Preservative-Free Nasal Drug-Delivery Systems

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Unpreserved nasal sprays are the latest trend in nasal drug delivery. Different technologies are discussed here in the context of mechanically protected systems, which may provide additional benefits. New test protocols are suggested to evaluate the improved microbiological protection that can be achieved.

Improving on current designs

A look at the driving forces behind the recent development of preservative-free nasal formulations unveils a few interesting aspects. Nasal formulations intended for use over a long period of time are generally preserved. However, it has now been recognised that preservatives have a negative effect on the ciliated tissue in the nasal cavity.[1,2,3] The ciliary epithelium plays a decisive role in the function of the nose. The movement of the cilia is responsible for transporting inhaled particles that are trapped on the nasal mucosa; the debris is guided towards the throat and subsequently removed by swallowing. This clearing function prevents foreign particles from reaching the lungs. The effect of preservatives on the ciliary beat frequency can be described as cilio inhibiting. In the case of a nasal infection such as perennial rhinitis the mucus in the nasal cavity is highly contaminated and it is important to remove the infected mucus as quickly as possible. To treat the infection, the patient applies a preserved nasal spray up to three times a day over a period of up to three months in cases of a severe allergy. However, the preservatives do exactly the opposite and slow down the clearing of the mucus.

The German health authority (BfArM) recently published a risk statement concerning the widely used preservative Benzalkoniumchloride.[4] The patient information leaflet must mention that frequent administration of Benzalkoniumchloride irritates the nasal mucosa and therefore alternative unpreserved products should be used.

Determining efficiency

Unpreserved nasal products are common in unit- and bi-dose delivery systems, which deliver one or two doses into the nostril(s). These devices are disposable, thus, there is no risk of contamination during the period of use. Multidose systems are different in functional design and are to be used daily by the patient for a period of up to six months. In the case of unpreserved content, the drug-delivery product will certainly become contaminated during the period of use.

A complete nasal drug product consists of a mechanical dispensing system and a container, which are both stationary and mounted together (Figure 1). This primary packaging exposes two flaws that could allow a contaminant to enter the system. The first is the orifice where the product is expelled; the second is an opening in the pump system that is dedicated to allowing ventilation into the container and maintaining the pressure balance. Both of these features need to be investigated to prevent th possibility of contamination.

Figure 1: Multidose preservative-free nasal spray system.

Orifice design

An essential prerequisite in the development of preservative-free nasal spray systems is that they must be sterilisable. Polymeric materials can be selected that resist gamma irradiation and maintain their properties.

To prevent any ingress of microbial contaminants into the system via the orifice, two basic options can be considered. The first option is to introduce a chemical additive into the nasal actuator that is in contact with the formulation and environment. Whether it makes sense to remove a preservative from the formulation and add a disinfectant into the primary packaging is not within the scope of this discussion. Various bacteriostatic agents have already found their application in medical appliances. Most common is the implementation of materials that release silver ions into the device.

However, the bacteriostatic activity largely depends on a high ratio of surface area to surrounding volume. In addition, efficacy in inhibiting bacterial growth depends on the microbiological burden and the nature of the contamination. Therefore, it is essential that the microbiological efficacy is challenged and validated using a variety of different bacteria in the test procedure. The chemically protected systems (with chemical additive in the actuator) discussed above are basically open systems, which means microorganisms can enter via the orifice and contaminate the formulation inside the nasal actuator.

A different approach is adopted in preservative-free systems, which are based on mechanical principles. The main difference is that a mechanically protected dispensing system seals directly behind the orifice. The mechanical barrier inherently prevents any microorganism from entering the system. Figure 2 shows the different mechanisms of action.

In an open system, two competing reactions take place: one is the growth of permeated microorganisms; the second is the release of the disinfectant to prevent growth. In contrast, in a mechanically protected system, a spring-loaded mechanical barrier is characterised by a Go or No-Go function and the one-way valve is either open during the spray or closed during storage time.

Figure 3 shows a basic mechanical principle of a sealing mechanism. A small spring-loaded pin seals the orifice at the end of the nasal actuator. As soon as the patient actuates the dispensing system, the pressure inside the pump increases. At the moment the pressure in the pump system becomes higher than the spring force (as a result of incompressibility of the liquid formulation), the pin will retract and will release the metered dose. Depending on the volume of the dispensed dose, the velocity of the particles expelled from the orifice is 50–70 km/h. After the dispensing act, the pressure in the volume chamber drops and the pin will reseal the orifice. In contrast to systems protected by a chemical additive where the growth-inhibiting effect depends on the nature of the contamination, a mechanical protection barrier behind the orifice remains independent of the contamination source.

Controlling pressure balance

As described above, the dispensed volume is generated under pressure in the container. In the most common preservative-free delivery systems, an embedded filter will prevent contamination entering the packaging. Two types of filter can be employed, depending on the design of the delivery system:

- A depth filter comprises pore sizes that are large enough for germs to penetrate; however, the travel distance is long enough to allow the microorganisms, which adhere to dust particles, to be retained.
- An absolute microbiological filter consists of a thin membrane with pores small enough to hold back any microorganism. Usually 0.2-µm membranes are used. An absolute filter may have some advantages

Figure 2: Illustrated kinetic profiles of the protection principles.

