Bio- Materials Analysis Technology Inc.

Doxil® _ *Doxorubicin HCl liposome injection*

- ***Observing the morphology and size distribution by electron microscopy***

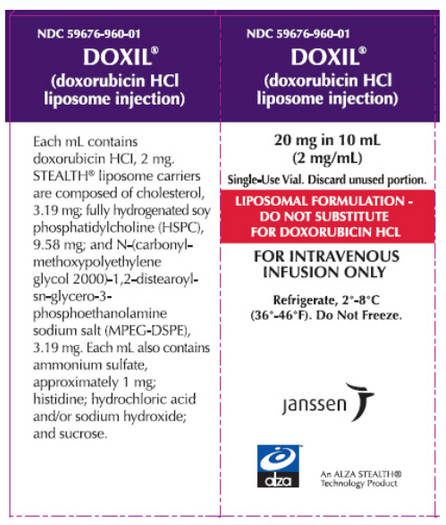
High quality electron microscopy analysis services for the regulatory requests!
Providing data support with physicochemical characterization for your products!!

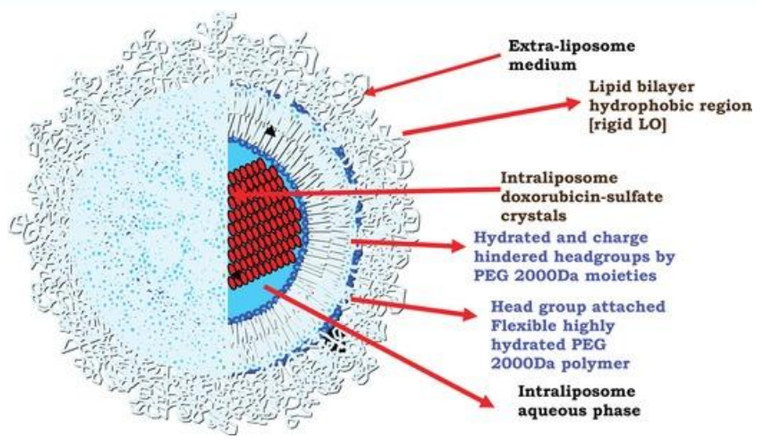
Does ANDA ≈ RLD?

**** US FDA 2010 _** Contains Nonbinding Recommendations "**Draft Guidance on Doxorubicin Hydrochloride".***

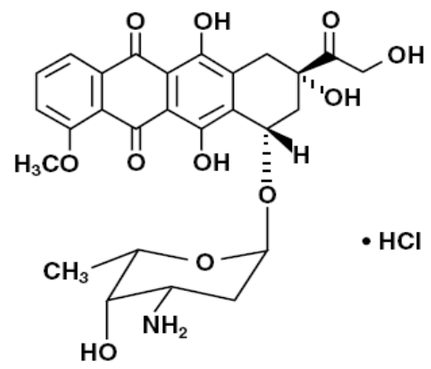
1. In vivo bioequivalence study.

