

# Selecting a nasal spray pump

## Considerations that can reduce time to market in the face of increasingly stringent regulations

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For developers of nasal spray products, the selection of a spray pump to deliver a formulation can have a significant impact on the success of the development project and the time to market. Because the container closure system (CCS) and the drug delivery system form an integral part of the drug product, pharmaceutical companies face design and regulatory challenges that can potentially slow down development. Making sure that the pump is appropriate for the formulation and choosing a high-performing, well-characterized, and reliable device can minimize those challenges and speed up time to market.

Regulatory challenges and the ensuing pressure on pharmaceutical manufacturers to minimize the time to market for new products will likely only increase in the years to come. Fortunately, manufacturers of nasal spray dispensing systems who take a highly proactive approach are continuously developing innovations designed to overcome these challenges. For developers, knowing what factors to consider in selecting a device and keeping up with the innovations in spray pump technology can pay off through an easier path to approval.

### Compatibility between formulation and system

Most nasal spray formulations contain a number of excipients to enhance solubility and stability, to increase viscosity, or to prevent microbial contamination in addition to one or more active ingredients. The first step in selecting a pump should be ensuring that none of these ingredients affect the function and integrity of the CCS and vice versa. EU and FDA

guidelines [1, 2] require special attention to each of the critical components of the CCS, which are defined as:

- Any part that comes into contact with the patient's mouth or nose, or with the formulation
- Components that affect the overall performance of the device
- Any additional protective packaging.

Some ingredients may prove incompatible with certain types of plastic, and many pumps contain parts with metal balls and springs that are prone to cause problems. Even those metal parts made of non-corrosive material can rust or may discolor the formulation due to impurities or contamination with lower grade material during the manufacturing process. Ensuring that all non-metal components of a pump are made solely of medical- or pharmaceutical-grade polyolefins can help to minimize problems with interactions, and a CCS containing no metal parts in the fluid path avoids numerous potential problems [3] (Fig. 1).

### Particle size distribution

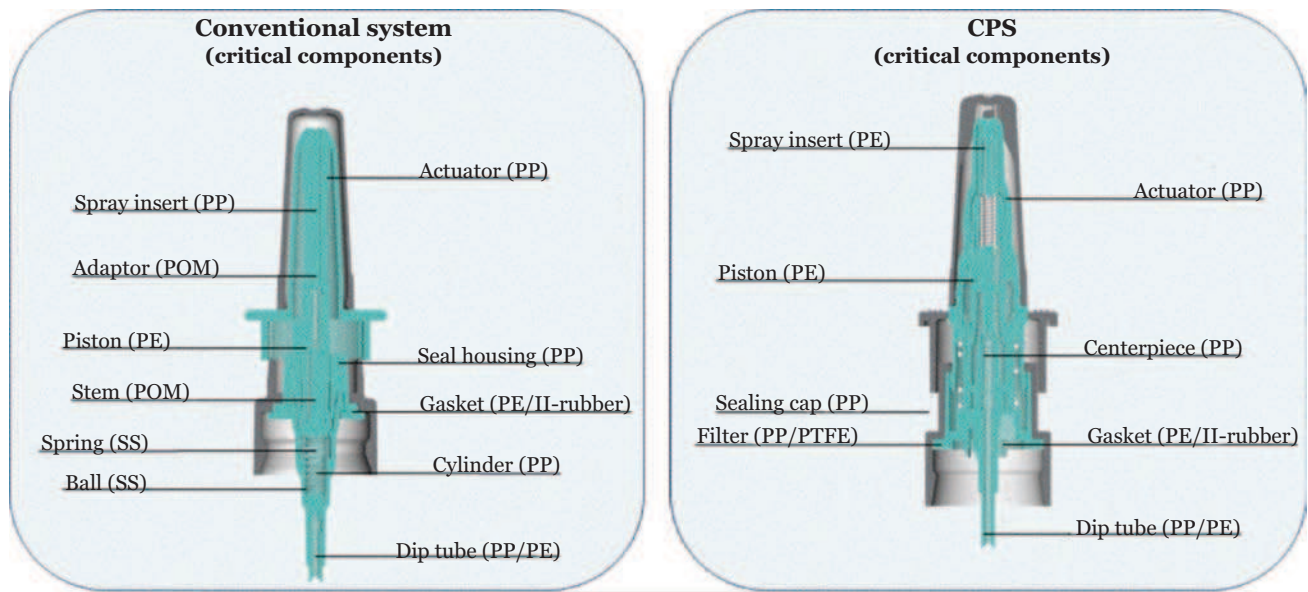
Selecting a pump capable of producing as narrow a particle size distribution as possible can help to increase confidence in the accuracy and uniformity of the delivered dose, resulting in a quicker path to approval for two main reasons. First, during nasal breathing, fine particles less than 10  $\mu\text{m}$  median aerodynamic diameter can reach the lower airways [4]. Depending on the active ingredient, auxiliary compounds, and the total amount delivered, this fine particle fraction may cause side effects. Therefore, authorities require characterization of the fine particle fraction. At the other end of the size range, very large droplets (>300  $\mu\text{m}$ ) can form at the beginning and end of the spray (Fig. 2). Such large particles may irritate the nasal mucosa, causing discomfort in addition to causing uncertainty in the dosing.

