ADVANCED DELIVERY DEVICES

A Proactive Approach to Developing the Cartridge Pump System (CPS) in a Pressurized Market Environment

By: Degenhard Marx, PhD

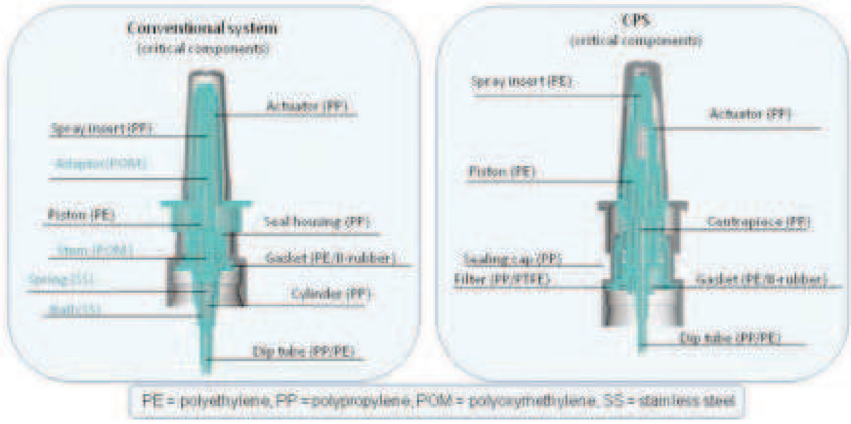
The process of drug development and the subsequent approval procedure has become a tough and time-consuming business in recent years. Worldwide, agencies responsible for new drug approvals have introduced new guidelines to increase safety and efficacy. The pharmaceutical industry now has to spend much more time and money to meet these requirements. Compared with oral formulations, drugs delivered by special devices, such as spray pumps, present additional challenges, as the container closure system (CCS) and the drug delivery system are integral to the drug product. Due to this complexity, anything that can be done to smooth the development process and shorten the time to market is desirable. Manufacturers of CCS and administration devices can contribute by providing high-performing, well-characterized, and reliable devices.

The Cartridge Pump System (CPS) is a newly developed multi-dose pump system, characterized by a metal-free formulation flow path and a consistent spray pattern. The construction of the CCS ensures microbial integrity without the use of oligodynamic compounds and allows its use as a preservative-free system.

COMPATIBILITY BETWEEN THE FORMULATION & THE SYSTEM

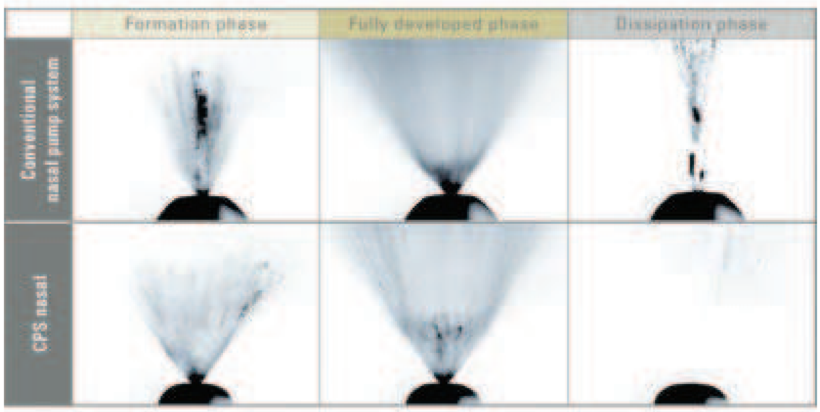
Developing a formulation with one or more active ingredients is a lengthy and challenging process. Rarely is a formulation just a simple water-based solution. Auxiliary compounds often have to be added, for example, to enhance solubility and stability, to increase viscosity, or to prevent microbial contamination. When the final formulation is available, the next step is to ensure the

FIGURE 1



Comparison of materials used in the conventional pump and the CPS.

FIGURE 2



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

ingredients do not affect the function and integrity of the CCS. According to EU and FDA guidelines, relevant information should be provided on the characteristics of each of the critical components of the CCS.[1,2] Critical components are defined as: (1) those that come into contact with the patient's mouth or nose or with the formulation, (2) those that affect the overall performance of the device, and (3) any additional protective packaging.[1] Parts with metal balls and springs are prone to cause problems. Even if they are made of non-corrosive material, the surface can rust or discolor the formulation due to impurities or contamination with lower grade material during the manufacturing process.

A unique property of the CPS is that there are no metal parts in the fluid path. All other components of the pump are made solely of medical- or pharmaceutical-grade polyolefines. The materials used in the conventional pump and the CPS are compared in Figure 1.