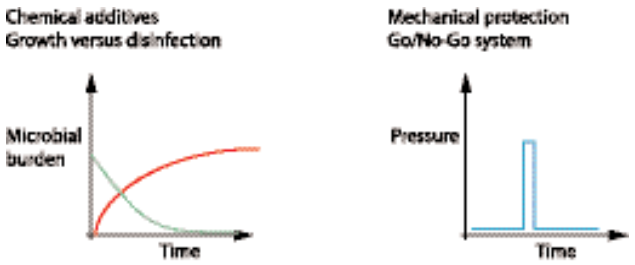


Figure 3: Function of a mechanical preservative-free system.

because nonadhered bacteria and bacteria spores are more efficiently retained.

Microbiological evaluation

The Food and Drug Administration Guidance for Industry, "Nasal Spray and Inhalation Solutions, Suspensions and Spray Drug Products," includes microbial requirements: "For device-metered, aqueous-based inhalation spray drug products, studies should be performed to demonstrate the appropriate microbiological quality through the life of the reservoir and during the period of reservoir use. Such testing could assess the ability of the container system to prevent microbial ingress into the formulation."[5]

A currently recommended test procedure was developed and published in Germany in 1998.[6] The test should follow the daily, real-life use of a nasal spray and detect any deviation in quality. In addition, when employing this test procedure, it must be determined whether the microbiological test is to be regarded as a challenge of the system or as quality control. A challenge procedure uses a nutrient medium, wheras a quality-control test uses the real product.

Test protocols

This proposed test procedure, which is illustrated in Figure 4, has some flaws and needs to undergo modifications to allow a more meaningful interpretation of test results. The areas requiring change are described below.

- The pump is dipped into the bacteria suspension to allow contamination to be sucked into the nasal actuator. However, the pump's valve closes after the spray as a result of a pressure drop in the volume chamber (either the actuator is kept in an actuated position or is released). This means that dipping the actuator into the contaminated medium after the spray has released has no significance because the valve is already closed. Therefore, the procedure must be modified to include "actuation and release" mode for immersion in the bacteria suspension, as illustrated in Figure 5.[7]
- Possible contamination in the nasal actuator must be checked at an earlier time than after three days otherwise it does not represent the real user situation. In an open but chemically protected system, examination after three days of storage time allows the residual volume in the pump system to evaporate. Under these dry conditions it is unlikely that contamination will survive and subsequently be detected. Thus, a kinetic profile of the inhibiting or bactericide action must be generated. After three days, the concentration of the released additive is high enough to inhibit some growth. However, it is important to look at the inhibiting kinetic during the first hours after contamination. In particular, following use by a real patient, the first eight hours of the inhibiting profile should be characterised in detail. A mechanical Go or No-Go system obviously does not need to consider a bactericide profile or sampling time point because there is no critical time for full activity to develop, as is the case with a bactericide. Nevertheless the real user scenario must be applied in the same way.
- The test procedure is missing an investigation of the microbiological filter. The efficacy of the ventilation filter can be evaluated in a simple test method.[7] A sleeve is put over the pump system and appropriately sealed to avoid any exchange with the outside environment (Figure 6). The air space inside the sleeve is highly contaminated. Dispensing is actuated and released several times. The low pressure inside the system will be balanced by the ventilation flow through the filter. After appropriate incubation time a possible microbial growth is checked according to Chapter 71, "Sterility Tests," as described in the United States Pharmacopeia 25.

Figure 4: Illustration of a test protocol.