2. In vitro liposome size distribution _ D_{10}, D_{50}, and D_{90}





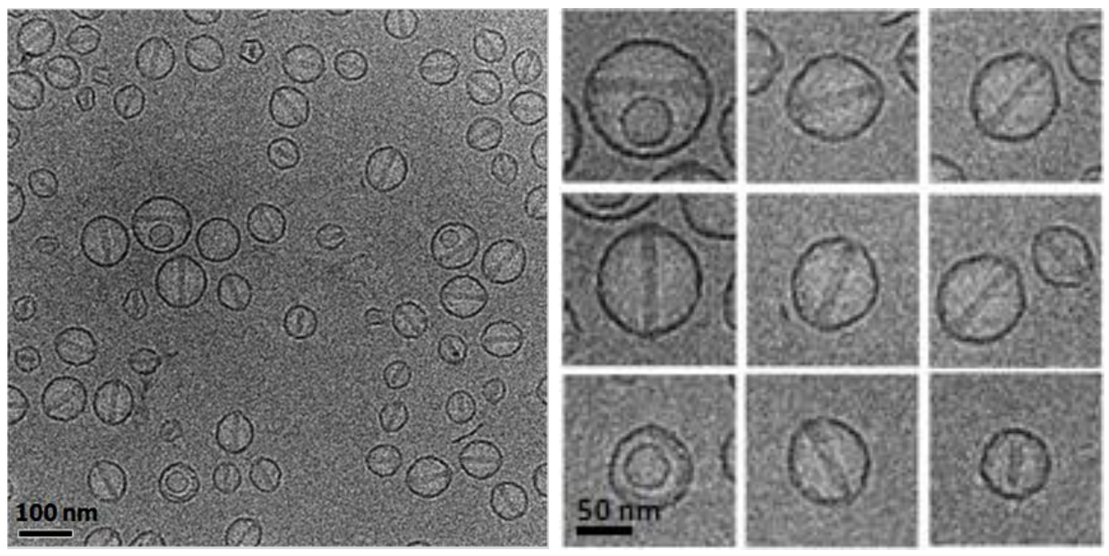
Excipient: MPEG-DSPE / Cholesterol



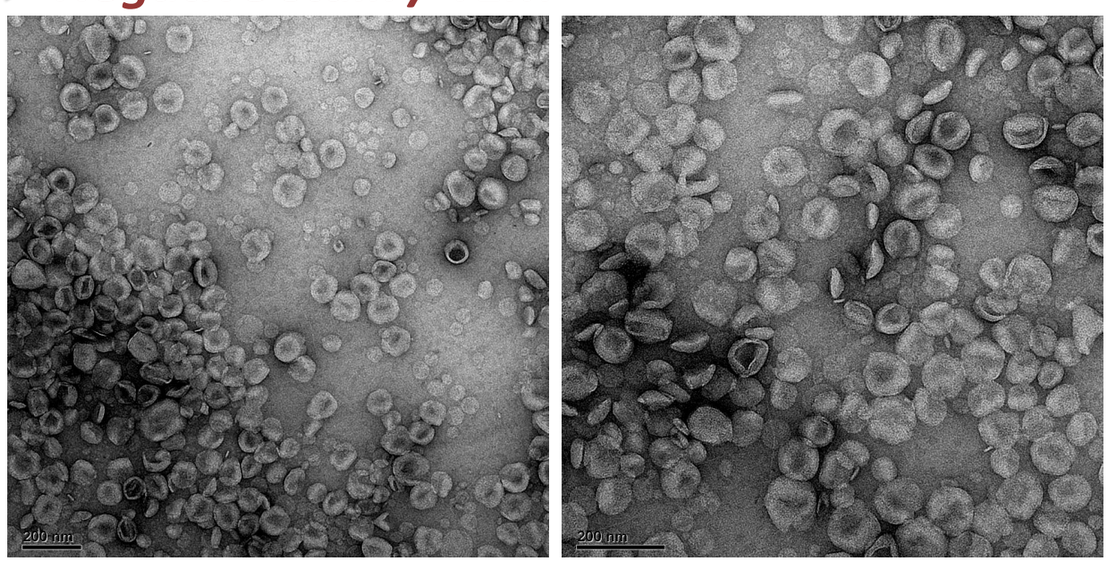
API: Doxorubicin

TEM _ *Morphology and Size distribution of ANDA vs. RLD*

➢ *Cryo-TEM*



➢ *Negative stain / TEM*

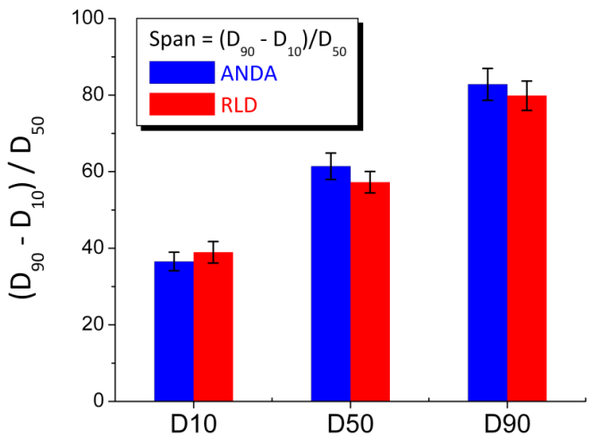


Three batches of ANDA vs. RLD

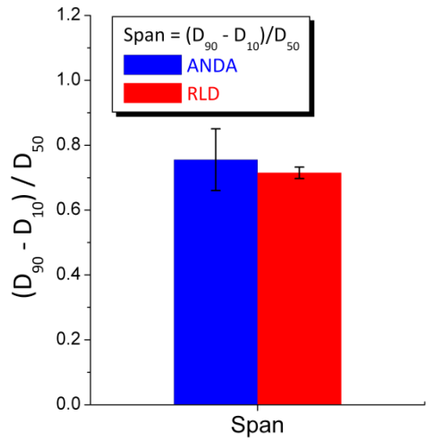
Name	D_{10} (nm)	D_{50} (nm)	D_{90} (nm)	Span	Number
A. ANDA					
Lot- #1	35.6	57.9	78.9	0.748	412
Lot- #2	39.3	64.8	82.3	0.664	508
Lot- #3	34.7	61.5	87.2	0.854	434
B. RLD					
Lot- #1	37.9	60.4	80.3	0.702	403
Lot- #2	42.1	56.2	83.4	0.735	411
Lot- #3	36.8	55.1	75.8	0.708	405