OPTIMUM SPRAY PERFORMANCE

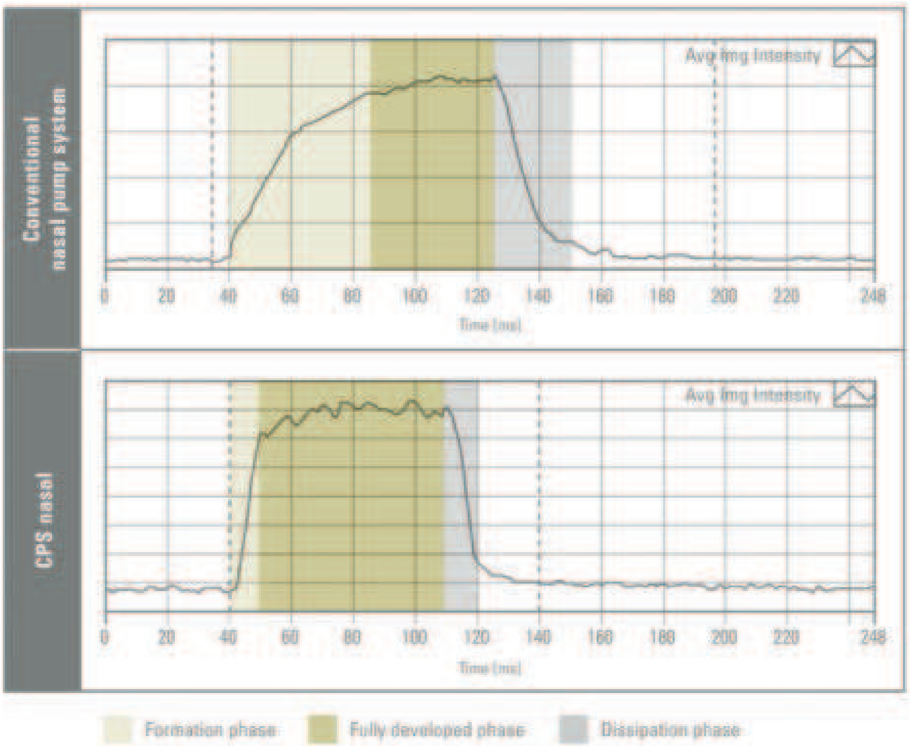
Technical performance of the device is very important for sprays intended to deliver the drug substance into the lungs or to the nasal mucosa. For multi-dose systems, dose uniformity during the lifetime of the device is mandatory. To ensure safety and efficacy, authorities request a detailed description of the spray. The events that follow the pump actuation can be described as the spray formation phase, fully developed phase, and dissipation phase.[1] The fully developed phase is the most important because the formulation will be delivered with the optimum droplet size. During the formation and dissipation phases, larger droplets are formed. Figure 2 compares the three phases in a conventional nasal

TABLE 1

	Test System	n	Short Test Description	Results
Venting System	Artificial dust contaminated with *B. subtilis*	20	Repeated actuations until half the bottle volume was dispensed	No bacterial contamination
Tip Seal	Suspension containing *P. aeruginosa*	20	Repeated actuation of the primed pump with the tip dipped into the contaminated suspension over 5 days	No bacterial contamination

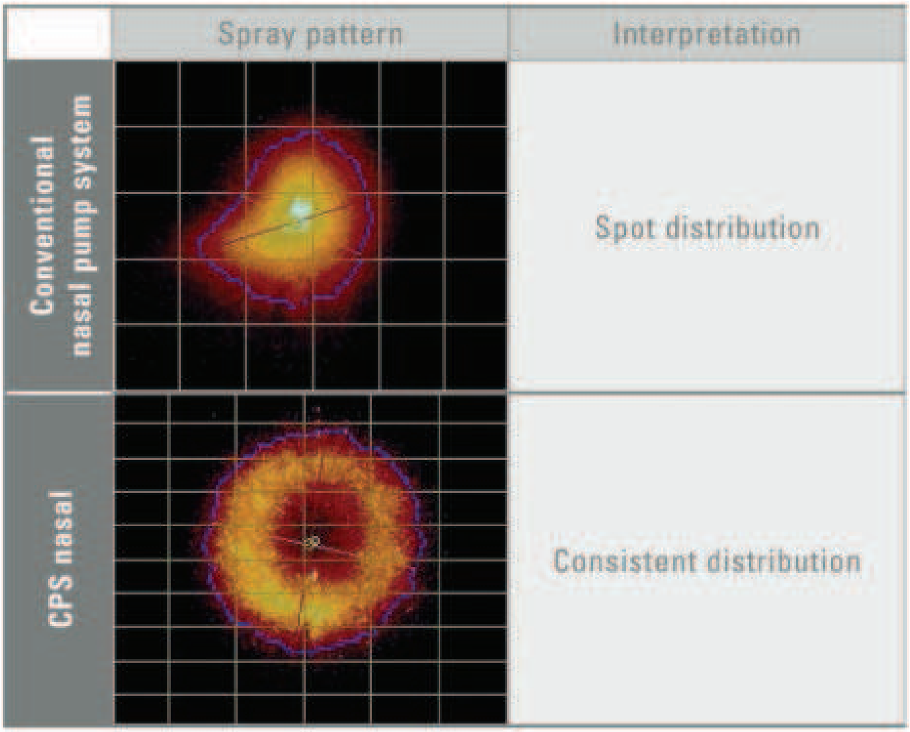
Summarized Results From Microbial-Integrity Testing