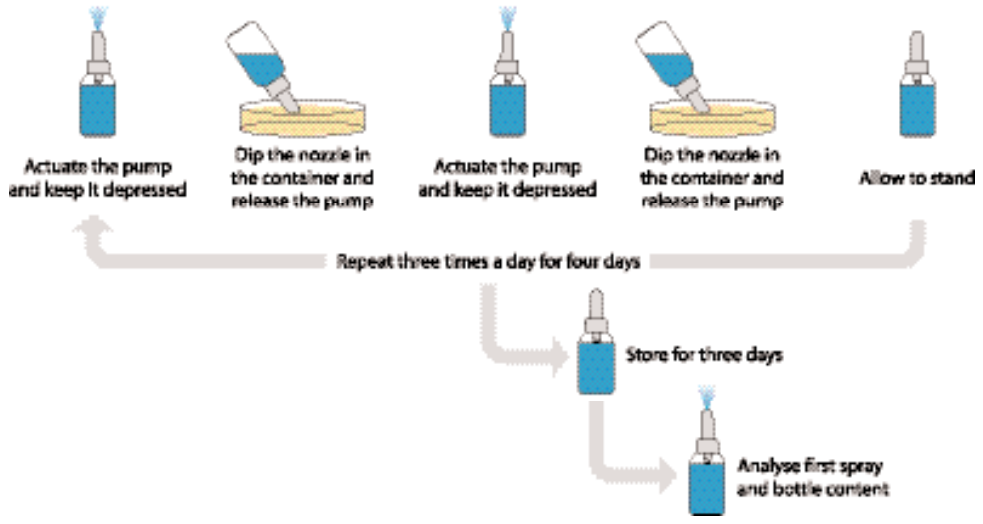
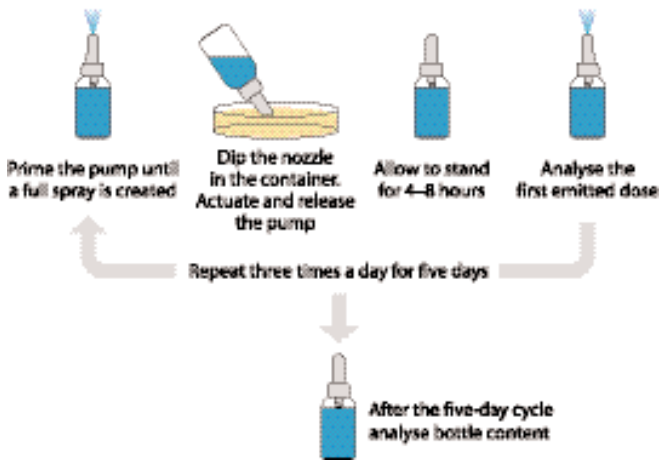


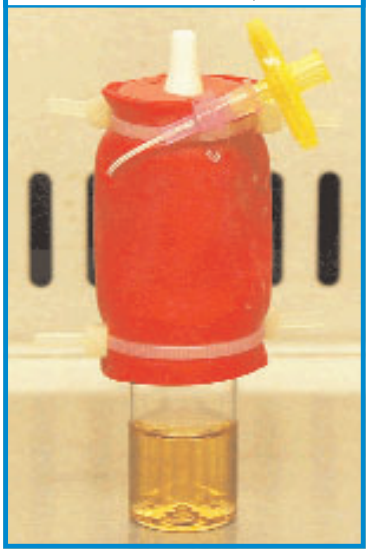
Figure 5: Illustration of an optimised test protocol.



Market outlook

The nasal drug delivery market is valued at US$7billion. It is not as saturated as the oral drug-delivery market and enjoys a two-digit annual growth rate. The development of preservative-free nasal sprays is much more complex than traditional dispensing systems and requires close co-operation of various disciplines in the drug-delivery business. Preservative-free systems were developed in response to changes in the nasal market. In addition to the general lack of new molecules, major nasal products are losing their patent protection. Driven by the increasing generic threat, pharmaceutical companies are advised to reformulate their products to receive further patent protection. From the user's perspective, a less irritating therapy through the application of preservative- and additive-free nasal sprays is appreciated.

Figure 6: Experimental setup for the evaluation of the filter efficacy.



Greater yet economic protection

Unpreserved nasal sprays are the latest major trend in the nasal device business. The two existing principles of the microbiological protection of the content are present in the market, but a mechanically protected system may reveal additional benefits. Direct sealing at the orifice also protects the system from evaporation and subsequently from crystallisation of the ingredients. In particular, with steroidal nasal formulations, which mostly exist as suspensions, the potential for clogging is dramatically reduced.

From the medical device supplier's viewpoint, a shift in responsibilities can be observed. Microbiological protection in a preserved nasal drug product has depended on the effectiveness of the preservative in the formulation. With the removal of preservatives, microbiological integrity depends on the delivery device and therefore becomes the responsibility of the medical device supplier.

In the course of a product life-cycle management and fuelled by regulatory authorities' and patient awareness, preservative-free nasal sprays are gaining market share. This increasing market penetration is an example that economical issues and patient-related factors do not necessarily have to be mutually exclusive, but can be inline with the interests of industry and patients.

Acknowledgement

This article is written in memory of our late colleague Alex Stihl.

References

1. P. Merkus et al., "Classification of Cilio-Inhibiting Effects of Nasal Drugs," *Laryngoscope*, **111,** 4, pp. 595–602 (2001).
2. H.J.M. van de Donk et al., "The Effects of Preservatives on Cilliary Beat Frequency of Chicken Embryo Tracheas" *Rhinology*, **18,** pp. 119–130 (1980).
3. H.J.M. van de Donk et al., "The Effects of Nasal Drops and their Additives on Human Mucociliary Clearance." *Rhinology*, **20,** pp.127–137 (1982).
4. www.bfarm.de/de/Arzneimittel/am_sicher/stufenpl/Benzalkoniumchlorid.pdf (6 January 2004).
5. FDA Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension and Spray Drug Products — Chemistry, Manufacturing and Controls Documentation.
6. B. Wiedemann and B. Kratz, "Konservierungsmittelfreie Nasalia," *Deutsche Apotheker Zeitung*, **138**, 7, pp. 529–533 (1998).
7. K. Hennes and W. Zwisler, Qualis Laboratorium (2003), integrity-1.pdf, www.qualis-laboratorium.com

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