

Unit-dose aseptic packaging of nasal drugs

Development of new Form Fill Seal technology offers significant economic and functional benefits to aseptic packaging and delivery of intranasal drug products

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Intranasal drug delivery has been undergoing a rapid expansion in the US and global pharmaceutical markets over the past several years. US sales of intranasal drugs totaled approximately \$1.94B for 2007 and are expected to reach \$2.15B in 2008 and \$2.66B by 2010 [1]. With the rapid increase in the development of therapeutic substances delivered systemically through the nose [2-6], the demand for systemic intranasal delivery systems capable of reliable, precise, and cost-effective delivery of sterile therapeutic compounds is growing as well.

The standard intranasal drug delivery system for topically administered over the counter (OTC) intranasal products is a multi-dose spray pump that utilizes a central drug reservoir. This conventional delivery system typically has limited control over the spray plume characteristics, requires priming, and must include a preservative or antibacterial to ensure the continued sterility of the drug compound once the device has been opened. Therefore, in the case of formulations under development for indications such as pain management, migraine, and seizure, and for biologics such as vaccines, which require a delivery system with precision control over spray plume geometry and deposition to the nasal mucosa for systemic uptake, pharmaceutical manufacturers have turned their attention to unit-dose, aseptic intranasal drug products [7].

This type of delivery system for intranasal drugs presents challenges due to the cost and difficulty of aseptic packaging of the drug and device components. However, a new development in unit-dose aseptic packaging based on a novel Form Fill Seal (FFS) technology is showing great promise as a cost-effective alternative [8].

The benefits of unit-dose delivery

Conventional multi-dose pumper/sprayer intranasal drug delivery systems face several major challenges. The drug must retain its stability during prolonged use over its application lifetime, and the system must deliver consistent drug doses over time. Most importantly, the drug formulation must emerge sterile from the manufacturing, filling, and packaging process before it ever gets to the patient, and the formulation must remain free of microbial contamination throughout its use.

One common strategy to prevent the contamination of multi-dose nasal spray products during prolonged use has been the addition of antimicrobial preservatives, one of the most popular having been benzalkonium chloride [9]. This additive, however, has well known side effects and a mutagenic potential and, as a result, has been banned in Germany, leading many European manufacturers to reformulate nasal spray products to remove it. Some manufacturers of multi-dose spray pump devices use mechanical methods such as tip seals and aspirating microfilters to reduce the potential for microorganisms to enter and contaminate the drug product reservoir, but the addition of such components can add complexity and cost to a device. Further, the design of the filtration device can be tricky since any vacuum created when the pump is activated can reduce dose reproducibility. In addition, some spray pumps require priming, resulting in drug waste. For opiates and other controlled substances, the elimination of a priming step and of post delivery residue remaining in the device is of special concern.

Pharmaceutical companies involved in intranasal drug products have, in recent years, begun focusing on unit-dose sterile drug delivery systems [10] that

do not require priming while effectively eliminating the potential for product contamination and the need for drug preservatives. For typical unit-dose intranasal drug delivery systems that utilize single-dose pumps, the aseptic packaging of the sterile individual dose eliminates the need for preservatives because the patient does not reuse the device.

The challenges of unit dose packaging

As a result of their inherent complexity, single dose drug delivery systems pose greater challenges for production and packaging than do multi-dose reservoir systems. Ensuring the correct dose for each of small compartment containing the drug formulation necessitates very accurate liquid filling and weighing, and each reservoir must deliver precisely to ensure consistent dose delivery. Further, due to the sensitivity of the active drug component(s) of a product, the use of heat or irradiation used in terminal sterilization strategies may degrade the drug, rendering the formulation non-feasible. In these cases, manufacturers may want to fill unit-dose compartments under aseptic operating conditions.

Aseptic liquid filling processes generally use closely controlled heat or irradiation to pre-sterilize the delivery system components incorporated in the assembly and packaging of the single-dose devices, and filtration and other methods are used to render the drug formulation sterile. Pre-sterilized components are brought together inside a tightly controlled aseptic environment in a barrier isolator system using automated manipulations that are carefully designed to ensure that the preservative-free drug product is sterile.

