at 510 265 8903 or at bd@aradigm.com.