Chemically Specific Sizing

Particle size of active pharmaceutical ingredient (API) directly correlates to bioavailability and drug effectiveness. For topical semisolid formulations the API particle size distribution correlates to biological performance. The API particle size distribution should be stable to ensure reproducible bioavailability within the storage period. FDA recommends a thorough characterization of particle size distributions when the performance of a drug product depends on particle size. Therefore there is a need for fast, detailed and highly reproducible particle characterization techniques.

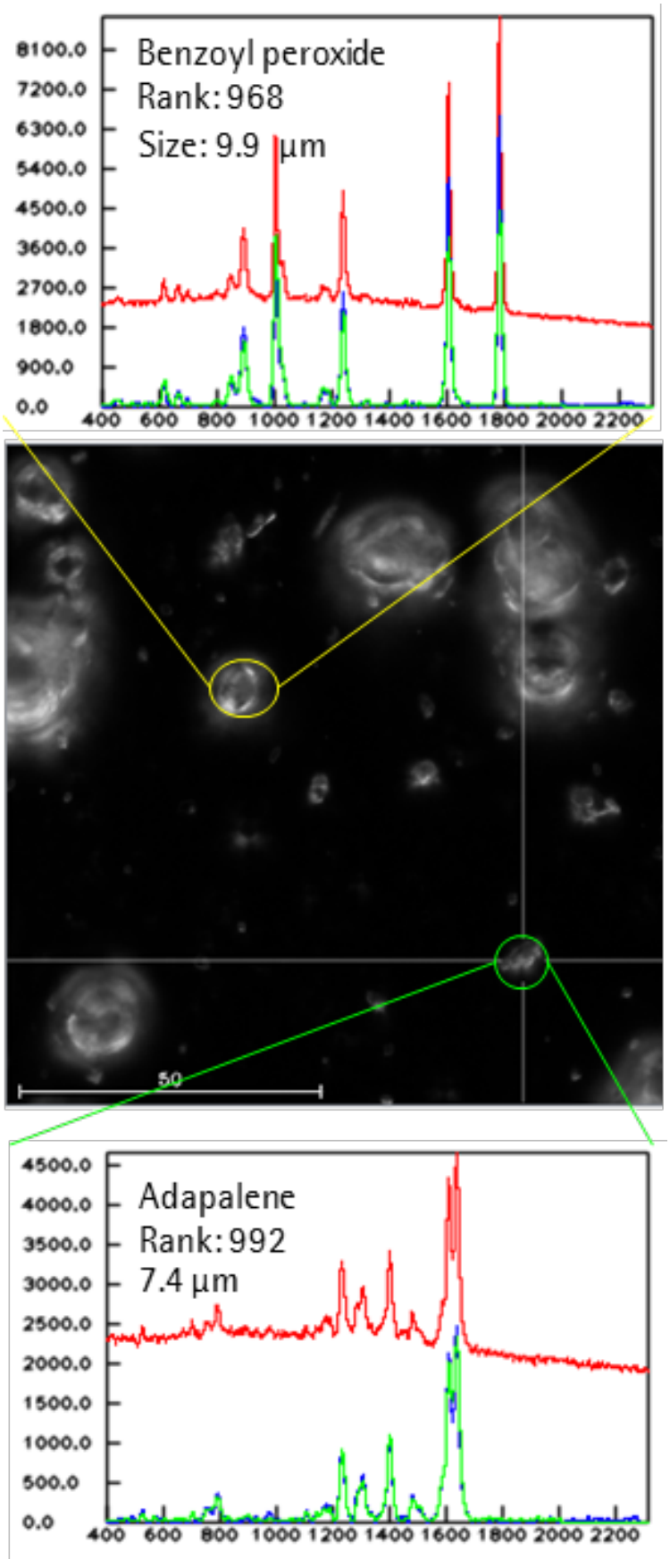

Fig. 1: Benzoyl peroxide and adapalene particles images and spectra. Spectra were acquired for 3 s at 12% laser intensity.

Chemically Specific Particle Size Distribution in Cream

For this experiment we used a cream containing 0.1% adapalene and 2.5% benzoyl peroxide gel. A thin layer of a cream sample was smeared on a gold coated microscope slide. 1.6x1.6 mm area was analysed in automated regime using the Single Particle Explorer instrument. Microscope pictures were taken, particles were counted and their sizes were measured and chemical composition was identified through Raman spectroscopy. Incident green laser with 532 nm wavelength was used.

Illumination and image processing parameters were optimized for the accurate particles recognition. Settings for Raman analysis were optimized for reliable high throughput analysis.

As seen in Figure 1, benzoyl peroxide and adapalene exhibit very clear Raman spectra that allow consistent identification of these API particles from one another as well as from inactive ingredients at just 3 seconds.