FIGURE 3



Delivered dose following actuation of a conventional nasal pump and a CPS nasal, using deionized water as medium. Spray intensity versus time was assessed 30 mm away from the orifice using Proveris' SprayVIEW NSP equipment.

FIGURE 4



Spray pattern of a conventional nasal pump compared with a CPS nasal, using deionized water as medium. Spray geometry was assessed 30 mm away from the orifice using Proveris' SprayVIEW NSP equipment.

pump and a CPS nasal.

To improve the spray performance of a device, technical measures should be taken to keep the formation and dissipation phases as short as possible. The majority of the dose should be delivered during the fully developed phase, which is reached when the pump mechanism secures a certain pressure within the system. In the CPS, a spring-loaded tip seal keeps the system closed until a predefined pressure is reached, at which point the formulation is forced through the orifice with a well-controlled pressure. When the pressure drops at the end of the process, the tip seal immediately closes the orifice. Figure 3 illustrates the amount of delivered dose during the three phases of the actuation of a nasal spray pump. In a conventional system, only 30% to 40% of a dose is delivered during the fully developed phase, compared with 80% in the CPS nasal.

The technical measures already mentioned and the design of the swirling chamber have a positive effect on spray-pattern geometry (Figure 4). As a result, the CPS delivers a very consistent and regular spray pattern.

THE ROLE OF PARTICLE SIZE DISTRIBUTION

Two important features of spray pumps are the size range and distribution of the delivered droplet. The size of the particles or droplets depends on the intended use. If the spray is for oral inhalation of beta-agonists, for example, the majority of droplets should be from 1.5 to 6 microns in order to reach the middle and lower airways. Larger particles will be deposited in the pharynx. For nasal sprays, much larger droplets are required to get a good distribution and deposition in the nasal cavity. During the formation and dissipation phases, very large droplets (> 300 microns) can be formed, which may irritate the nasal mucosa and induce discomfort. At the other end of the size range, particles with less than a 10-micron median aerodynamic diameter can reach the lower airways during nasal breathing.[4] The authorities therefore consider that droplets less than 10 microns in diameter in the spray should be characterized.[1] Depending on the active ingredient, any auxiliary compounds, and the total amount delivered, this fine particle fraction may cause side effects.

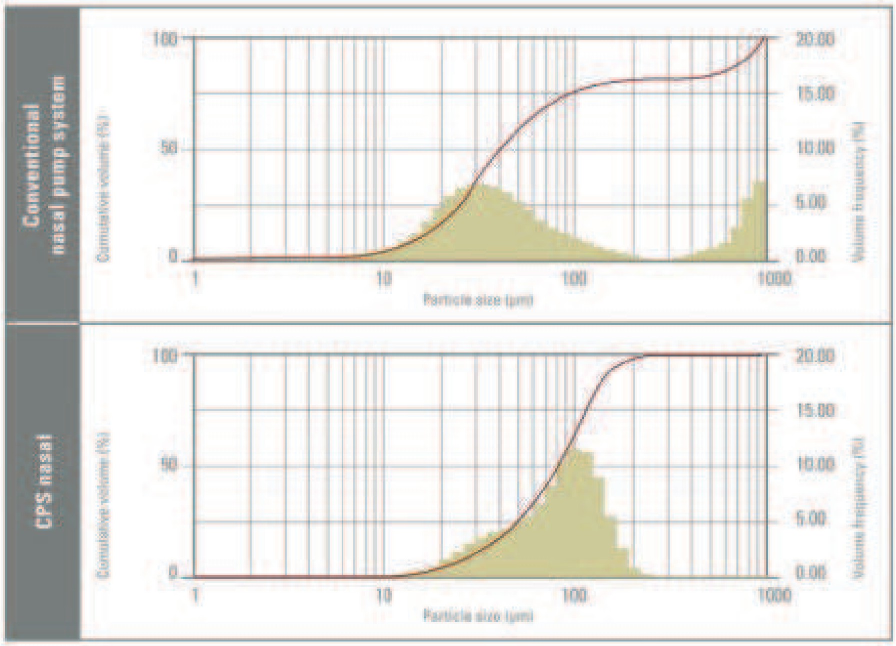
When using deionized water, the number of droplets less than 10 microns in diameter is significantly lower in the CPS nasal, compared with a conventional pump, and no droplets larger than 300 microns are created (Figure 5), so it is less likely to cause problems.

