Advantages and Challenges in Implementing New Analytical Methods that Arise from Regulatory Science Initiatives

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Outline

- GDUFA research science initiatives on new analytical methods:
  - A.1: Characterization of complex active and inactive ingredients
  - A.2: Characterization of complex particulate systems
- Examples of new analytical methods and impact on generic drug development and review
  - ^{1}H and ^{13}C NMR to characterize polymer structure
  - MDRS and Raman Microscopy to characterize particle formulations
  - Capillary electrophoresis and isotope to characterize free and encapsulated drug
- Routes to engage FDA on new analytical methods

FY2019 GDUFA Science Initiatives

15 research priorities to accelerate access to generic drug products were identified at the May 24, 2018 GDUFA Public Workshop.

Two were on new analytical methods:

A.1. Improve advanced analytics for characterization of chemical compositions, molecular structures and distributions in complex active ingredients

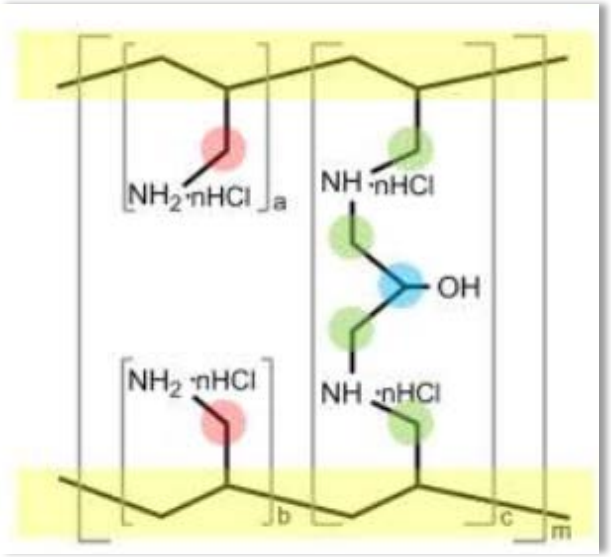
A.2. Improve particle size, shape, and surface characterization to support demonstration of therapeutic equivalence of suspended and colloidal drug products

A.1. Characterizing Complex Active and Inactive Ingredients

- A generic drug product needs to contain identical amounts of the identical active ingredient(s) as the reference listed drug (RLD).
- New analytical methods may be used to characterize and compare sameness of complex ingredients such as,
  - heterogenous mixture of moieties:
    - e.g., conjugated estrogens, pentosan polysulfate, glatiramer acetate
  - heterogenous chemical structures:
    - e.g., sevelamer, colesevelam, patiromer, poly(lactide-co-glycolide)

A.1. Case Study: ^{13}C-NMR of Sevelamer HCl & Sevelamer Carbonate

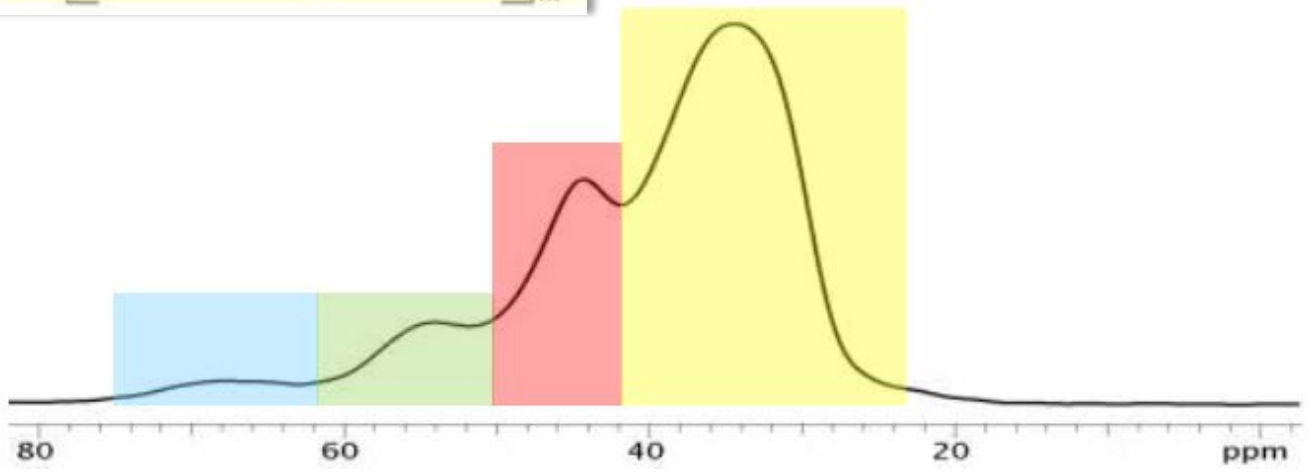
- Renagel® (sevelamer HCl) & Renvela®(sevelamer carbonate)
- Polyallylamine cross-linked with epichlorohydrin
- Phosphate binder indicated to control serum phosphorus in patients with chronic kidney disease on dialysis
- Regulatory Timeline:
  - 2008: Initial PSG (BE)
  - 2009, 2010, 2011: PSG revisions (BE)
  - 2012 – 2014: FDA internal studies
  - 2015, 2016: PSG revision (API + BE)
  - 2017: 1st sevelamer carbonate powder approval
  - 2017: 1st sevelamer carbonate tablets approval
  - 2019: Nine approved ANDAs



