CONTROLLED PARTICLE DISPERSION™:

EFFECTIVE NASAL DELIVERY FROM A VERSATILE, FLEXIBLE TECHNOLOGY PLATFORM

Today's nasal delivery technology – the spray pump – has been the status quo for over 25 years. Despite the fact that up to 90% of the drug ends up in the stomach, somehow spray pumps became accepted as nasal drug delivery devices. Increasing demands for targeted deposition, less peripheral delivery, fewer side effects, compliance monitoring and dose counting, render spray bottle technology ever more inadequate. Clearly, says Marc Giroux, Chief Executive Officer of Kurve Technology, the pharmaceutical industry needs a comprehensive, versatile technology platform that addresses the inevitable paradigm shifts coming in nasal drug delivery.

Figure 1: The ViaNase™ electronic atomizer

INTRODUCING CONTROLLED PARTICLE DISPERSION™

Controlled Particle Dispersion (CPD) is a technology platform that pharmaceutical companies can use to deliver most compounds regardless of characteristics or target conditions. Whether the applications are systemic or topical, solutions or suspensions, CPD meets the demands of today and tomorrow's full nasal delivery product line. CPD offers a vast improvement in efficacy and performance while presenting design flexibility for maximum compliance.

Building a more efficient nasal drug delivery device requires not only better device design but a far more versatile technology platform; one that delivers optimal nasal deposition, with formulation flexibility to work successfully with the many variables of the formulation itself.

Rather than build a single device, Kurve Technology developed CPD – a comprehensive nasal drug delivery technology platform. Using new principles such as vortical flow, CPD effectively disrupts inherent nasal cavity airflows to deliver compounds to the entire nasal cavity, the olfactory region and the paranasal sinuses. CPD optimises droplet size and trajectory to saturate the nasal cavity, lengthens compound residence time, and minimises deposition to the lungs and stomach. This leads to more effective and efficient treatments than delivery via traditional nasal spray bottles that deliver compounds only as far as the anterior portion of the nasal cavity.

CPD's adjustable variables include:

- droplet size variability from 3 to 50 μm
- atomisation rate
- delivery of solutions, suspensions and dry powder
- small and large molecules
- proteins and peptides
- preservative-free, unit-dose ampoules
- targeted deposition including to the paranasal sinuses and the olfactory region
- variable medication volumes in the device and in the nasal cavity
- wide viscosity range
- vortex characteristic variability
- electronics and power (compliance monitoring, dose counters, etc)

CPD powers ViaNase™ – Kurve Technology's electronic atomiser (see figure 1). Understanding the flexibility of these parameters as it pertains to ViaNase is key to appreciating the versatility of CPD.

DROPLET SIZE VARIABILITY

As a nasal drug delivery company, Kurve's goal is to get close to 100% of the drug into the nasal cavity and onto the nasal mucosa. To accom-

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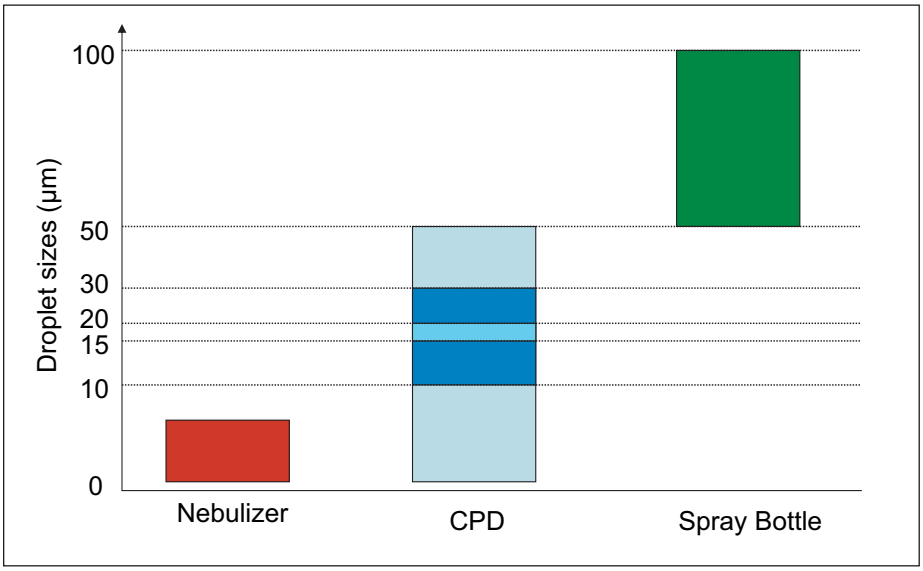


Figure 2: Droplet size comparison (CPD, nebulizers, and spray bottles)

plish this, ViaNase delivers droplets ≥ 8 µm in order to avoid pulmonary deposition. In fact, ViaNase is capable of generating narrow droplet distributions from 3-50 µm. However, for optimal nasal drug delivery device, Kurve uses a size range between 10 and 30 µm.