** Span = $(D_{90} - D_{10}) / D_{50}$*

D_{10}, D_{50}, and D_{90}



Span



* ***ANDA:*** Abbreviated New Drug Application, ***RLD:*** Reference Listed Drug

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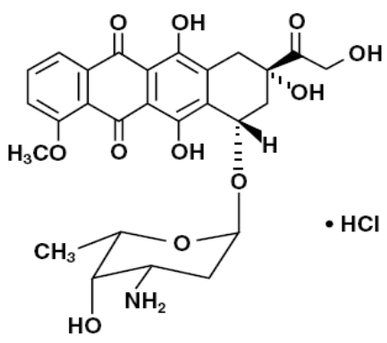
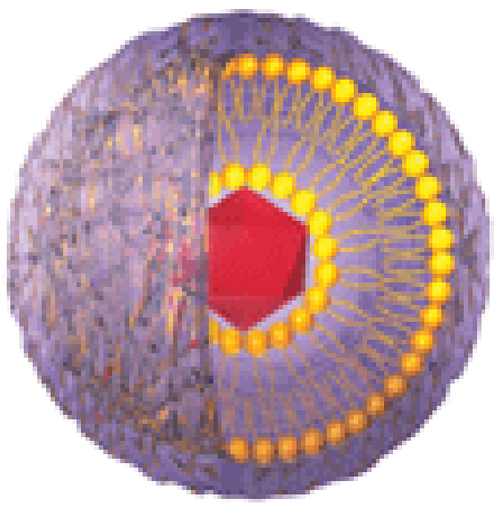
Bio- Materials Analysis Technology Inc.

Doxil® Analysis by Cryo-TEM

_ Analyzing drug encapsulation, lamellarity, and size distribution of liposomes

Does ANDA ≈ RLD?





Contains Nonbinding Recommendations

Draft Guidance on Doxorubicin Hydrochloride

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Doxorubicin hydrochloride

Dosage Form; Route: Injectable, liposome; Injection

Recommended Studies: Two studies

In Vitro Study:

2. Type of study: Liposome Size Distribution

   Design: in vitro bioequivalence study on at least three lots of both test and reference products

   Parameters to measure: D10, D50, D90

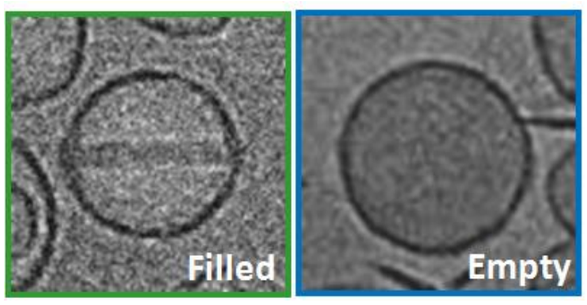
   Bioequivalence based on (95% upper confidence bound): D50 and SPAN [(i.e. (D90-D10)/D50] or polydispersity index using the population bioequivalence (PBE) approach.

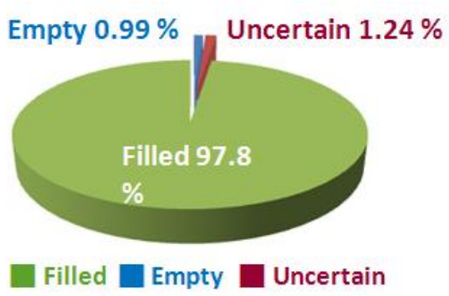
   Refer to the product-specific recommendation for budesonide inhalation suspension for additional information regarding PBE analysis procedures (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM319977.pdf)

Dissolution test method and sampling times: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods Web site, available to the public at the following location: http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).