^{13}C-NMR

Characterization of Polymer Structure

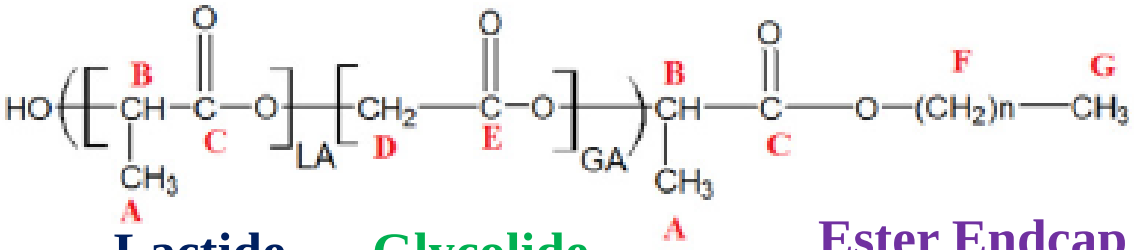
Relative peak areas are proportional to the number of carbon atoms in each electronic environment



J. Pharm. Sci. 101 (2012), 2681-2685

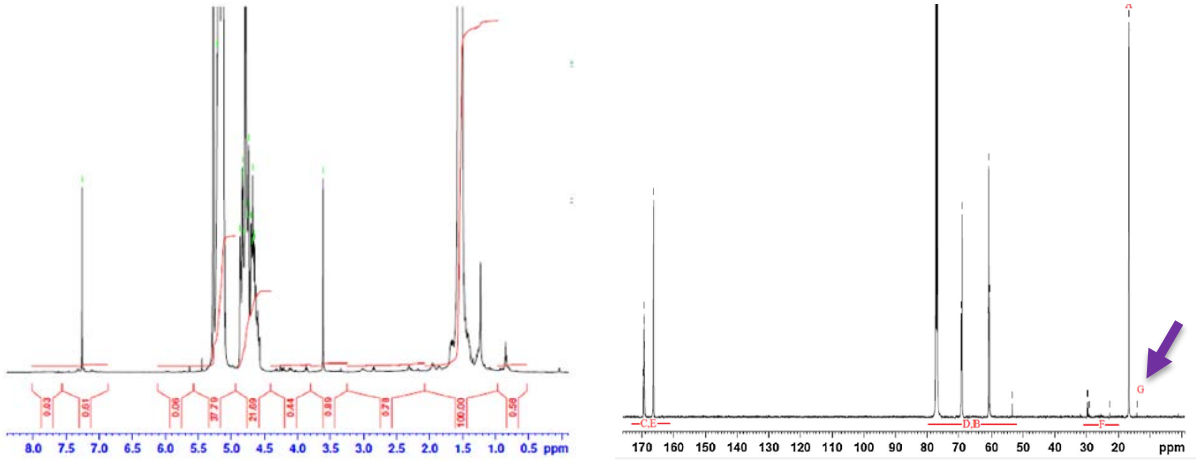
A.1. Case Study: ^{1}H and ^{13}C-NMR of Poly(lactide-co-glycolide) (PLGA)

