Viscosity and pH in One Step - Quality Parameters for Nasal Sprays

Nasal drug delivery has become a popular route of drug administration also as an alternative to oral or injectable dosage forms. To fulfill the expected performance critical parameters such as viscosity and pH value have to be controlled.

Relevant for: pharmaceutical industry

Sample type: nasal sprays, eye drops

1 Introduction

Administration of drugs via spray dosage form through the nose is a non-invasive and rapid drug delivery method. As the nasal dosage form is cost-effective, easy to use and self-administrable, it has a high patient compliance. Traditionally, nasal drug delivery was limited to treating common cold and nasal allergies. Recently, there has been a growing interest in developing nasal drug delivery systems as an alternative to oral or injectable dosage forms, including small molecular weight drugs, peptides, proteins and vaccines. This enables the delivery of the drug directly to the central nervous system, bypassing the blood brain barrier.

2 Critical Parameters

Nasal spray formulations are broadly categorized into two types: solutions and suspensions, whereas each can be either aqueous or non-aqueous.

When formulating aqueous nasal spray products, it is critical to control properties such as viscosity, pH value, buffer capacity and osmolality.

2.1 pH

The local pH value inside the nasal cavity will have a direct effect on the rate and extent of absorption of drugs; the optimal range for pH value of the nasal spray formulation is suggested to be between 4.5 and 6.5.

2.2 Viscosity

By increasing the residence time of the medication on the nasal mucosane membrane, the efficiency of drug absorption through the nasal mucosa is improved. A common approach is increasing the viscosity of the formulation by incorporating viscosity-enhancing agents. On the other hand, increasing the viscosity impacts the droplet size distribution, resulting in altered deposition in the nasal cavity. Therefore, it is crucial to find and set the correct viscosity for the special application.

The US FDA Chemistry, Manufacturing and Controls (CMC) guidance on nasal sprays recommends measurement of pH value, osmolality and viscosity as part of the drug product specification.

3 Instrumentation

3.1 Lovis 2000 M Microviscometer with pH ME Measuring Module

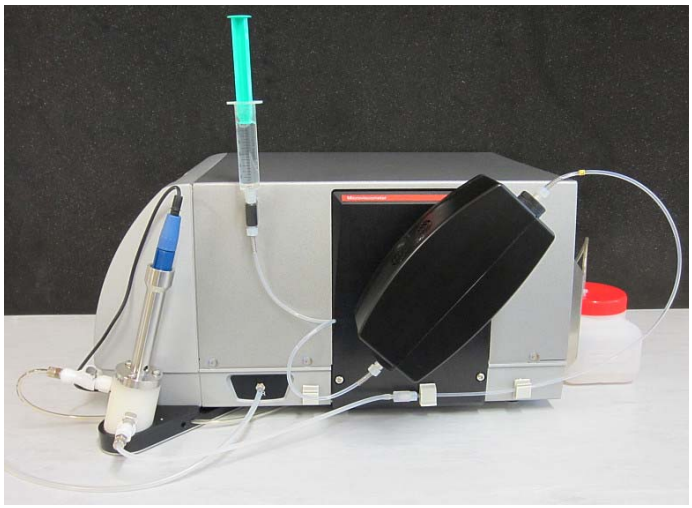

Fig. 1 Lovis 2000 M Microviscometer with pH ME Measuring Module

Lovis 2000 M Microviscometer measures the rolling time of a ball in an inclined capillary through transparent and opaque liquids.

The measured samples are brought to the desired measuring temperature via Peltier elements extremely fast and with utmost accuracy. Three inductive sensors measure the rolling time of a metal ball inside an inclined capillary. The measurements can be performed at variable angles, analogue to measuring at different shear rates.

Combining Lovis 2000 M Microviscometer with the pH ME Measuring Module enables the simultaneous measurement of both viscosity and pH value. All of the measurements and adjustments are performed via the Lovis 2000 M Microviscometer and the results are directly shown on the Lovis instrument.