### Optimum spray performance

Just because a pump produces droplets in the optimum size range for delivery of the drug to the nasal mucosa during the fully developed phase of the spray does not mean that it aerosolizes the entire dose in the proper size range. Following actuation of the

**Figure 1**

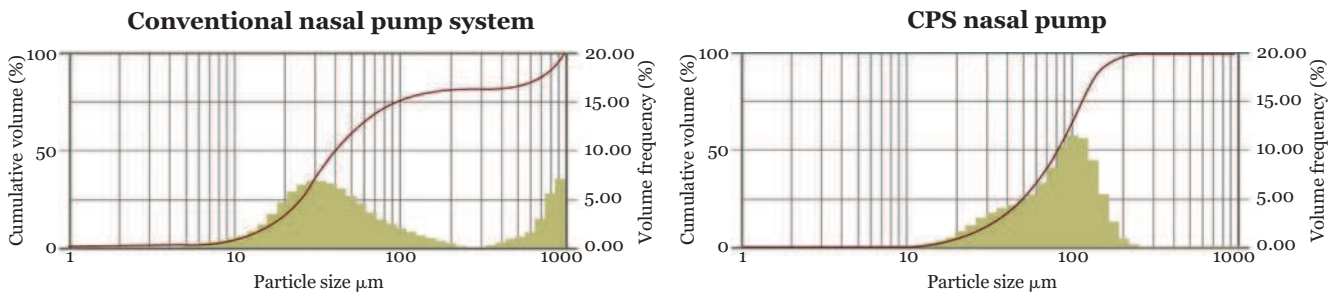
**A conventional nasal pump system compared to an all plastic pump**



PE = polyethylene, PP = polypropylene, POM = polyoxymethylene, SS = stainless steel

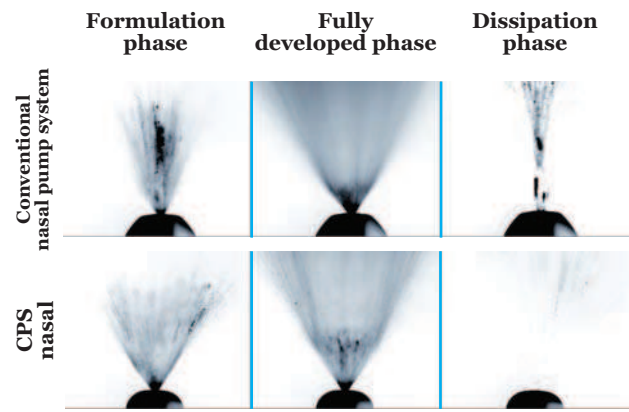
**Figure 2**

**Droplet size distribution of the full spray of a conventional nasal pump compared with a CPS nasal pump, using deionized water as a medium**