- PLGA is a biodegradable copolymer excipient used to enhance drug release.
- Raito of lactide to glycolide monomer units, polymer molecular weight, and end group chemistry can affect polymer degradation rate.
- ~19 approved products contain PLGA:
  - Lupron Depot, Zoladex Depot, Sandostatin LAR, Atridox, Nutropin Depot, Trelstar, Somatuline Depot, Arestin, Eligard, Risperidal Consta, Vivitrol, Ozurdex, Propel, Bydureon, Lupaneta Pack, Signifor LAR, Zilretta, Sublocade, Perseris



^{1}H-NMR: **L**:**G** Ratio

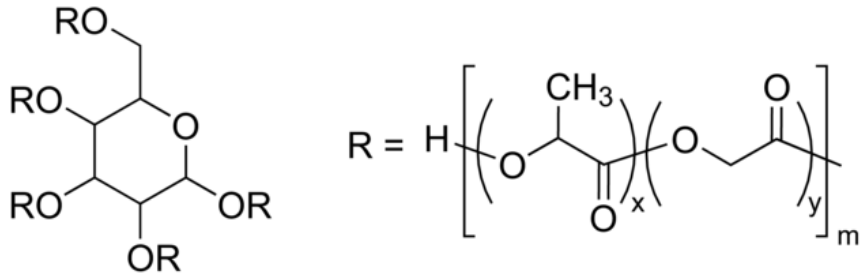
^{13}C-NMR: End Group



J. Garner, et. Al International Journal of Pharmaceutics 495 (2015) 87–92

A.1. Case Study: Triple Detection SEC/GPC of Linear and Star PLGAs

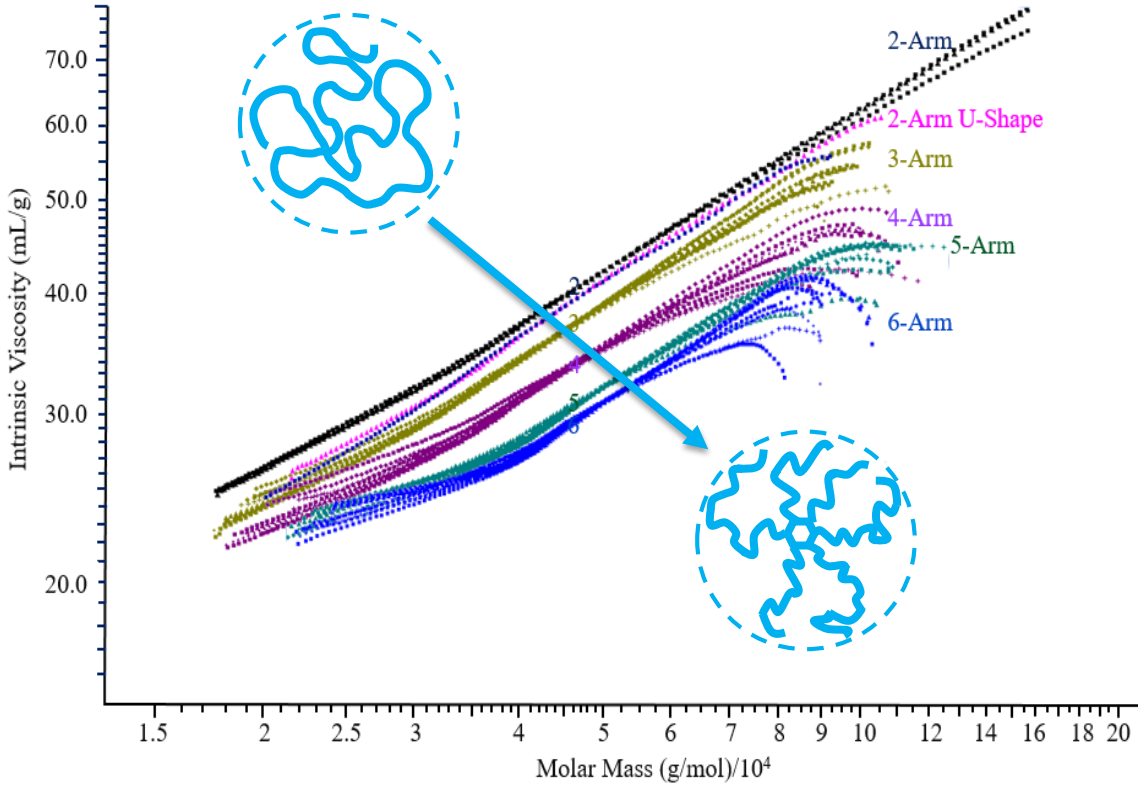
- Glucose-star-PLGA is a biodegradable copolymer excipient



