



Semisolid sizing

Particle size is an important parameter in the production of semisolid drug products. **Mark Flanagan**, Unilever, and **Paul Kippax** and **Stephen Ward-Smith**, Malvern Instruments, present a new way of measuring particle size at elevated temperature in semisolid formulations

Semisolid drug formulations are becoming increasingly widespread and today constitute a large proportion of the available pharmaceutical dosage forms. A significant factor is that semisolids can offer a solution to the bioavailability issues common in many new drug candidates.

Both the efficacy and safety of semisolid pharmaceutical compounds depend to a large

degree on particle size and size distribution, parameters that can influence a host of attributes, including bioavailability, dose uniformity, storage and packing properties.

The focus here is on semisolid drug formulations and the relationship between particle size and product performance, presenting data generated via a novel approach to analysing particle size in these materials.

Fig. 1: Elevated temperature measurement with the Mastersizer 2000

The laser diffraction method described uses a dispersion cell and a water bath to enable measurements at elevated temperature in the liquefied sample.

semisolid dosage forms

Around 40% of new chemical entities exhibit poor aqueous solubility and present a major challenge to modern drug delivery systems because of their low bioavailability.¹ Such hydrophobic drugs do not always lend themselves to conventional methods of drug delivery.² Semisolid formulations can provide a good solution for these, and also for the safe delivery of drugs with a high potency. In addition, semisolids offer an avenue for developing new formulations for existing drugs, extending a product's life and reaching new markets. Patient compliance is high since semisolids allow painless delivery and avoid many of the side-effects associated with oral dosage forms.

Semisolid drugs include topical preparations used for localised action on skin layers, such as local anaesthetics and antiseptics; and transdermal drugs that do not primarily target the skin, but access the body via the percutaneous route for systemic drug delivery. In recent years advances in transdermal delivery technology, including slow release patches, have encouraged the development of many products in semisolid form.

When a transdermal patch is applied to the

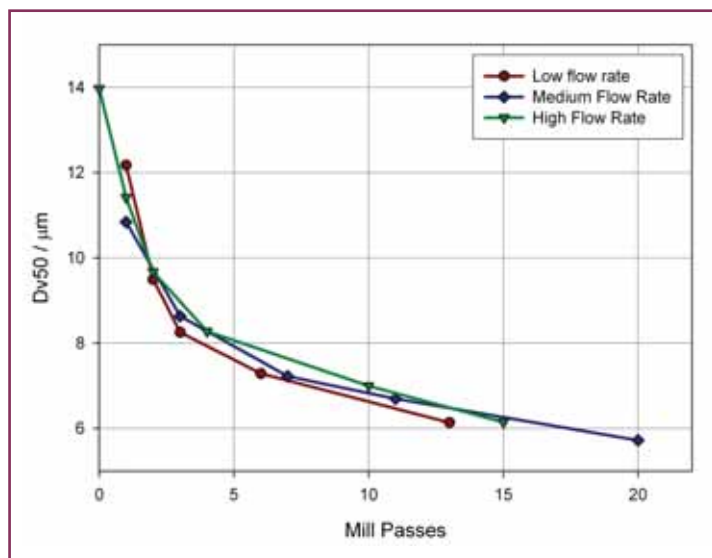


Fig. 2: Volume median (Dv50) particle size as a function of the number of mill passes for three different flow rates through the mill

body, the drug diffuses onto the skin and enters the circulation via hair follicles, sweat ducts or through the stratum corneum, the outermost layer of the epidermis. Adhesion and the ability of transdermal drugs to release the active ingredient depend on the rheological properties of the semisolid, and on particle characteristics. Particle size and shape can be key factors in determining quality attributes, manufacturing processability and other physical properties, including rheological behaviour.³

For topical and transdermal drug delivery, particle size especially is critical. It can be a key regulator of flux for drugs suspended in a vehicle, and smaller particles can promote drug delivery by increasing the dissolution rate.⁴ Particle size is also a major influence on the penetration pathway: for example particles greater than 10µm remain on the skin, those between 3–10µm concentrate in hair follicles, and any smaller than 3µm can pass through both the follicles and the stratum corneum.^{3,5}

Careful design of a drug's particle size supports the efficient targeting of a particular entry route, and can maximise local efficacy or restrict adverse reactions. Because product performance is so dependent on particle size, its control is essential. Any settling or sedimentation

of an active ingredient within a semi-solid suspension can lead to irregular delivery and may compromise efficacy.

