



Bioequivalence (BE), Safety and Efficacy Consideration for Injectable Complex Formulations

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Challenges for Bioequivalence (BE) Standards of Injectable Complex Formulations

- Plasma AUC and C_{max} may not be able to distinguish difference between generic and RLD injectable complex formulations
- Total drug plasma profiles can not distinguish drug-carrier delivered together or separately for injectable complex formulations
- Injectable complex formulations may have different intracellular uptake in cancer cells, which may not correlate with plasma profiles
- Injectable complex formulations have formulation specific tissue distribution, which may not correlate with plasma profiles, but correlate with efficacy and toxicity profiles

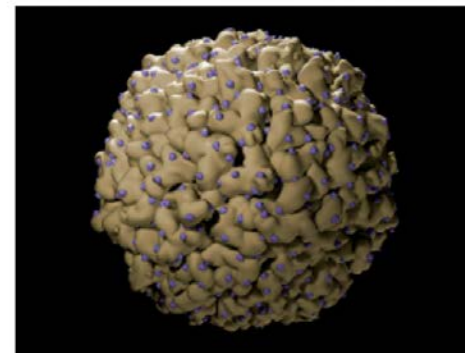
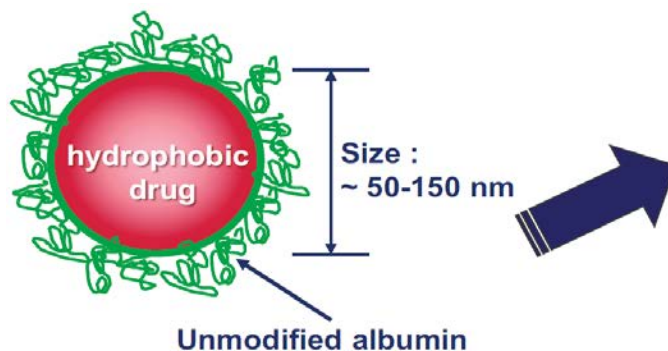
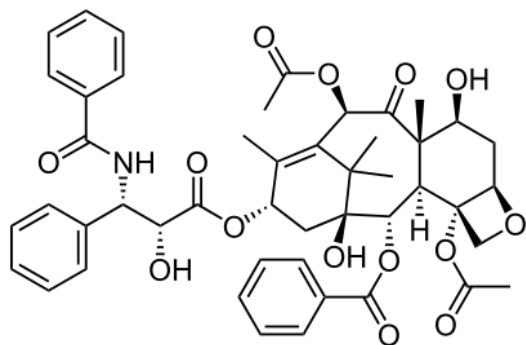
Albumin Paclitaxel Nanoparticle (Abraxane) Shows Different Clinical Efficacy From Paclitaxel --- not BE

- **Paclitaxel indications**

- Breast cancer, Ovarian cancer, non-small cell lung cancer, AIDS related sarcoma

- **Abraxane indications**

- Metastatic breast cancer
 - After failure of combination chemotherapy for metastatic disease or relapse with 6 months of adjuvant chemotherapy
- Locally advanced or metastatic non-small cell lung cancer
 - First line treatment in combination with carboplatin
- Metastatic pancreatic cancer
 - First line therapy in combination of gemcitabine



Plasma AUC and Cmax May not be Able to Distinguish Difference Between Generic and RLD Injectable Complex Formulations

AUC has no Difference between Abraxane and Taxol in Humans --- BE?

Total Drug Plasma Profiles Can not Distinguish Drug-carrier Delivered Together or Separately for Injectable Complex Formulations in Humans

Humans: cannot distinguish

Mice: can distinguish

Injectable Complex Formulations May Have Different Intracellular Uptake in Cancer cells, which May not Correlate With Plasma Profiles

Abraxane has higher intracellular uptake than poor HSA formulation

Injectable Complex Formulations Have Formulation Specific Tissue Distribution, Which May not Correlate with Plasma Profiles, but Correlate with Efficacy

Abraxane and mouse Abraxane have high accumulation in lung, pancreas, and breast fatpad, which correlates with clinical indication

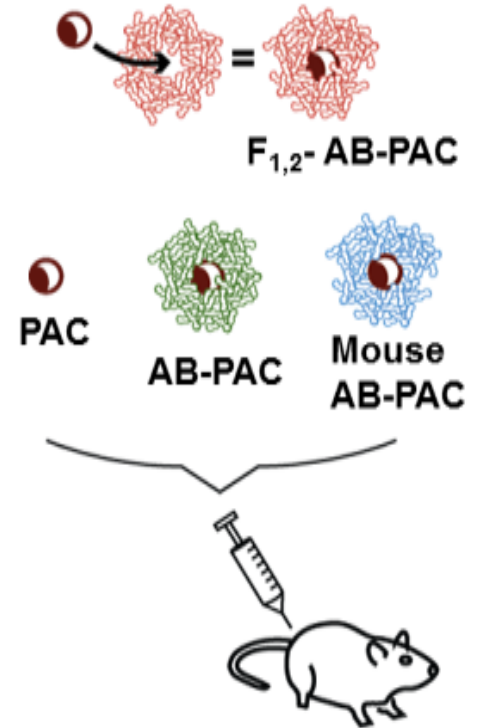
Proposed Studies for Injectable Complex Formulations

