doi:10.1017/S1431927619007104
Microsc. Microanal. 25 (Suppl 2), 2019

Characterization of Encapsulated Liposomal Irinotecan

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Since the U.S. Food and Drug Administration (FDA) first approved DOXIL® in 1995, several new and generic liposomal drug products have been approved by the FDA [1]. Among these is ONIVYDE® (irinotecan liposome injection), a topoisomerase inhibitor, indicated in combination with fluorouracil and leucovorin, for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy.

The characterization of liposomal drugs typically focuses on the composition of the liposome bilayer and its surface chemistry [2-3]. Although currently there is no FDA product-specific guidance (PSG) on irinotecan liposomal drug products, current guidance of similar liposome products recommends that manufacturers provide information documenting the physiochemical properties of the encapsulating liposomes [4]. However, studies of the physical state of the encapsulated drug inside liposomal formulations are few. Limited studies suggest that encapsulated drugs can exist as a solution, amorphous precipitate, or crystalline precipitate [1]. The physical state of the drug is expected to affect the amount of free drug dissolved inside the liposome, and ultimately its drug release profile.

The physical state of encapsulated irinotecan in ONIVYDE® has not been experimentally characterized. Here, we use cryo-transmission electron microscopy (cryo-TEM) and small angle X-ray scattering to investigate drug crystallinity. Irinotecan appears as an electron-dense precipitate within an electron-lucent, aqueous liposomal interior (**Figures 1A-B**). Like many other liposomal drug products, encapsulated irinotecan distorts the liposome, giving it a prolate spheroid geometry. While most liposomes appear to be encapsulated with irinotecan, many liposomes also contain smaller, membrane-bound structures as well (**Figure 1B**). These structures are both electron-dense and electron-lucent and are not typically found in other liposomal drugs.

Additionally, the mean diameter of particles measured with cryo-TEM is smaller than that obtained by dynamic light scattering (**Figure 2**). This is likely due to the isotropic orientation of particles on the TEM grid. Particles orientated in the direction of the electron beam may appear circular in 2D projection images but are actually prolate spheroids in 3D.

Cryo-TEM is a unique analytical tool that can elucidate the complex structure of irinotecan drug precipitate and corresponding non-spherical geometry of liposomes in ONIVYDE. This information can help researchers, industry, and regulatory agencies better understand and characterize the complex structure of liposomal drug products [5].

References:

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[5] Drs. Noble and Jog, as well as L. Chen were supported in part by an appointment to the Research Participation Program at the Center for Drug Evaluation and Research administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the U.S. Department of Energy and FDA. The authors would like to acknowledge the Advanced Characterization Facility at the FDA and CDRH/OSEL/DBCMS and CDER/OPQ/OTR for instrument use.

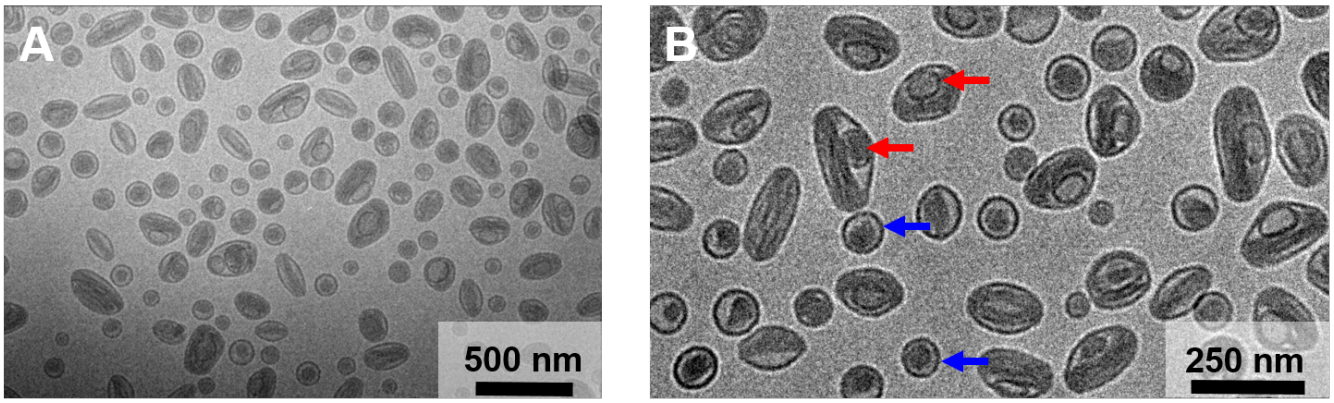

Figure 1. Low-magnification (A) and high-magnification (B) of ONIVYDE® particles. Red arrows indicate what appear to be encapsulated, membranous structures present within the liposome. Blue arrows identify ONIVYDE® particles that appear approximately circular due to their orientation in the direction of the electron beam.

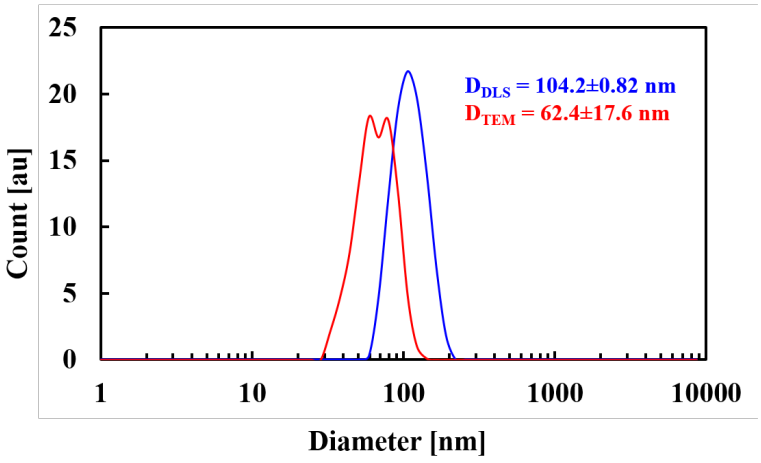

Figure 2. Particle size distributions obtained from DLS (blue) and cryo-TEM (red). The size difference is attributed to the isotropic orientation of particles on the cryo-TEM grid. D_{DLS} and D_{TEM} are expressed as mean and standard deviation. TEM sample size = 969.

https://doi.org/10.1017/S1431927619007104 Published online by Cambridge University Press