Thixotropic sprays: Popular with patients, challenging for developers

Analysis of particle size and morphology provides essential information for formulators developing thixotropic suspensions

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To improve ease of patient compliance, many nasal sprays are now formulated as thixotropic suspensions or solutions, which require only a quick twist of the wrist to ensure that the spray is ready for use with the active ingredient evenly dispersed.

The nasal route is becoming a preferred delivery channel for a range of drugs because the tissue has a large surface area with high permeability and the location of lymphoid tissue at the back of the nasal cavity offers rapid transport into the circulatory system. These attributes make it an ideal route of delivery for pain relief drugs and treating conditions such as migraines. The olfactory region at the top of the nasal cavity is also of interest for many therapeutic areas.

The challenge in developing a nasal delivery device is to fashion the particle/droplet size to ensure the drug is deposited within the nasal passages, not the lungs or gastro-intestinal tract. Research has shown that a particle size of greater than 10 to 20 μm largely achieves this objective.

Confirming the particle size and ensuring that the suspended drug particles are evenly dispersed within a thixotropic solution creates a number of challenges. This article will discuss the issues that formulators have to address when creating a thixotrophic suspension and the types of analyses that are available to determine the extent to which the nasal spray has been optimized.

Benefits of thixotropic suspensions

A thixotropic product appears as a gel or viscous liquid until shaken or a shear is applied; for example, when the nasal spray is activated. Then the viscosity decreases and it behaves like a liquid.

The major benefit is physical stability. The gel will hold particles of an API (active pharmaceutical ingredient) in place rather than allowing them to sediment to the bottom of the container. Consequently, a patient using a thixotropic product only needs to gently shake it before use, unlike the vigorous shaking that is required to disperse an API that has settled out of a liquid formulation.

Additionally, thixotropic solutions can help improve the absorption of nasally delivered drugs. Following the initial spray, they become more viscous on the point of contact, increasing the time required for nasal mucociliary clearance and thereby extending contact time with areas of the nose where absorption can take place.

Thixotropic solutions do, however, present challenges for drug formulation and analysis. If the gel is too viscous, air bubbles can become trapped in the matrix, which will affect the dose uniformity. If the gel is not sufficiently viscous, the suspended drug particles could sediment, giving a non-homogeneous suspension and possible causing caking of the drug.

Confirming the particle size of drug in suspension can also be problematic because the thixotropic agent creates suspended material, usually microcrystalline cellulose, which makes it difficult to distinguish between the drug and the excipients.

To identify these issues and take appropriate action, formulators have ready access to appropriate analyses. A number of approaches are emerging that can provide the rapid results that formulators need.

Formulation challenges

The typical compound used to give structure to thixotropic formulations is microcrystalline cellulose (MCC). It is normally used in the form of Avicel, in which the MCC has been partially hydrolysed with acid and reduced to a fine powder. The MCC crystals swell when water is added to create a mesh that holds the API in suspension and prevents it from settling out.

To ensure good dispersal, high speed mixing or homogenization is required during manufacture to create an adequate shear. The order in which ingredients are added is also important. The Avicel colloidal should be dispersed in water before other ingredients are added. A protective colloid, such as xanthan gum or carboxymethylcellulose, should be added soon after to prevent flocculation. Temperature and pH are also critical factors; if the pH is less than 4, another protective colloid may be required. Managing increasingly hydrophobic APIs may require the addition of surfactant.

If the Avicel in the thixotropic solution is properly dispersed, one will see a very even crystalline pattern under polarized light. If the pattern is not evident, one or more of the factors above may be the cause. Physical stability of the suspension is evaluated by selective sampling at ten discrete locations within a batch of formulation, followed by analyses. This test for homogeneity may be repeated 72 hours after production to ensure that physical stability is retained.

Particle size analysis

For inhaled products, the size of the droplet determines where the drug is deposited. Changing the proportions of excipients in the formulation can impact particle size. Traditionally, a Next Generation Impactor (NGI) is used to determine the aerodynamic particle size, but this test can be very time consuming.

To gain information, particularly when regulators will evaluate a drug-device combination, other techniques may be more valuable.

Of particular note is laser diffraction, which allows for complete aerosol and spray droplet characterization and particle analysis for dry powder inhalers. A new laser diffraction technique, the Malvern Spraytec, allows sprays to be tested for droplet size. The spray is passed through a laser beam and the angular intensity of the scattered light is measured. This scattering pattern is then analyzed using an optical model to produce a size distribution.

It is possible to screen a batch of formulations rapidly, accelerating development times and making this an valuable tool in the early stages of product development. Results are available within minutes and show the size of particles or droplets over a range of sizes, from approximately 0.1 to 900 μm.