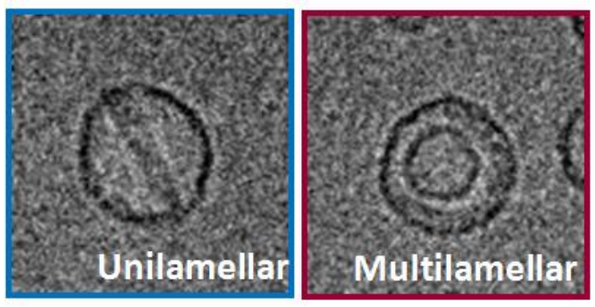
Recommended Feb 2010; Revised Nov 2013, Dec 2014, Apr 2017

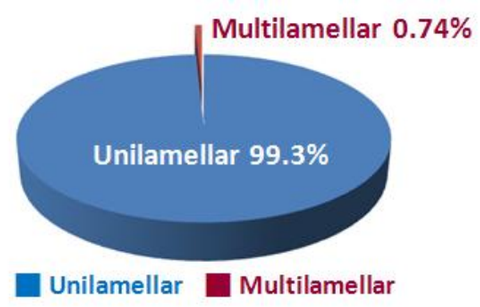
Drug encapsulation



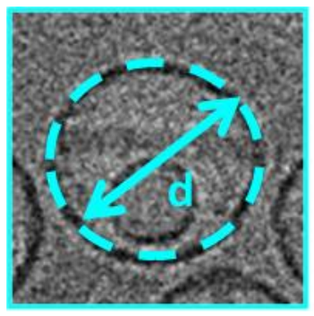


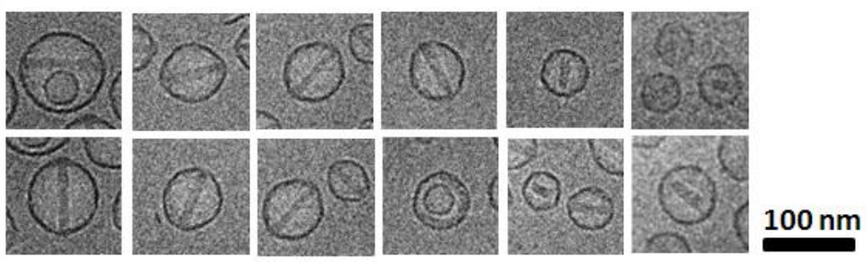
Lamellarity





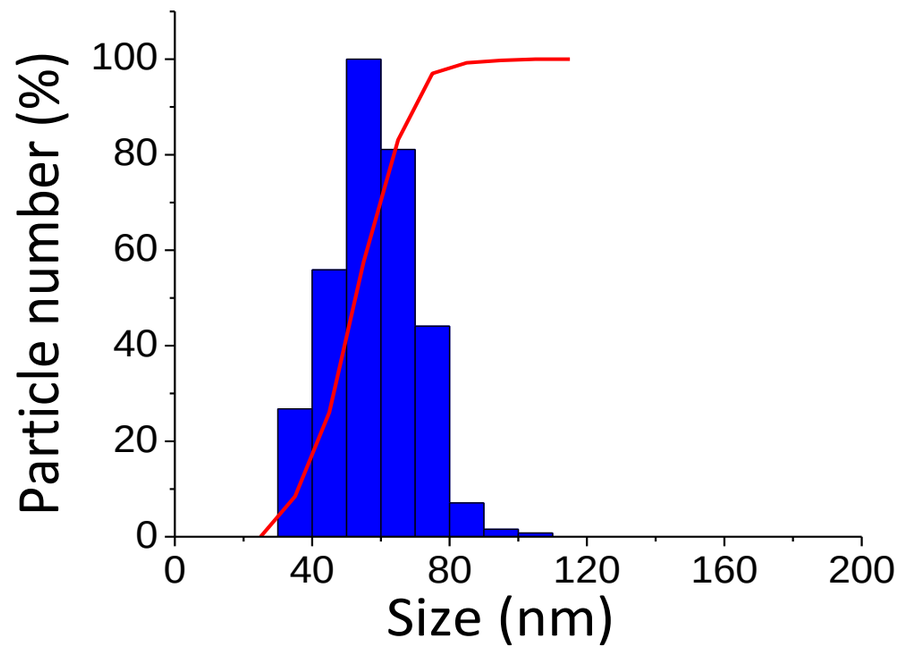
TEM _ Size/size distribution (D_{10}, D_{50}, D_{90})





Parameter	Size (nm)
D 10	36.8
D 50	55.1
D 90	75.8
Span: (D_{90} - D_{10}) / D_{50}	0.708

- ***Constituted particle:*** Original individual particle with defined physical boundaries.
- Total calculated particle n = 405



*** D50**, the median diameter, where half of the population lie below this value. ***D10***, the diameter of 10% population lies below this value. ***D90***, the diameter of 90% population lies below this value.

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