**Figure 3**

**High-speed camera pictures of the three phases following the actuation of a conventional nasal pump and a CPS nasal pump, using deionized water as a medium**

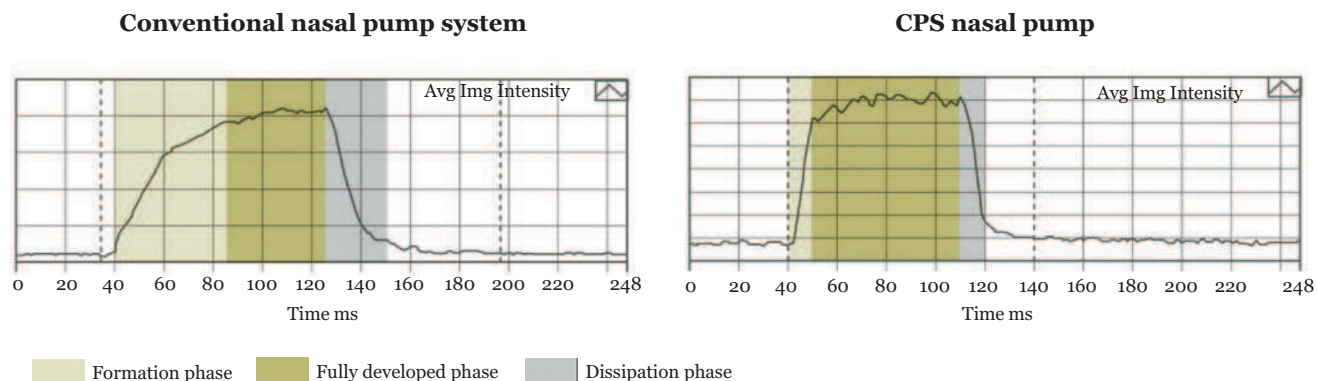


pump, the spray occurs in 3 distinct phases: the formation phase, the fully developed phase, and the dissipation phase. Only in the fully developed phase will the formulation be delivered completely within the optimum droplet size range; the formation and dissipation phases often produce larger droplets (Fig. 3).

Inconsistent production of the fully developed phase could make achieving the dose uniformity necessary for approval of multi-dose systems difficult. In addition, a device that produces relatively long formation and dissipation phases might result in poor results during trials because it may fail to consistently deliver a sufficient dose in the correct particle size range for absorption. In fact, conventional pump systems typically deliver only 30-40% of a dose during the fully developed phase.

Figure 4

Delivered dose following actuation of a conventional nasal pump and a CPS nasal pump, using deionized water as medium



Devices that minimize the formation and dissipation phases produce significantly better results. For example, a pump with an integral mechanism that maintains closure of the orifice until the system reaches the pressure necessary for production of the fully developed spray can deliver 80% of the dose during that phase. Controlling the pressure during that phase produces a consistent dose for each actuation, and a seal that immediately closes the orifice when the pressure drops at the end of the process can minimize the dissipation phase (Fig. 4). These measures also help to produce a more consistent spray pattern than that produced by conventional pumps (Fig. 5).