The two principal outputs produced by laser diffraction analysis using the Spraytec are a real-time plot (which provides specific information about particle-size distribution) and a transmission plot (which provides information about the efficiency of a spray).

The real-time plot shows the population of particle sizes at each point in time. A typical plot for a nasal spray will show that large droplets are released immediately after a plume is sprayed, since the energy forcing the spray out of the device causes particles to clump together. This is followed by a stable phase, where the droplet size is small and consistent. Finally, particle size increases in the dissipation phase. At this stage, the plume has started to disperse, so less drug is being delivered and the energy produced by the device is decreasing, which causes particles to aggregate. The sta-

ble phase is the important phase to consider for drug delivery, so the particle size distribution is averaged over this time and used for analysis.

The plot of optical transmission shows the consistency of the spray, which gives an indication of the device's efficiency. As the plume passes through the laser, the particles partially block the beam. This affects the percentage of the beam transmitted to the receptor. The transmission plot shows how this percentage changes over time. A steady transmission plot with no spikes shows that a spray is producing a consistent plume. This will lead to efficient drug delivery to the patient.

Ease of use is a major benefit of laser diffraction. The results are easily repeatable and highly consistent because it is possible to set up a rig that ensures the spray is always held the same distance from the equipment.

Comparison of devices

Laser diffraction can be used to compare different devices and formulations. The shear created by actuation of the nasal device can alter the droplet size. To achieve the desired droplet-size profile, the device can be changed to a device suitable for the current formulation. Alternatively, the formulation can be changed so that the device performs better; for example, its viscosity or surface tension can be altered.

Since the results from these tests are available rapidly, the outcome can be used to make informed decisions about which formulations and devices to continue testing, ensuring experimentation is efficient and productive. It may only take a simple modification of the device to improve performance, which can easily be done between experiments.

Determining shelf life

The particle/droplet size distribution produced by laser diffraction can help determine the shelf life of a product by detecting when particles begin aggregating. If particles clump together, they become too large to be administered in a nasal spray. These large particles will show up as a spike on the real-time plot, providing an indication that the spray will no longer deliver the required dose to the patient.

Analysis of a thixotropic solution typically shows a bimodal distribution (see Figure 1). The API is visible at the "fine end," with particle sizes of approximately 1 µm. The second mode, around 7 µm, consists of the MCC particles. The particles detected at approximately 7 µm and above are agglomerated particles of swelled MCC.

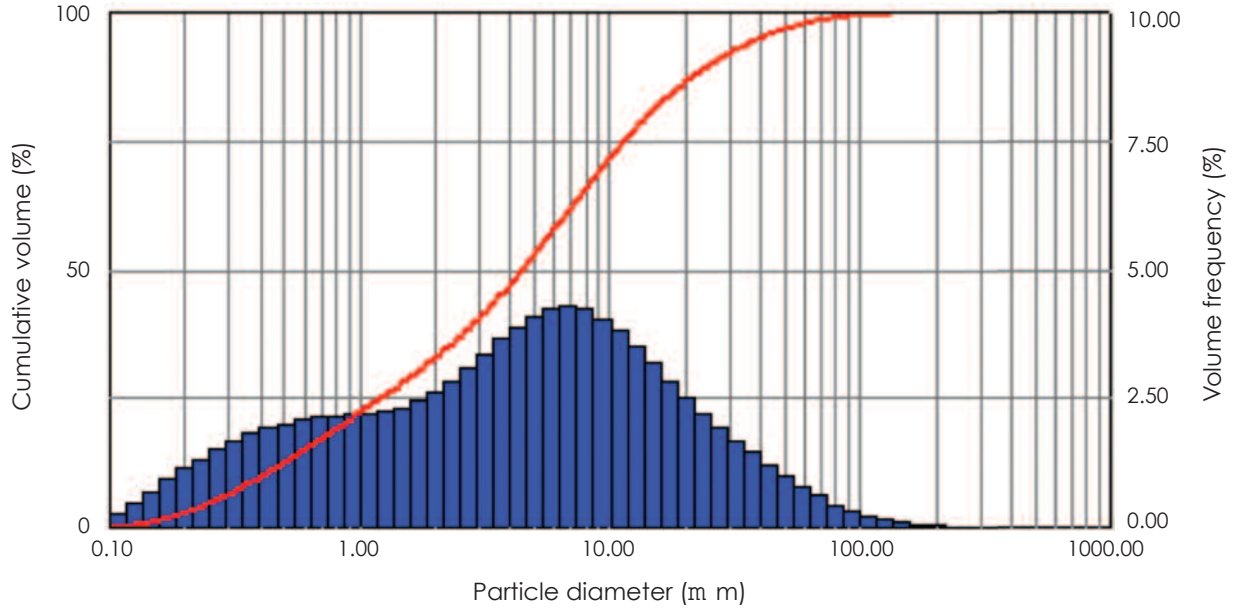
However, to verify that this second peak is the MCC and not another excipient or degradation particle, another technique and instrument should be used, for example, the Malvern Morphologi G3 with a Raman detector attached.