Particle size analysis of semisolid products has always been difficult to achieve. A variety of techniques have been applied, including imaging (confocal or scanning electron microscopy) and X-ray tomography. Although each of these can provide a wealth of information about the structure of semisolids, complexity of sample preparation means that they are generally applied only during product development. In addition, these techniques sample only a small amount of material, which can be problematic when attempting the characterisation of larger samples during scale-up or batch release.

laser diffraction

One technique now well-accepted within the pharmaceutical industry for particle size analysis is laser diffraction. This is because of its rapid measurement capabilities, accurate and reproducible analysis, broad measurement range and the flexibility to measure many different sample types, from emulsions to dry powders. It is especially sensitive to changes in coarse particle fraction and is, therefore, an

excellent tool for studying the sample instability that results from, for example, agglomeration, creaming or sedimentation. Modern laser diffraction systems offer full automation, user-friendly software and compliance with important regulations such as 21 CFR Part 11.

Using laser diffraction for particle sizing in semisolids does, however, raise some technical issues since the samples are not liquid at room temperature. By equipping a laser diffraction system with a dispersion cell and waterbath, it has been possible to make detailed particle size measurements of semisolid samples at elevated temperature, as the following study illustrates.

hot sample dispersion

The sample described here is a semisolid suspension at ambient temperature, but it melts upon heating, necessitating measurement at a temperature above 70°C. This was achieved by placing the Hydro 2000SM small volume sample dispersion unit for the Mastersizer 2000 laser diffraction particle size analyser (Malvern Instruments, UK) in a waterbath to achieve hot sample dispersion. The dispersant used to dilute the semisolid prior to measurement was heated in the water bath before addition to the dispersion unit. Once in the dispersion unit, the liquid was allowed to equilibrate for five minutes before starting measurements to ensure that the background light scattering observed from the dispersant was at a low level.

Manufacture of the semisolid product involves milling the solid component at elevated temperature and then cooling the resulting suspension. Initially the hot dispersion particle size analysis method was used to track the milling process and determine optimal conditions: flow rate through the mill and number of passes. Figure 2 shows data generated by analysing molten liquid samples extracted directly from the mill.

The particle size data indicate a progressive size reduction as the number of mill passes increases. Lower flow rates give greater particle size reduction per pass, as would be expected, but the differences are subtle. Reduction to the required particle size, a median (Dv50) of around 6µm, is achieved in around 13 to 17 passes. Figure 3 gives a full particle size distribution for the final product.

The second part of the study involved investigating the impact of cooling on product homogeneity. Cooling of the semisolid matrix is not instantaneous. Instead, the temperature, and therefore the product's viscosity, changes gradually once processing is complete. Forced cooling may affect the overall consistency of the product, giving rise to a crystalline matrix that is too fine, so gradual cooling is preferable. However, this slow development of structure raises the possibility of segregation and inconsistency in the final product.

A sample was stored for one day, post production, under ambient conditions. Material taken from the top and bottom of the sample container was then analysed using the hot dispersion technique. Figure 4 shows the results obtained.