- Number and size of polymer ‘arms’ can affect polymer properties including viscosity and degradation rate.
- Approved products containing non-linear PLGA: Sandostatin LAR

Triple Detection SEC/GPC

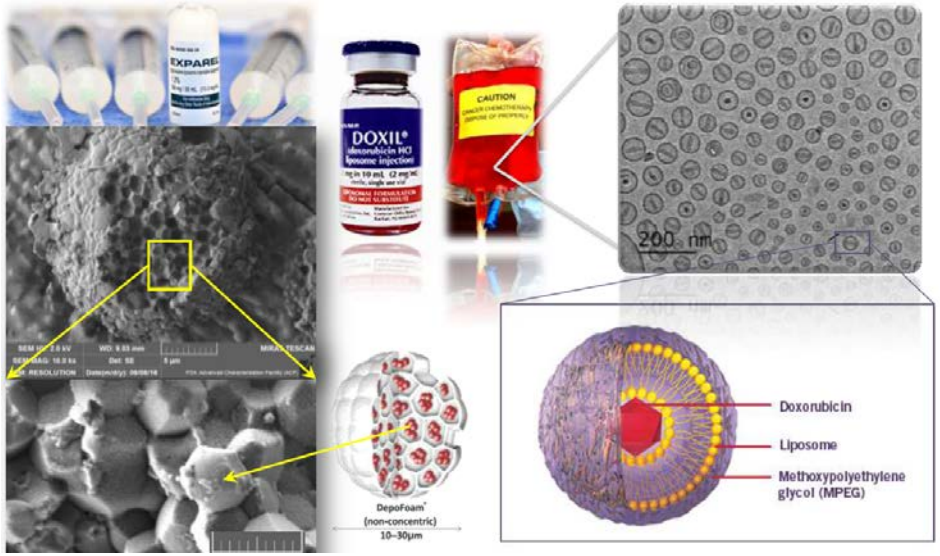
Combines light scattering, viscometer, and refractive index (RI) detectors to characterize polymer size and structure



A.2. Characterizing Particle Size, Shape, and Surface

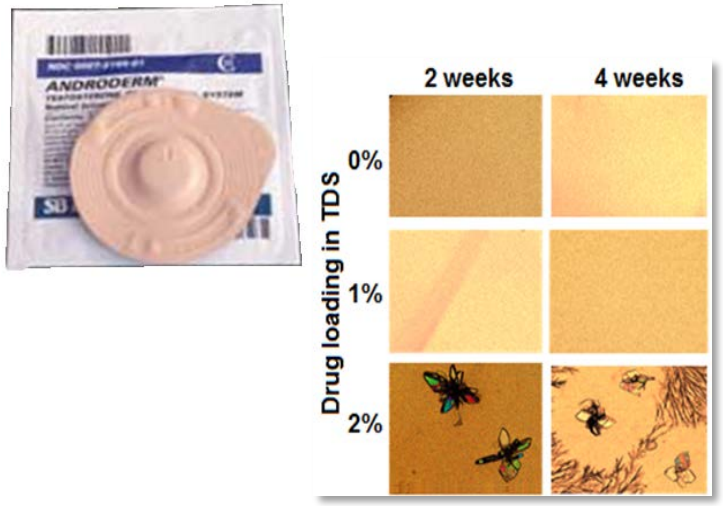
- Performance and quality of drug products can depend on the properties of particles in the formulation.
- New methods may provide a more accurate characterize of complex particles and particle mixtures, which can support equivalence determination.

