Characterization and quantification analysis of Onivyde irinotecan liposome injection

T1030-06-32

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PURPOSE

- To establish analytical methods for the characterization of Onivyde (irinotecan liposome injection).
- To study the release characteristics of Onivyde *in vitro* and *in vivo* and provide a reference for its manufacturing.

METHOD(S)

- Particle size by Dynamic Light Scattering
- Quantification of irinotecan by UPLC-FLR
- Quantification of lipids by UPLC-ELSD
- Irinotecan encapsulation (%) was determined by separating free drug with TOYOPEARL HW-55F packing material loaded column
- *In vitro* release was performed at 55℃ in 10mM phosphate buffer saline (PBS)
- Pharmacokinetic study was conducted in mice at 15 mg/kg intravenously
- Free irinotecan in plasma of Onivyde was separated by Waters Corp Oasis HLB Cartridge
- Concentration of irinotecan *in vivo* was quantified by UPLC-MS

RESULT(S)

Characterization and quantification of Onivyde

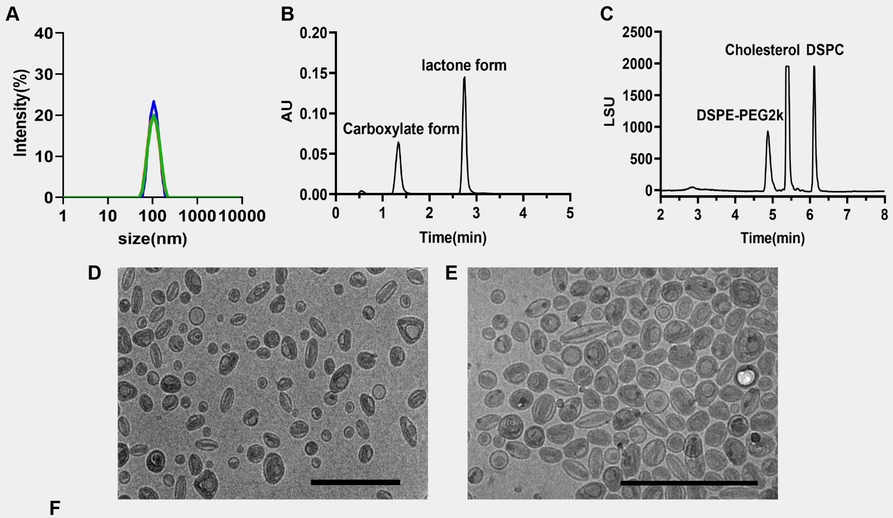

Figure 1. Characterization and quantification of Onivyde. A. Particle size distribution of Onivyde (intensity-weighted results). B. UPLC chromatograms of two forms of irinotecan. C. UPLC-ELSD chromatograms of lipids in Onivyde. D, E. Cryo-TEM images of undiluted Onivyde, scale bar represents 500 nm. F. Important formulation characteristics of Onivyde. All values are presented as mean ± SD (n=4).

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Lot No.	Size (nm)	PDI	Irinotecan concentration (mg/mL)	Encapsulated irinotecan(%)	DSPC (mg/mL)	Cholesterol (mg/mL)	DSPE-PEG2k (mg/mL)
Label claim	110	-	4.3	100%	6.81	2.22	0.12
120518S	110.0±1.8	0.05±0.01	4.4±0.3	97.8±0.4	6.37±0.44	2.25±0.06	0.12±0.02
200048A	108.2±0.8	0.05±0.01	4.2±0.1	98.0±0.3	6.38±0.12	2.21±0.04	0.13±0.004

In vitro release of Onivyde

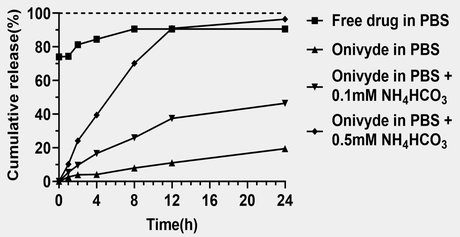
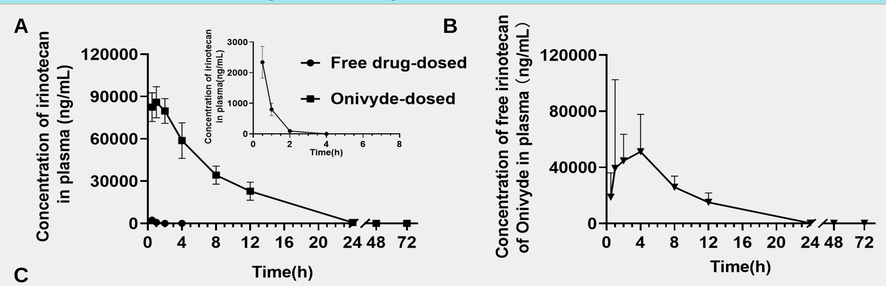


Figure 2. Cumulative release of irinotecan from free drug or Onivyde in PBS with different concentrations of NH_4HCO_3.

Pharmacokinetic study of Onivyde



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Group	Dose (mg/kg)	$AUC_{0-\infty}$ (h*μg/mL)	C_{max} (μg/mL)	$t_{1/2}$ (h)	Mean residence time (h)
Free drug	15	3.3±1.0	2.3±0.5	0.4±0.09	5.5±1.5
Onivyde	15	668.6±67.7	92.2±3.5	3.0±0.6	6.6±2.4

Figure 3. Pharmacokinetic study results. A. Concentration of irinotecan (determined as total drug) in plasma after administration of free drug and Onivyde in mice. B. Concentration of free irinotecan in plasma of Onivyde-dosed mice C. Main pharmacokinetic parameters (determined as total drug) calculated by Phoenix WinNonlin software. All values are presented as mean ± SD (n=4).

CONCLUSION(S)

- Quantification methods of irinotecan and lipids were established for analyzing critical quality attributes of Onivyde.
- Parameters of different batches of Onivyde including particle size, concentration of irinotecan, methoxy-terminated polyethylene glycol-distearoylphosphatidyl ethanolamine (DSPE-PEG2k), cholesterol and 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) are same as the label claim.
- NH_4HCO_3 promotes irinotecan release from Onivyde *in vitro*.
- Onivyde improves the area under curve ($AUC_{0-\infty}$) significantly compared to free drug.

ACKNOWLEDGMENT

This study is supported by United States (U.S.) Food and Drug Administration (FDA) Grant U18FD007054. The views and opinions presented here represent those of the speakers and should not be considered to represent advice or guidance on behalf of the U.S. Food and Drug Administration.

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