Morphology

Subtle differences in particle size or shape can have significant effects on product performance, including

Figure 1

A histogram generated by the Malvern Spraytec. The particles detected at approximately 7 µm and above are agglomerated particles of swelled MCC. This was confirmed using the Morphologi G3 to manually determine the sizes of larger particles and observe their shapes.

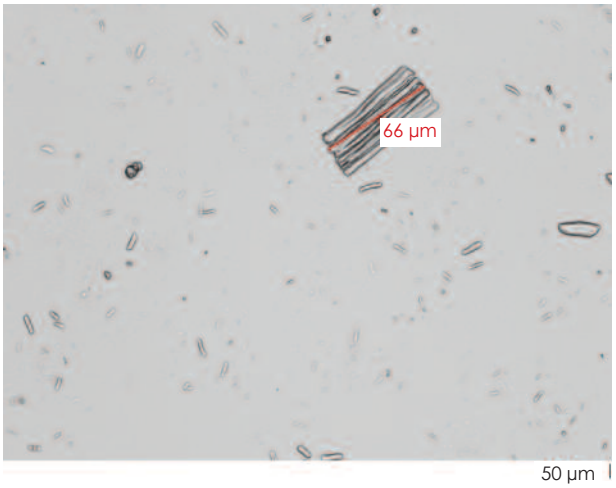


bioavailability, fluidity and product stability. Even within well-controlled API production, additional processing steps such as milling, blending and filtering can introduce variability into the product and consequently have to be precisely controlled.

The Morphologi G3 is an optical imaging tool that automates analyses which would previously have been done by analysts using optical microscopes. A complimentary technique to laser diffraction, it provides more information about individual particles and particles, giving data about their size, shape and solidity (see Figure 2).

Figure 2

Images created by the Malvern Morphologi G3. Detail in shape and size of images produced by the Morphologi G3 confirm that the population of large particles detected by the Malvern Spraytec are MCC and not agglomerated formulation.



The instrument runs automatically and can scan approximately 10,000 particles per hour, taking photographs of each particle it scans. These images allow a very detailed picture to be built up about particle characteristics. The system also allows anomalous results, such as those produced by two particles touching, to be disregarded from the analysis of particle size.

Although light microscopy or light obscuration techniques for sub-visible particle characterization are sufficient in many situations, the Morphologi G3 provides the benefit of automatically, accurately recording shape parameters for every particle. These can be grouped with similar particles to provide a "fingerprint" of each sample.

By providing greater consistency in the descriptions of the particle, it is possible to correlate morphology data against processing parameters such as flowability, active area or grinding efficiency. This enables the process either to be kept consistent or altered to improve performance.

Like laser diffraction, Morphologi G3 has the advantage of producing results rapidly so subsequent tests can be modified based on those results. This makes the technique beneficial for comparing prototypes.

Identification of particles

Many developers will need to go beyond knowledge of the size and shape of their particles to identify them. It may, for example, be necessary to distinguish between the API and other reagents in the formulation, such as cellulose. Both new and well-established techniques are available for identification.

Particle identification is extremely relevant for anyone developing thixotropic formulations. Larger particles detected by laser diffraction can indicate that the formulation has agglomerated, but within a thixotropic preparation, these particles could simply be the MCC, which was used to give the formulation its structure. Evaluating the formulation with the Morphologi G3 can distinguish between these scenarios, because MCC crystals have a distinctive appearance. If more information is needed about the particles, it is possible to identify them using high performance liquid chromatography (HPLC) or a Raman spectrometer.

Rising to the challenge

In an ever-evolving market of drug delivery, both nasal sprays and thixotropic formulations are increasing in popularity. Their advantages, including ease of patient use, and delivery of drug to the nasal passages where it can be easily absorbed, are accompanied by challenges for formulators and analysts. To take advantage of the large surface area and high permeability of the nasal cavity, particle size must be carefully controlled, presenting an important challenge for developers. Ensuring that the API is compatible with a thixotropic solution is another hurdle that must be tackled during formulation.

However, these challenges are also getting easier to overcome. Formulators now have access to analytical techniques that will rapidly provide the information they need to improve their formulations and produce drugs that are delivered effectively and efficiently to patients.

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