### Microbial integrity

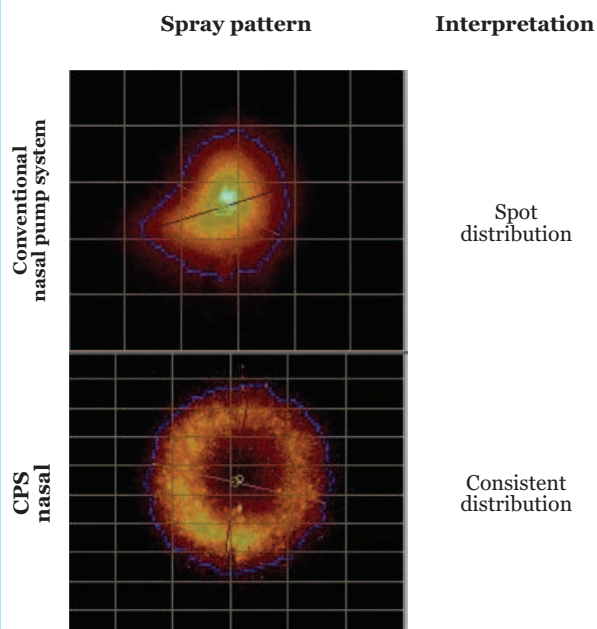
Nasal spray pumps generally use one of 2 basic approaches to the prevention of microbial contamination of the formulation after manufacturing that would affect the product's quality and shelf life. Depending on the drug, manufacturing and filling may take place under sterile conditions, or the manufacturer may treat the finished product using autoclaving or radiation to ensure inactivation of microbial contamination after filling. However, these approaches may not always be viable. As a result, manufacturers must either add preservatives to the formulation or select a pump with the capability to prevent the entrance of microorganisms.

With conventional pump systems, microorganisms can enter the system via the venting air or through the orifice, requiring the addition of preservatives such as benzalkonium chloride to control microbial contamination during the regular use of a multi-dose product. Adding preservatives provides a relatively simple and cost effective method of controlling microorganisms. However, the use of preservatives is controversial, especially in Europe, and where authorities allow its use, they require justification [1, 2, 5], a step that could potentially slow down the development process.

When the formulation cannot include preservatives, the pump must have the ability to keep microorganisms out of the system. Pumps may employ sterile filtration in conjunction with the venting system in order to prevent microorganisms from entering. Another common approach involves a mechanical tip seal that closes off the orifice at all times except during spraying of the formulation. Testing to confirm the integrity of a filtration system and tip seal takes relatively little time compared to sterility analysis during stability testing for preservative-based formulations.

Figure 5

Spray pattern of a conventional nasal pump compared with a CPS nasal pump, using deionized water as medium



As an additional benefit, a tip seal mechanism prevents the evaporation of volatile components from the formulation. Depending on the device and the ambient conditions, 3-5  $\mu\text{L}$  of water per day can evaporate from conventional open actuators. This loss may cause problems with shot weight accuracy and, more importantly, can lead to clogging of the nozzle with suspension formulations. By preventing any evaporation and clogging, a tip seal therefore increases the reliability of the system even in the event of misuse by patients with regard to storage, such as leaving the nasal spray in a hot car.

## References

1. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for industry: Nasal spray and inhalation solution, suspension, and spray drug products – Chemistry, Manufacturing, and Controls documentation. Rockville, MD: 2002.
2. Committee for medicinal products for human use (CHMP). Guideline on the pharmaceutical quality of inhalation and nasal products. London: European Medicines Agency, 2006.

3. For example, the CPS pump system from Ing. Erich Pfeiffer.

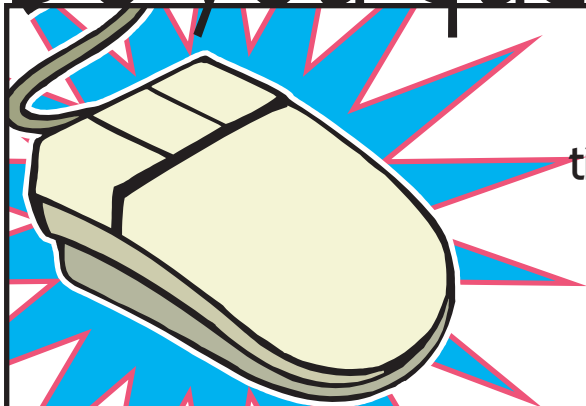
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5. The Japanese Pharmacopoeia, Fourteenth Edition, English version, General Information, Chapter 12, Preservatives—Effectiveness Tests: 1321.

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