The upper limit of 30 µm was determined because larger droplets are more difficult to control in vortical flow and deposition is reduced. CPD's ability to generate a range of droplets in tight distribution curves allows for small incremental changes in the mass median aerodynamic diameter (MMAD), so slight adjustments can be made to optimise performance of a particular formulation.

In early tests, droplet sizes of 15-20 µm consistently performed well across many compounds. CPD produces a droplet distribution curve with droplets at a Dv10 of 9 µm, a Dv50 of 19 µm and a Dv90 of 29 µm. This distribution not only leaves all of the droplets within a controllable range, but virtually eliminates peripheral deposition in the stomach and lungs.

Figure 2 compares droplet sizes from CPD, nebulizers, and spray bottles.

ATOMISATION RATE

CPD can control the rate at which the droplets are created and how quickly they will exit the device. Kurve designed its unique droplet generator for short treatment times – a characteristic necessary to improve compliance in patients frequently using the device.

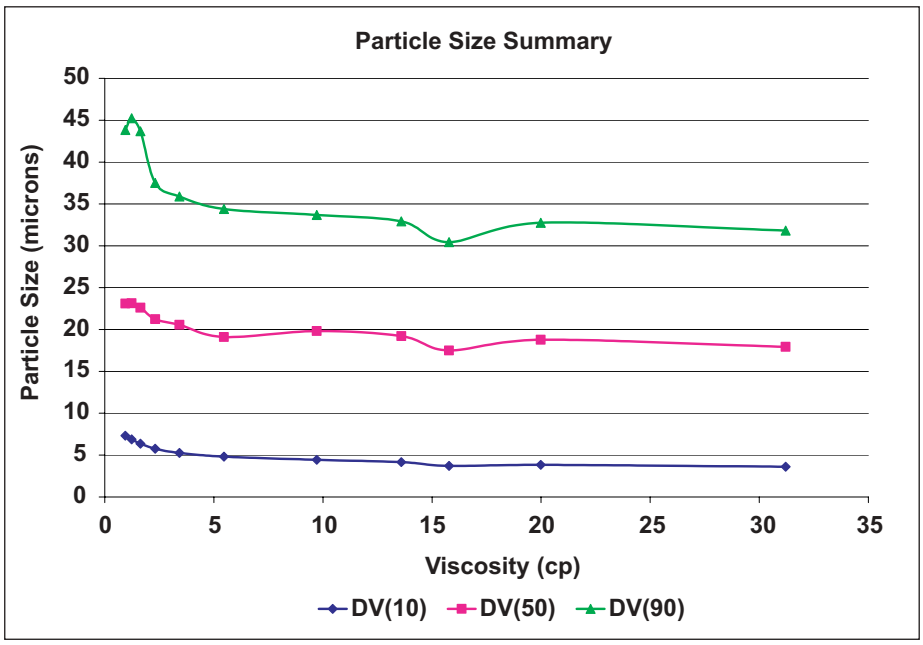


Figure 3. Droplet size versus formulation viscosity at three points along the volume diameter distribution curve

While a typical atomisation rate would be 1 ml/min, the droplet generator can achieve a volume rate of over 4 ml/min. This offers increased output capacity should a formulation warrant a larger volume to be delivered in a short treatment time. The rate at which the device generates droplets does not affect the droplet size to any measurable degree.

SOLUTIONS, SUSPENSIONS AND DRY POWDER

CPD can effectively deliver solutions and suspensions, and conceptual designs and development are already underway for dry-powder delivery. Of the current technologies available, none are capable of delivering all three formulation types. All the principles of CPD will be applied to dry powder delivery.

SMALL AND LARGE MOLECULES, PROTEINS AND PEPTIDES

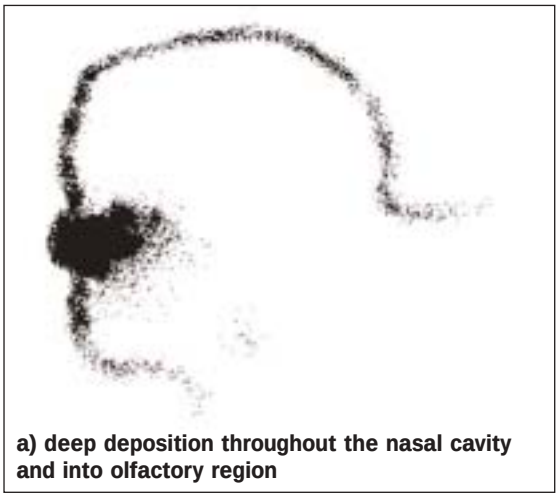
CPD can deliver more than small molecules. A potential pharmaceutical partner independently tested ViaNase with one small molecule and two large peptides (>20 amino acids). In each instance the droplets exiting the machine were 98% pure. In addition, Kurve also tested salmon calcitonin exiting the device and found minimal degradation. It is well known that salmon calcitonin is fairly durable, but one of the peptides tested was more fragile and it faired as well as the others. While ViaNase's droplet generator is fast, it is not overly harsh on compounds.