Unit-dose intranasal delivery systems can be costly relative to multi-dose systems on a per dose basis. In addition to the cost of processing and assembly for ensuring sterility, the variety of materials utilized in the assembly of the internal components of the delivery system adds cost. In at least one design, the drug comes into primary contact with four different materials before it is dispensed into the nose: a plunging

action causes a needle point to pierce a rubber stopper/plunger, and a second component presses the plunger downward, forcing the drug solution through a stainless steel needle and out through the plastic spray tip of the nasal adapter. Within this system, a sealed, single-use glass vial reservoir assures sterility of the drug; however, the critical piercing needle and the spray nozzle are protected only by the design's secondary outer packaging.

A novel solution

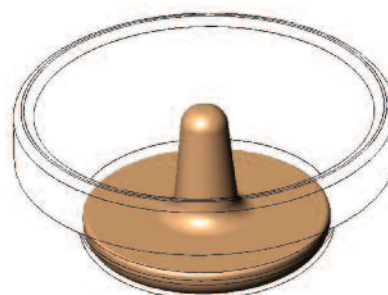
A relatively new and versatile unit-dose drug delivery platform based on a novel aseptic liquid unit-dose packaging technology utilizes a unique FFS-molded multi-laminate blister to contain the drug or vaccine [8]. The production technology incorporates high-precision, low-variability liquid filling processes to ensure accurate dose delivery and utilizes direct micro-filling of an aseptic drug formulation into the blister with a conventional low-volume delivery pump that has been fully evaluated and quantified.

The FFS drug packaging and sealing operation takes place in a barrier isolator system, fulfilling the requirements of Quality by Design (QbD) practices to ensure product aseptic quality and minimization of defect opportunities. A sterile forming process creates blisters in ultra-high-barrier composite films. The blisters are precision filled under aseptic conditions with the preservative-free drug formulation and sealed with an alternatively configured lid stock. Numerous film structures are available to accommodate most manufacturers' requirements for barrier properties, flexibility/rigidity, opacity/clarity, and drug contact materials. The FFS blister can be configured to accommodate a broad range of therapeutic formulations, from simple drugs to biologic agents to lyophilized vaccines, with a delivered dose capability ranging from 15-500 μL .

Each blister produced by this FFS process contains a proprietary micropump that controls dosing and intranasal delivery (Figure 1). Blister forming, filling, and sealing occurs within the aseptic zone on the

Figure 1

FFS blister





VersiDoser delivery device with blister

production line; the sealed blisters containing the drug formulation are then separated and loaded into an injection molded, single-use, disposable delivery device (see photo above). The product remains sterile until dispensed and comes into primary contact with only the laminate and the micropump, both of which are composed of USP class materials.

In addition to sterility, the system offers a versatile and easy-to-use intranasal delivery system. The micro-pump contained within the laminated blister generates and controls the characteristics of the emitted spray plume, optimizing delivery and deposition of a simple or peptide drug or vaccine into the nasal cavity for systemic uptake. The micropump is designed to produce an aerosol particle size range between 15 and 40 μm and can be adjusted to larger particle sizes if required. In addition, the micropump can be tuned to ensure optimum nasal capture for drug formulations with different additives, composition, viscosity, surface tension, and other compositional and physicochemical properties.

No priming is necessary, and the device locks up internally after use, eliminating reuse for other purposes. To unlock the device from its protect mode, which prevents accidental drug discharge, the user depresses the activation tab at the bottom of the device, causing an actuator platform to rise (photo right). The user positions the device horizontally into the nostril to avoid unintentional drug discharge to the upper sinuses and depresses the actuator button. Depressing the button causes an internal plunger to advance instantaneously to compress the drug-containing blister and aerosolize the drug formulation into the nasal cavity. The plunger advances only

when a fixed pre-engineered threshold force is applied to the actuator button, taking the human force factor out of the delivery efficacy equation and allowing for constant and precise drug delivery for any patient.

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Device with actuator platform raised

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