MICROBIAL INTEGRITY

During the manufacturing process, microbial contamination of the formulation will affect the product's quality and shelf-life. Depending on the product's intended use, microorganisms should be absent (products for inhalation) or as low in number as possible. Depending on the drug, the formulation may be manufactured under sterile conditions or treated using autoclaving or radiation to ensure inactivation of microbial contamination. These approaches are not always viable, however, and preservatives such as benzalkonium chloride may need to be added. The use of preservatives is controversial and has to be justified to the authorities.[1,2,5] For multiple-dose systems, preservatives may also be used to control microbial contamination during the regular use of the product. Microorganisms can enter the system via the venting air or through the orifice. In preserved formulations, the added preservative just controls microbial growth, and no measures need to be taken to prevent the microbial occupation in a conventional system. If the formulation cannot contain preservatives, the pump must be able to keep microorganisms out of the system.

The CPS uses a sterile filter in the venting system (0.2 micron nominal pore size) to prevent microorganisms from entering. The principle of sterile filtration is well recognized and widely used. To prevent contamination via the orifice, a pure mechanical approach is applied. The CPS' spring-loaded tip seal keeps the system closed until a defined pressure is reached, then the formulation is forced through the orifice. When the pressure drops at the end of the process, the tip seal immediately closes the orifice and no back-flow of contaminated particles is possible. This mechanism should therefore provide sufficient protection from microbial occupation.

FIGURE 5



Droplet size distribution of the full spray of a conventional nasal pump compared with a CPS nasal, using deionized water as medium. Droplet size distribution was assessed 30 mm away from the orifice using Malvern's Spraytec RTsizer.

To support this claim and to provide data on the microbial integrity of the CPS, challenging test procedures for the venting system and the tip seal were developed and used.[6] The tests were carried out at Qualis Laboratorium in Constance, Germany, using sterilized (gamma-radiated) pumps and glass bottles.

MICROBIAL INTEGRITY TESTS ON THE CPS

For both test series, glass bottles were filled with sterile bacterial culture medium, and the CPS nasal was mounted under sterile conditions.

VENTING SYSTEM: The pumps were wrapped in a rubber sealing, and the space between the pump and the sealing was filled with artificial dust containing spores of Bacillus subtilis (10^8 to 10^9 dry bacillus spores per gram). The primed pumps were then vortexed twice (topside up and upside down) for 3 seconds at 2500 rpm and actuated several times. This procedure was repeated until the bottle was emptied to half its filling volume. Next, the systems were incubated for 7 days at 30°C. At the end of the experiment, the culture medium in the bottle was analyzed for the presence of microbial growth. Even under these harsh test conditions, all spores were kept out of the system, and no bacteria could be detected inside the system.

TIP SEAL: A culture medium containing 10^7 colony-forming units (CFU) per ml Pseudomonas aeruginosa was prepared. The nasal actuator of a primed system was dipped into this suspension, then the pump was actuated and released in an upside-down position. The systems were then challenged twice a day for 5 days, and the tips were not wiped. Between the challenge procedures, the systems were incubated at 35°C. At the end of the experiment, the culture medium in the bottle was analyzed for the presence of microbial growth. The tip seal prevented the entrance of CFU into the system, and no bacteria could be found inside the system after 5 days.

CONCLUSION

It is likely that regulatory challenges and the ensuing pressure on pharmaceutical manufacturers to minimize the time to market for new products will only increase in the years to come. If manufacturers of dispensing systems are highly proactive in their development activity, they can significantly reduce the financial and human resources needed. Based on its experience with the development of the CPS, Pfeiffer is committed to applying this proven approach to future systems, continuing to provide measurable benefits to customers and patients.

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BIOGRAPHY

Following the study of veterinary medicine and the successful completion of his thesis at the University of Leipzig, **Dr. Degenhard Marx** joined the Arzneimittelwerke Dresden/Asta Medica co-operate research in 1992. In 2001, he took over a Senior Research position at Altana Pharma/Nycomed in Constance, Germany. During this time in the pharmaceutical industry, he collected ample experiences in the drug development of anti-inflammatory and cardiovascular drugs. In 2008, he was appointed Business Development Manager at Ing. E. Pfeiffer, Pharma Division.