FRESENIUS KABI

Product Development of Intravenous Emulsion/Suspension for ANDA

In-vitro BE requirements per the PSGs

The views expressed in this discussion should not be interpreted as unique or specific to Fresenius Kabi.

Overview

01 General Key Product Development Considerations

02 Supportive Comparative Characterization

03 **In-Vitro BE Studies**

04 Recommended PSG clarifications

General Key Product Development Considerations

- Qualitatively (Q1) and Quantitatively (Q2) the same as reference listed drug (RLD). **Same microstructure (Q3 physicochemical properties) as the RLD**.
- Typical critical process parameters for manufacturing unit operations, e.g., nano-emulsions: oil phase, aqueous phase, crude emulsion, and fine emulsion.
- Extensive QbD studies required to establish design space for critical formulation and process parameters to ensure consistent product quality.
- **Unique scientific and regulatory challenges.**

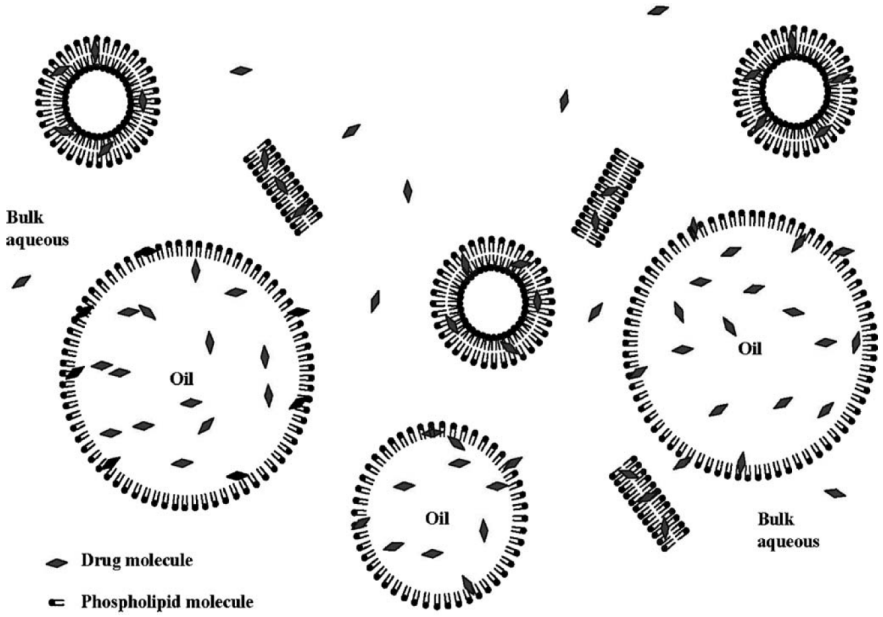

Fig. 5. Schematic illustration of emulsion infrastructure showing the different structures originated from the excess phospholipids and drug localization in various phases

Warisada et al., AAPS PharmSciTech 9(2), 2008.

Supportive Comparative Characterization (Q3)

- Minimum 3 batches each of Test (T) and Reference Standard (RS/RLD) products
- One unit from each batch
- Viscosity
- pH
- Zeta-potential
- Osmolality
- Globule/ Particle size distribution (GSD/PSD)
- Microstructural characteristics: Phase distribution of the API
  - Ultracentrifugation
  - Non-invasive (as-is): Two-dimensional (2D) ^{1}H diffusion ordered spectroscopy (DOSY) NMR to obtain oil GSDs and 1D NMR to understand microstructure (drug phase distribution)*

*Deyun Wang, Jiayi Li, Kang Chen, The AAPS Journal (2024) 26:78

In-Vitro BE Studies

Population Bioequivalence (PBE) for GSD/PSD

- Minimum 3 batches each of T and RS products.
- Full GSD profiles.
- Z-average and PDI OR D50 and SPAN [(D90-D10)/D50].
- PBE analysis with no less than 10 data sets from at least 3 batches each of T and RS products.
- BE based on 95% upper confidence bound.

Comparative IVRT

- Minimum 3 batches each of T and RS products.
- At least 12 units from each batch.
- BE based on comparative analysis of dissolution profiles using an appropriate statistical method, e.g., similarity factor (f2).

➢ Method development and validation to support both in-vitro BE studies.

Recommended PSG clarifications

- **In-vitro (characterization) studies vs In-vitro BE studies**
  - Q3 vs In-vitro BE
  - FDA draft Guidance for Industry: Handling and Retention of BA and BE Testing Samples (March 2024): "Not all in vitro studies are BE studies. Generally, product-specific guidances (PSGs) explicitly describe in vitro tests as either in vitro BE studies or in vitro characterization studies. However, reserve samples should be retained for all studies that the PSGs describe as in-vitro BE studies".
  - Consult with the FDA for any needed clarification at early stage of the product development to plan sample retention.
- **Batches vs Exhibit batches**

THANK YOU!

- This presentation was a joint effort with my colleague, **Deepali Vartak**.
- Fresenius Kabi US colleagues