VISCOSITY

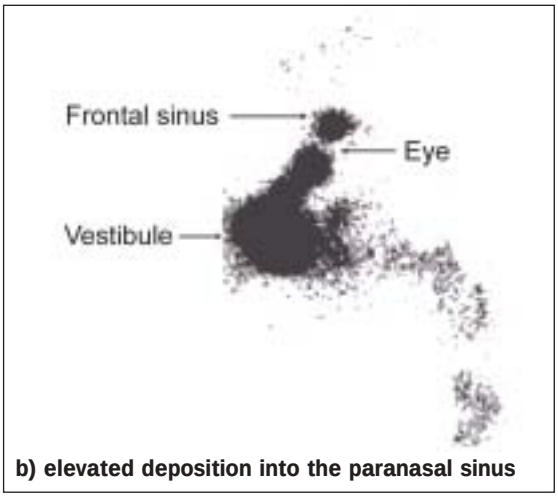
Viscosity of a formulation is not a limiting factor with CPD. Viscosities ranging from 1 to 30 centipoise were tested with no significant change in droplet size (see figure 3). The atomisation rate changed slightly, but droplet sizes remained consistent.

PRESERVATIVE-FREE PACKAGING

The pharmaceutical industry is shifting away from preservatives given the inherent difficulties with side effects and production. Kurve designed ViaNase to use form, fill and seal unit-dose ampoules. Filled sterile and used within minutes of opening, unit-dose ampoules are the least expensive packaging for formulations. Ampoules eliminate the need for costly preservatives and minimise preservative-induced side effects.



a) deep deposition throughout the nasal cavity and into olfactory region



b) elevated deposition into the paranasal sinus

Figure 4: Scintigraphy studies showing CPD's ability to target deposition in different areas of the nasal cavity

TARGETED DEPOSITION

Published scintigraphy studies show CPD's capability to reach the paranasal sinuses[1] and the olfactory region[2]. Kurve found that manipulating CPD's many available parameters resulted in significantly different deposition patterns (see figures 4a & 4b). While testing continues in vivo, a large test result database allows adjustment of parameters to optimise deposition regions for any compound.

VOLUME

Delivering greater medication volumes to the nasal cavity often provides an added therapeutic effect. Unlike current methods, CPD allows the formulator to deliver these larger volumes. This is particularly important for relatively insoluble compounds

ViaNase's droplet generator requires only minimal space in the device housing. This allows a large volume in the chamber itself. As much as 5-6 ml is possible in the existing device while even more volume is possible with a slight retrofit.

VORTEX CHARACTERISTICS

CPD induces a vortical flow on the droplets as they exit the device. The induced vortical flow characteristics can be altered in circular velocity and direction to achieve different droplet trajectories. Variations can be added to the vortical flow characteristics involving rate of spin, series of vortices and combinations of vortices. Deposition differences are noticeable with vortex variation and testing is ongoing.

THE FUTURE – ELECTRONICS AND POWER

With the US FDA advocating dose counting and compliance monitoring, new methods of nasal drug delivery are a must for the device industry. Physician monitoring and web-based downloads also are under discussion. With built-in electronics and power, the ViaNase device offers these functions upon request.

CONCLUSION

From its inception, CPD was designed as a technology platform. With its many controllable parameters, CPD offers pharmaceutical partners a nasal drug delivery device that meets industry needs – today and tomorrow.

Although used for 25 years, the spray pump, was never a viable system. When 90 percent of the drug delivered is swallowed, nasal drug delivery is at best, a misnomer. Spray pumps in fact use the nose as an alternative route to the stomach. Most of the devices available today are simply variations on this single theme – and most of the compound still ends up in a region other than the nasal cavity.

Based on the CPD technology platform, ViaNase is a truly viable nasal drug delivery device, demonstrating that the key to effective nasal drug delivery is a flexible technology platform upon which a product line can be built and expanded. After 25 years of falling far short of the intended target – saturation of the entire nasal cavity – the future of nasal drug delivery brings change. This much needed paradigm shift is Controlled Particle Dispersion.

REFERENCES

1 Giroux M, "Controlled Particle Dispersion: applying vortical flow to optimize nasal drug delivery". Drug Delivery Technology, March 2005, Vol 5, No 3, p 44.

2. Hwang P, Woo R, Fong K, "Intranasal deposition of nebulized saline: a radionuclide distribution study". 50th Annual Meeting of the American Rhinologic Society, New York, NY, US, Sept. 2004.