4 Measurement

- All determinations included in this report were performed by flow-through filling with a syringe (without autosampler).
- The measurements were performed at two different temperatures (room temperature 25°C and body temperature 37°C).
- The measurements were also performed at different shear rates (690 to 250 1/s).
- As the measured nasal spray was a water based solution it was not necessary to measure the density for the subsequent calculation of the viscosity. For the calculation of the dynamic viscosity the density of water was taken according to IAPWS 2008 and entered as follows:
  Density of water at 25°C: 0.9970 g/cm^3
  Density of water at 37°C: 0.9933 g/cm^3

4.1 Sample

Aqueous nasal spray with amidephrin-mesylate as active component

Additional ingredients:
n-cetylpyridiniumchlorid, sodiumdihydrogenphosphate, sodiummonohydrogenphosphate, sorbite and cleaned water

4.2 Instrument settings

Measuring Method: Standard and Fixed Angle Scan

Measuring Settings Lovis:
Measuring Temp.: 25°C and 37°C
Equilibration Time: 20 s
Measurement Cycles: 3

Measuring Angle: Auto Angle for the standard measurements and 20° to 70° for the Fixed Angle Scan (FAS)

Variation Coefficient: 0.5 %
Measuring Distance: Long

Measuring Settings pH ME Module:
Delay Time: 60 s

Used Material Lovis:
Capillary Material: Glass
Capillary Diameter: 1.59 mm
Ball Material: Steel
Ball Diameter: 1.5 mm

Used Material pH ME Module:
pH Electrode: Hamilton Polilyte Lab

4.3 Filling and cleaning of the measuring system

The measuring system (Lovis with pH Module) was filled by flow-through using a syringe. To fill both instruments a minimum sample volume of 6 mL is necessary.
To avoid any cross-contaminations between the measurement of different samples it is recommend to rinse the whole system thoroughly with water and afterwards dry it with the internal pump.

5 Results

Sample Name	*Dyn. Visc. [mPa·s]*	*Lovis Angle [°]*	*Shear Rate [1/s]*	*Av. Runtime [s]*	*pH Value*	*Var. Coeff. [%]*	*Fw/Bw Dev. [%]*
Nasal spray 25°C	0.997	37	440.9	20.154	6.39	0.02	0.04
Nasal spray 37°C	0.772	28	441.9	20.112	6.38	0.05	0.08
Nasal spray 25°C FAS	0.995	70	689.6	12.887	6.39	0.01	0.02
Nasal spray 25°C FAS	0.996	60	635.0	13.997	6.39	0.02	0.03
Nasal spray 25°C FAS	0.997	50	561.2	15.834	6.39	0.02	0.09
Nasal spray 25°C FAS	0.997	40	470.8	18.873	6.39	0.03	0.06
Nasal spray 25°C FAS	0.998	30	365.8	24.308	6.39	0.01	0.07
Nasal spray 25°C FAS	0.999	20	249.4	35.739	6.39	0.05	0.24

6 Conclusion

By combining the Lovis 2000 M Microviscometer with the pH ME Module it is possible to obtain viscosity and pH values with just one sample filling.

Calibrations, temperature calibrations, adjustments and several kinds of measurements are performed by the Lovis 2000 M Microviscometer software. The results are either directly stored and displayed on the Lovis instrument or can be printed directly after each measurement. The software of the Lovis 2000 M Microviscometer fulfills all requirements of the 21CFR Part 11 (electronic records, audit trail and electronic signatures).

Due to its modular concept, the Lovis 2000 M Microviscometer and pH ME Module can be easily combined also with other Anton Paar measuring instruments such as Density Meter DMA Generation M, or upgraded at a later stage. For that reason, the instruments can be individually configured to match customer's requirements.

Automation with different modules of sample changer is also possible, providing useful support especially in case of large numbers of samples (measurement up to 96 vials is possible).

If the user is working under GMP (Good Manufacturing Practice) surrounding or if the department has to work with the FDA 21 CFR Part 11 the instrument can be delivered with a full pharma qualification package (PQP - Pharma Qualification Package). This package includes a Risk Analysis, Traceability Matrix, Deviation List, all steps of the qualification procedure (DQ, IQ, OQ and PQ) and a SOP (standard operating procedure). This makes all the procedures (qualification of the instrument and validation of the methods) fully traceable and perfectly suited for pharmaceutical applications.

7 Similar Application: Eye Drops

7.1 Introduction

Water solutions of eye drops belong to the most often used ophthalmic drugs. Such solutions are applied to the cornea or into the conjunctiva sack in the amount of 1-2 drops, twice to four times a day. Because of the lacrimal system dynamics, eye drops are easily washed away with lacrimal fluid and removed from the eye. Therefore the time of direct contact of the fluid with the eye surface is short. Prolongation of the time when the therapeutic substance remains in the application spot can be achieved by applying higher viscosity systems, which enable longer contact with the eye surface.

Therefore **viscosity** has to be measured for eye drop formulation but also during stability tests. The **pH value** of the eye drops has to be within a limit of 6 to 8, which also needs to be controlled during production and storage.

7.2 Measurement

See chapter 4 “Measurement” on page 2

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