Although the particle size distributions are quite similar there is a small but significant difference that provides evidence of sedimentation. ►

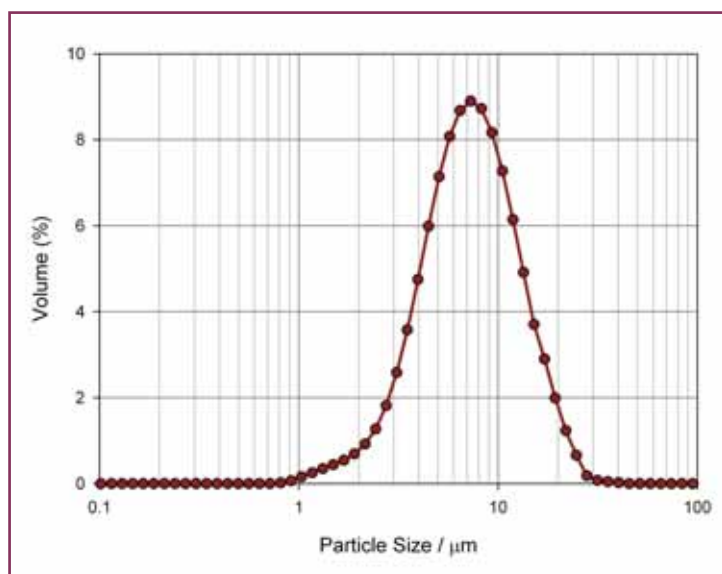


Fig. 3: Particle size distribution for the solid suspension extracted from the process following the final mill pass

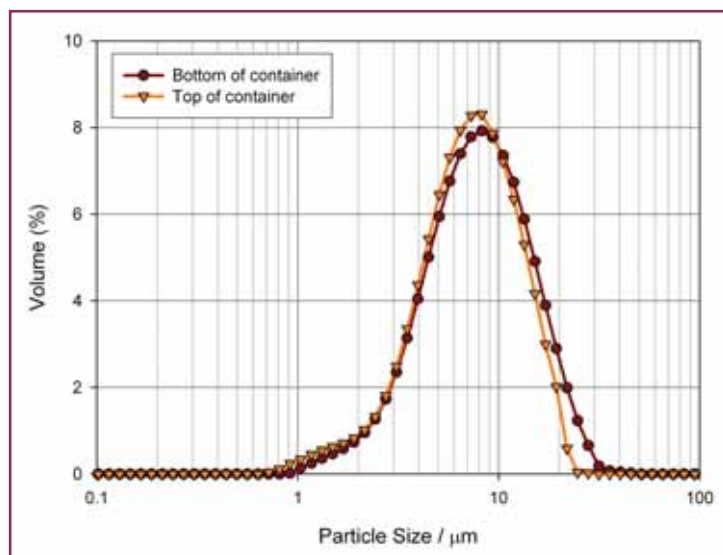


Fig. 4:
Particle size distributions for samples taken from the top and bottom of the product container

◀ Compared with the size distribution shown in Figure 3, the sample taken from the top of the container has fewer coarse particles. A corresponding increase in coarse particle concentration is observed in the other sample.

This example highlights the sensitivity of particle sizing by laser diffraction and its value in industrial applications. Alternative image-based methods could not detect any difference between the upper and lower samples. These data can be used to optimise the process and reduce the likelihood of sedimentation.

In conclusion, particle size is an important

parameter in the production and quality control of semisolid pharmaceutical products. It affects skin penetration and can also influence the flux rate of the active ingredient. In addition, particle size and shape may be key factors in determining processability and the rheological behaviour of a formulation. Laser diffraction is a powerful technique for particle size measurement and is suitable for many different materials, including semisolids, provided the dispersion conditions are selected correctly.

The novel hot dispersion method described here for the Mastersizer 2000 is proving highly

effective for the preparation of semisolid samples, enabling their successful analysis by laser diffraction. The studies undertaken here confirmed that laser diffraction can be used to track the milling process used for manufacture of the product and to detect subtle changes in particle size distribution that are indicative of sedimentation, during cooling. The results enable optimisation of both the processing method and the product. [mc](#)

references

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