1. Formulate Different Quality of Albumin-Bound Paclitaxel

Pharmaceutical Equivalence

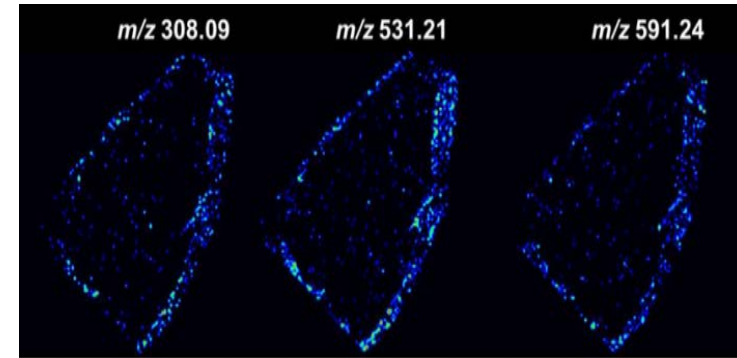
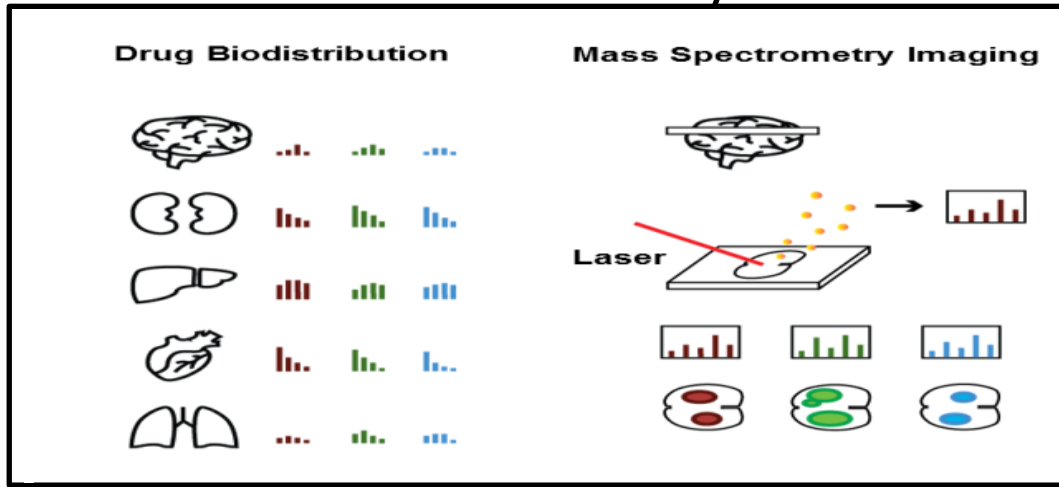
- particle size and morphology
- surface potential
- paclitaxel crystallinity
- fraction of free and bound paclitaxel or albumin in reconstituted suspension
- nature of bond between paclitaxel and albumin
- *in vitro* release kinetics
- albumin characterization

Formulation Development

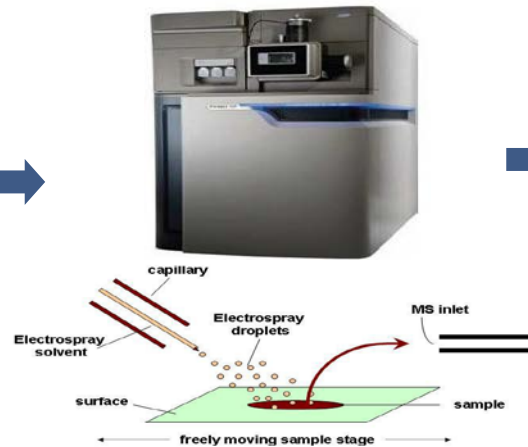


Proposed Studies for Injectable Complex Formulations

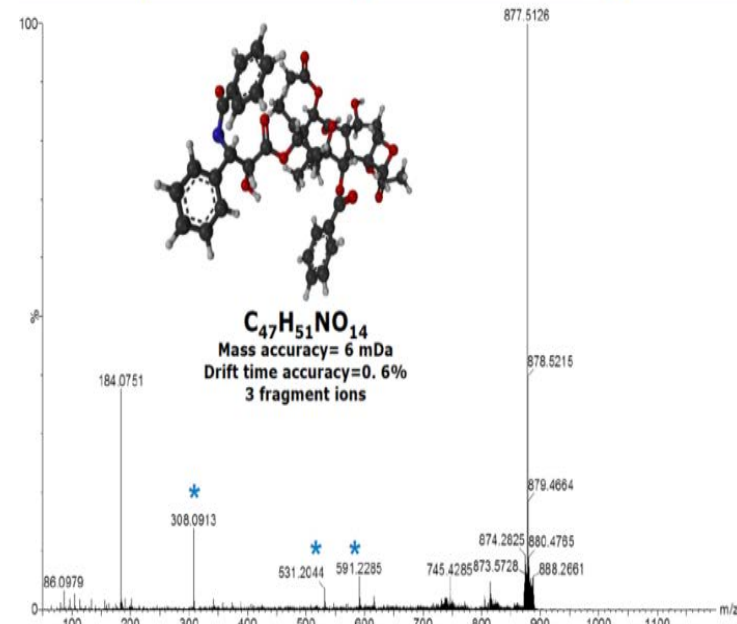
2. Study Tissue Distribution, Imaging, and Cellular Uptake of Different Quality of Albumin-Bound Paclitaxel



Frozen Tissue Section



Mass Spectrometry Imaging



Proposed Studies for Injectable Complex Formulations

3. PBPK Modeling of Drug Distribution and New BE Standard

