Coherent anti-Stokes Raman scattering microscopy to analyze adhesive mixtures for inhalation

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PURPOSE: To image the spatial distribution of fluticasone propionate, budesonide, salmeterol xinafoate and salbutamol sulphate on the surface of lactose carrier particles using coherent anti-Stokes Raman scattering microscopy.

METHODS: CARS Imaging was performed using a home built CARS system consisting of a synchronously pumped optical parametric oscillator (OPO) and a modified commercial inverted microscope (Olympus IX71) with a 60X objective. Coherent anti-Stokes Raman scattering (CARS) spectra were collected from the pure starting materials to identify peaks at which to image. Adhesive mixtures containing 0.4% (w/w) of drug on a coarse lactose carrier (250-315 µm) were prepared. Lactose images were recorded at 2888 cm\(^{-1}\) while budesonide, fluticasone, salmeterol and salbutamol were collected at 3043 cm\(^{-1}\), 3055 cm\(^{-1}\), 3050 cm\(^{-1}\), and 3066 cm\(^{-1}\) respectively. Z-stacked CARS images (512x512 pixels) were collected with 1 µm distance between each frame and each frame taking about 5 seconds to record.

RESULTS: CARS microscopy shows that the API is distributed in clusters on the surface of the lactose particles and Z-stacked CARS imaging shows that the API does not penetrate into the lactose particle. Figure 1 shows Z-stacked CARS images of a lactose particle coated in budesonide. Each Z-stacked image consists of 21 frames and took about 2 minutes to collect. Figure 1A is a CARS image (512x512 pixels) of budesonide recorded at 3043 cm\(^{-1}\) and false colored red. Figure 1B is a CARS image (512x512 pixels) of lactose recorded at 2888 cm\(^{-1}\) and false colored green. Figure 1C is an overlaid image consisting of figure 1A and figure 1B and figure 1D is the transmission light image.

CONCLUSIONS: CARS microscopy is capable of chemical specific imaging and was able to rapidly image the distribution of budesonide, fluticasone, salmeterol and salbutamol on the surface of lactose carrier particles. It therefore forms a promising technique for monitoring changes in distribution and degree of agglomeration of the drug on the carrier surface in the presence of lactose fines that are of similar shape and size as the drug particles.