There is an increasing number of drugs being administered to humans by the nasal route. The efficacy of such drugs is directly dependent on the particle size in the administered aerosol. In recognition of the importance of this aspect, the FDA has issued a draft guidance document on nasal particle characterisation. Semi-automated laboratory systems have been developed for testing of nasal sprays in accordance with these guidelines.

Nasal sprays and aerosols are becoming increasingly popular methods for drug delivery. The nasal route is a non-invasive way of administering drugs with rapid uptake into the bloodstream and is considered to be important for the systematic delivery of proteins and other macromolecules.

A key parameter in defining the efficiency of nasal aerosol delivery systems is the particle size distribution of the aerosol cloud, as this is a predictor of the deposition site for the drug within the nasal passages.

To increase nasal deposition and minimise deposition in the lungs and gastro-intestinal tract, aerosol droplets should generally have a mass median aerodynamic diameter greater than 10 to 20 microns. Below this range reduced naso-pharyngeal deposition and increased pulmonary deposition occurs. Droplet size distribution measurements are thus critical during the development of nasal drug delivery systems.

The characterisation of nasal sprays and aerosols is now covered by a draft guidance from the US Food and Drug Administration (FDA). This details a series of tests which must be carried out to assess the bioavailability of nasally-delivered drug formulations. These tests include: dose content uniformity; delivery dynamics with respect to particle size; and spray pattern and plume geometry measurements.

The FDA has recommended laser diffraction as an accurate and reproducible method for determining droplet size distribution in nasal sprays and aerosols for local action. It has also recommended that automated actuation stations are used for all comparative in vitro bioequivalence tests on nasal sprays in order to decrease result variability associated with manual actuation. This in turn increases the sensitivity for detecting differences between different devices and formulations.

Automating nasal spray analysis

Recently a transatlantic collaboration has been set-up between Malvern Instruments (Malvern, UK) and InnovaSystems (Moorestown, New Jersey, US) to launch a new actuation station for the semi-automated testing of nasal spray systems. Called the NSP3000, it is scheduled to be introduced at Pittcon 2003 and is the latest addition to the range of pharmaceutical accessories for the Spraytec laser diffraction particle size analyser. When interfaced with the Spraytec, this station enables the complete testing of nasal spray systems following the FDA guidance.

Traditionally, actuation of nasal spray devices has been carried out manually during product development and testing. However, the force and velocity profiles used during manual testing are operator dependent, leading to poor result reproducibility. This can cause problems during drug applications to the FDA due to the broad product specifications that must be adopted to allow for operator bias. Controlled actuation reduces operator-related uncertainty, allowing for a more complete understanding of the performance of a given product and enabling more realistic specifications to be set during both product development and production testing.

Several devices exist for automating the actuation of nasal pump sprays. These either control the velocity of actuation or the force of actuation. Both control methods can yield reproducible results during product testing. The NSP3000 system uses a pneumatic actuation system to provide force control. The advantage of force control is that it more closely mimics human pump actuation, allowing pump use by different patient groups to be modelled. Full control is provided over the way the force is applied, with both the force and distance profiles being logged for further analysis. Important to the process are the ability to store and recall user defined actuation parameters including the number of actuations; the maximum actuation force; the force rise and fall time; the hold time before release of the pump; and the delay between actuations. Feedback is also obtained about the actuation distance and time, to ensure that the pump has been fully actuated during testing. The distance travelled during actuation and the applied force can also be calibrated. Using the NSP3000, accurate testing can be carried out following the FDA guidance. Monitoring the effect of changes to the force profile can also lead to a better understanding of the differences seen during manual actuation, and can therefore aid the development of new nasal pump spray devices and pharmaceutical formulations.

Particle size analysis

CI or MSLI measurements can be time-consuming and therefore
PARTICLE SIZE ANALYSIS

Figure 1. Time history showing the variation in the Dv10, Dv50, Dv90 and Transmission measured during the actuation of a nasal spray. The transmission relates to the concentration of particles in the measurement zone. The formation, stable and dissipation phases are clearly seen.

represent a significant bottleneck in the development of pharmaceutical aerosol devices. They also only provide a time-averaged size distribution. The technique of laser diffraction is therefore rapidly gaining acceptance in the pharmaceutical industry as a non-invasive technique for size analysis. Rapid data acquisition speeds of up to 2500Hz (one measurement every 0.4ms) are possible using laser diffraction. This allows the aerosol dynamics to be assessed for each pump actuation along with the average size distribution delivered by a given device. Results can be obtained within a few minutes, allowing the rapid screening of different formulations.

The capabilities of the laser diffraction technique correspond well with the FDA’s request for information on the dynamics of spray formation from each pump rather than just an average particle size, hence the recommendation to use the technique with the draft guidance document.

The FDA specifies three regions of interest during the actuation of a nasal spray system, these being:

The Formation Phase - This occurs at the beginning of the pump actuation cycle where the pressure and flow rate through the pump are low, yielding a large particle size.

The Stable Phase - This occurs once the correct atomisation pressure has been reached, yielding the "optimum" particle size.

The Dissipation Phase - This occurs towards the end of the actuation cycle where the flow rate through the pump tails off, yielding a large particle size.

Each of these regions can be easily recognised using laser diffraction measurements (Figure 1). The NSP3000’s ability to control the actuation force yields reproducible results, allowing pump and formulation differences to be identified which otherwise would have been hidden by the error associated with manual pump actuation (Figure 2). This allows the pump characteristics to be determined over the entire lifetime of the pump as well as during tail-off studies.

Complete nasal spray characterisation

As well as being used with the Spraytec system, the NSP3000 provides a flexible workstation for the complete characterisation of nasal sprays, applying the benefits of automatic actuation and improved result reproducibility to each of the tests specified in the FDA draft guidance.

Dose uniformity data can be obtained by actuation into an integrated collection device, allowing the spray to be sampled for further analysis. This allows the dose profile to be determined during each stage of the unit’s lifetime and during tail-off studies.

The FDA guidance also suggests the use of a suitable impaction target such as a Thin-layer Chromatography (TLC) plate for spray pattern determination. Pattern analysis is achieved by actuating the spray against the impaction target. Traditionally measurements are then made by developing the TLC plate followed by manual analysis of the impaction images. Modern image analysis systems, such as the EZ Spray™ imaging system (InnovaSystems), can automate TLC plate analysis, yielding the key pattern parameters including the minimum and maximum spray diameters as well as the

Figure 2. Comparison of the results obtained for manual and automatic actuation. The error bars relate to the result variation (standard deviation expressed as a percentage of the mean) error over 3 actuations.

Figure 3. Spray pattern image analysis using the EZ Spray software.

Conclusions

Nasal pump sprays and aerosols are becoming increasingly more popular as drug delivery systems, especially for the treatment of local complaints. This is reflected in the publication of the FDA’s recent guidance document which has set out the controls necessary to ensure reproducible drug delivery. Within this it is clear that the use of automated nasal spray actuation stations provides a robust method for obtaining reproducible, accurate results during product testing. The combination of Malvern Instruments and InnovaSystems’ experience has yielded an integrated system for the characterisation of nasal spray systems. This significantly reduces the effort required in following the FDA recommendations for nasal spray analysis, providing a means for better understanding the performance of nasal delivery systems and how reproducible drug delivery may be achieved.

References


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