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Microscopical Characterization of Controlled Release Pharmaceuticals: A Complementary Approach

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Pharmaceutical products, with their multi-component formulations and varied dosage forms (biodegradable implant, capsule, liquid, tablet, etc.), notoriously present a challenging matrix for characterization and analysis. Knowledge of structural and chemical properties of the active ingredient(s) and excipients is essential for drug development and analysis of component distributions is key to achieving the desired time-release properties. Unfortunately, there is no "one size fits all" method for approaching these complex analyses and a combination of techniques is often the best solution. In these studies, a complementary approach has been implemented utilizing a number of microscopies for the investigation of a delayed release capsule and a controlled release implant.

Delayed release pellets from a product used to treat gastrointestinal conditions were evaluated by a combination of light microscopy (LM), scanning electron microscopy with energy dispersive spectroscopy (SEM-EDS), and confocal Raman microscopy (CRM). Of particular interest was the spatial relationship and distribution of the active pharmaceutical ingredient (API) and selected excipients related to the API's rate of release. SEM-EDS mapping for selected heteroelements (nitrogen, sodium, and sulfur) associated with the ingredients in the formulation provided information on the distribution of these elements, which allowed us to make assumptions regarding the localization of ingredients (FIGURE 1). Analysis of the pellets by CRM provided detailed chemical information on the key ingredients present and their spatial relationship within the microenvironment examined.

Another example of the use of combinatory microscopical techniques illustrated here is the investigation of a controlled release anti-infective implant. The goals of the study were to assess the particle size of the active ingredient and its distribution within the formulated product. Polarized light microscopy (PLM) of the API - a hydrochloride salt, and the primary excipient, polyethylene glycol (PEG), showed different morphological characteristics and general size information (FIGURE 2). SEM-EDS of cross-sectioned samples allowed visualization and sizing of the API crystals based on their unique chemistry and morphology. Spectral mapping of the cross sections by confocal Raman microscopy confirmed the distribution of the API within the PEG matrix, and also revealed multiple phases believed to be polymorphs of the drug (FIGURE 3).

These examples demonstrate that a combination of microscopic techniques is often the best way to fully evaluate the structure of complex pharmaceutical formulations. The versatility of microscopy allows for studies over a wide range of areas in the industry including product formulation, quality assurance/quality control, and intellectual property matters.

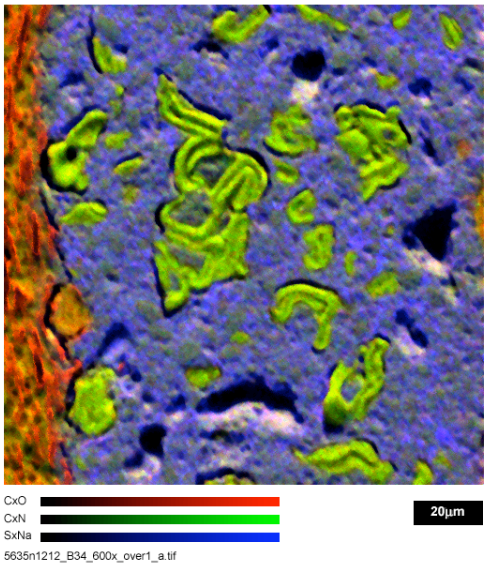

FIGURE 1. Colorized and overlaid SEM-EDS maps of the API (green) distributed within a surfactant (blue), and a melt coating (red).

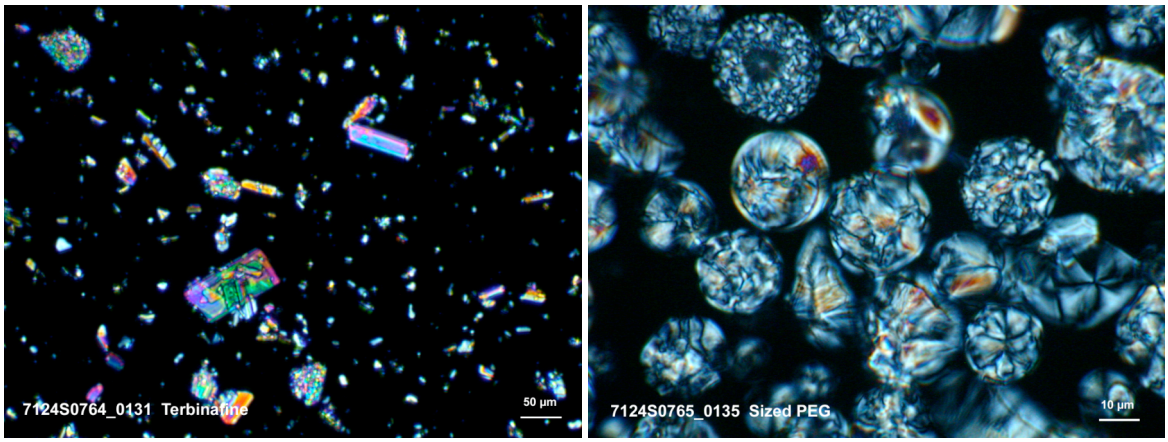

FIGURE 2. Polarized light micrographs of typical API crystals in the raw pharmaceutical material, (left) and of typical PEG particles in the raw excipient material (right).

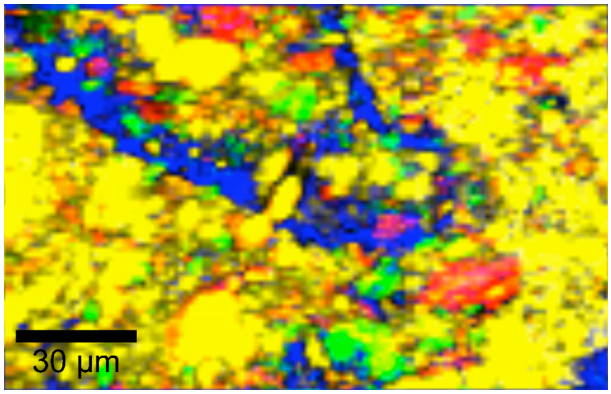

FIGURE 3. Raman phase distribution map showing three phases of the API (red, yellow, and green). Blue indicates the primary excipient, PEG.

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