It can also be seen in Figures 1-3 that adapalene particles appear to be smaller than benzoyl peroxide particles. Total of 4000 particles were analysed for this cream sample in 3 hours. For

comparison, ultra-fast Raman imaging of a 1.6x1.6 mm area would take at least 17 hours (950 spectra per second). The size distributions of adapalene and benzoyl peroxide particles were determined. Cumulative size distributions of benzoyl peroxide and adapalene are shown in Figure 4. D_{50} and D_{90} values are lower for adapalene then for benzoyl peroxide.

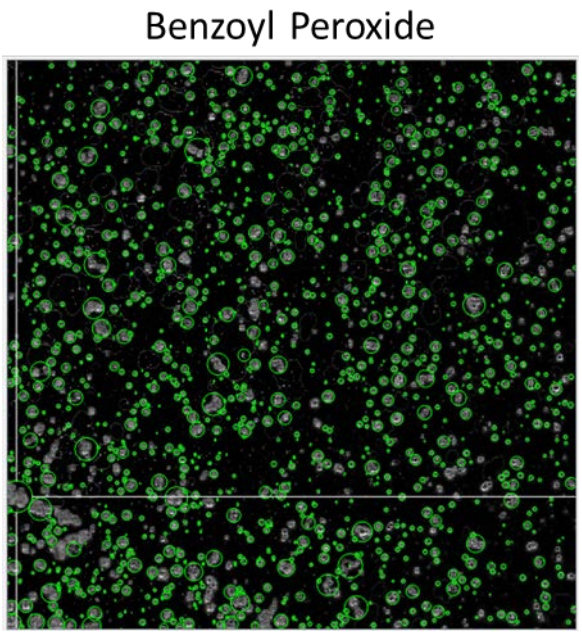

Fig. 2. 50x dark field image of a 1.6x1.6 mm cream sample. Benzoyl peroxide particles are marked in green.

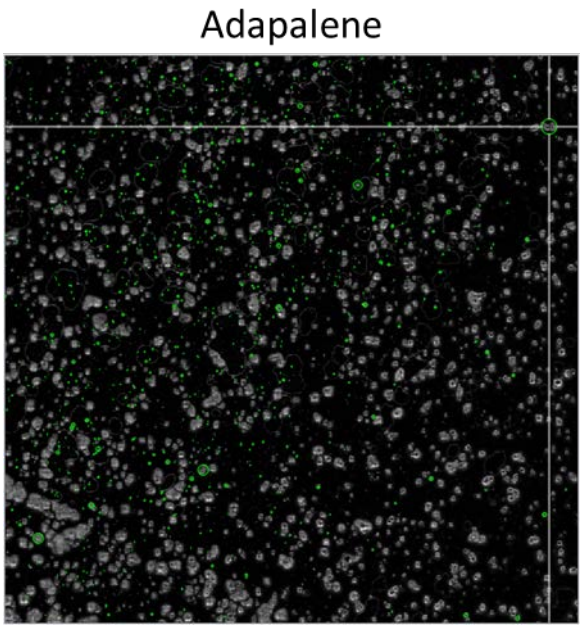

Fig. 3. 50x dark field image of a 1.6x1.6 mm cream sample. Adapalene particles are marked in green.

To generate a particle size distribution plot for the low concentration of 0.1% active ingredient, a relatively large area of sample needs to be scanned. Image directed Raman spectroscopy delivers an elegant solution for this task.

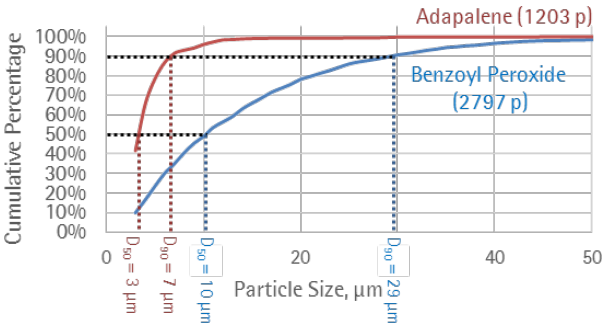

Fig. 4. Cumulative distribution of 2797 benzoyl peroxide particles and 1203 adapalene particles. D_{50} = 10 um, D_{90} = 29 µm for benzoyl peroxide; D_{50} = 3 um, D_{90} = 7 um for adapalene.

Conclusions

Here we used an automated image guided spectroscopy for a comprehensive analysis of number, size, and composition of particles present in topical formulation for precise API characterisation. This technique can provide chemical specific particle size distribution analysis within a couple of hours for thousands of particles. With this method, the Single Particle Explorer can provide rapid reliable characterization of samples for development of formulations as well as for quality control and product monitoring within the storage period.