M8011

Evaluating Complex Emulsion and Liposome Morphology in Propofol Drug Products with High Resolution Cryogenic Electron Microscopy

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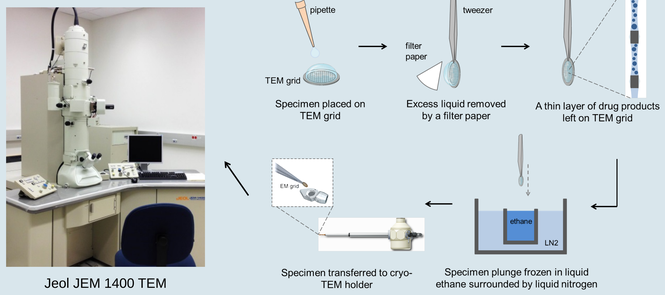
PURPOSE

Propofol (2,6-diisopropylphenol) is a commonly used intravenous drug for the induction and maintenance of general anesthesia or sedation. Due to the insolubility of propofol in water, it is formulated as an oil-in-water emulsion stabilized by egg lecithin phospholipids. Addition of excess phospholipids will, in practice, give rise to the formation of both emulsion and liposomes, i.e. vesicular structures formed of a bilayer of phospholipids, in the formulation. However, the presence, amount, morphology and potential impact of these structures is relatively unknown. In this study, we investigate the use of high resolution Cryo transmission electron microscopy (cryo-TEM) to measure the presence, content and structures of liposomes formed in four propofol injectable emulsion products. Cryo-TEM can be used to quantify the size distribution and composition of complex coexisting structures which can be used to support drug product quality and equivalence assessment.

METHODS

- Cryo transmission electron microscopy (cryo-TEM) was performed using a Jeol 1400 TEM/STEM equipped with a Leica EM GP grid plunge freezer.
- Dynamic light scattering (DLS) and zeta potential were performed using a Malvern Zetasizer. Three separate dilutions were run with at least 5 measurements per sample. Samples were diluted 1000X with DI water and borate buffer for DLS and zeta potential, respectively.
- Capillary electrophoresis (CE) was performed on an Agilent 7100 Capillary Electrophoresis system. For injection samples, a volume of 1 µL propofol sample is mixed with 100 µL sodium tetraborate buffer (Agilent; 20 mM, pH 9.3) and 5 µL dimethyl sulfoxide (DMSO) solution (1%, v/v in water; electroosmotic flow marker).

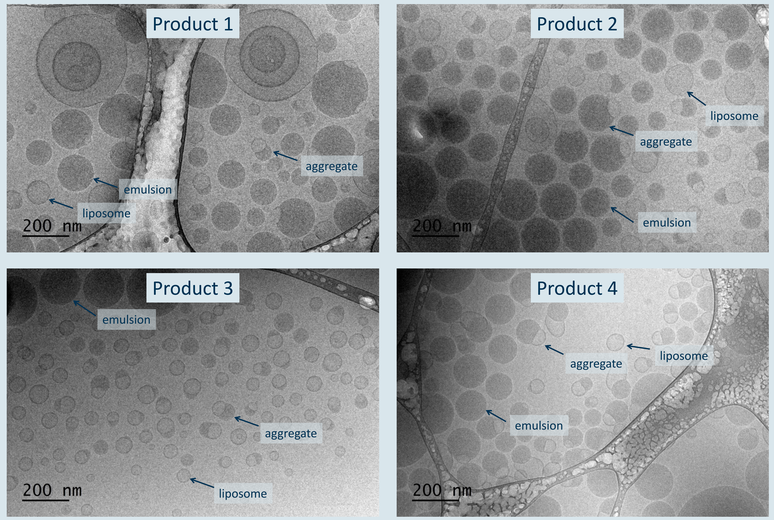
Cryo-TEM sample preparation procedure



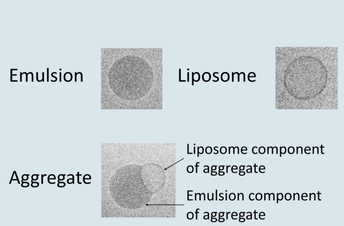
Jeol JEM 1400 TEM

RESULTS

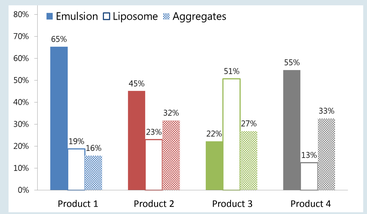
Cryo-TEM micrograph of propofol samples



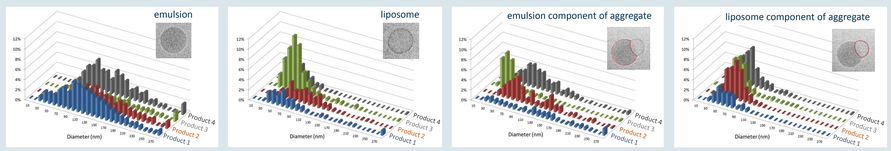
Cryo-TEM enables discrimination and measurement of nano and micro-structures within complex formulations such as the presence of both emulsion droplets and liposomes in propofol emulsion products from different manufacturers.



Proportion of emulsion, liposome and aggregate



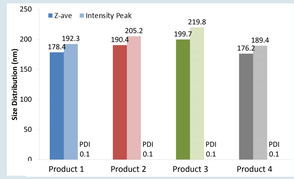
Particle size distribution of emulsion, liposome and aggregate



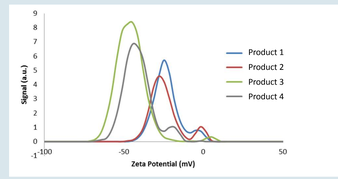
The population and size distribution of by-product structures, liposome and emulsion/liposome aggregate, varied among products.

RESULTS (CONT'D)

Hydrodynamic Size of Propofol by DLS

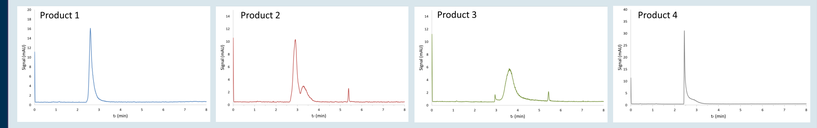


Zeta Potential Measurement



The multi-component property of propofol was not discerned by dynamic light scattering or zeta potential measurements.

Capillary Electrophoresis (CE)



- The capillary electrophoresis separation shows different retention time, indicating potential differences in particle size and/or surface charge populations in each of the products.
- Broadened peak indicates heterogeneous particle size distribution.

CONCLUSIONS

- Cryo-TEM results demonstrate that all propofol products contain a mixture of oil-in-water emulsions, liposomes and emulsion/liposome aggregates.
- All products contain similar proportion and particle size distribution of the emulsions (the main carrier of the drug substance) whereas slight differences of the by-product structures (liposomes and aggregates) are observed.
- Cryo-TEM is a powerful characterization technique for analyzing complex drug products comprising coexisting morphologies.

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