Liposome Structures

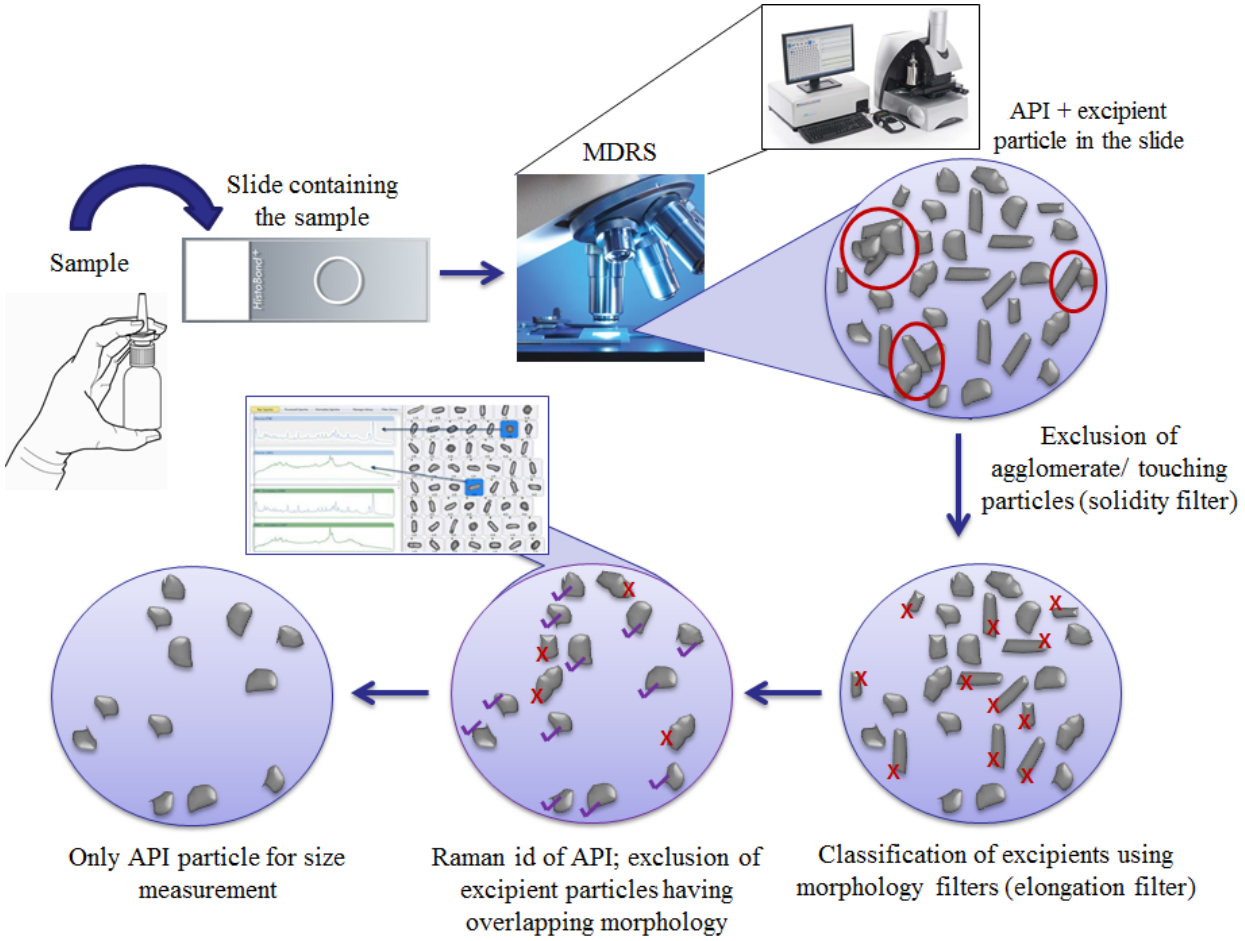


Non-spherical & Mixed Particles

Drug Crystal Formation



A.2. Case Study: MDRS of Mixed API and Excipient Particulates

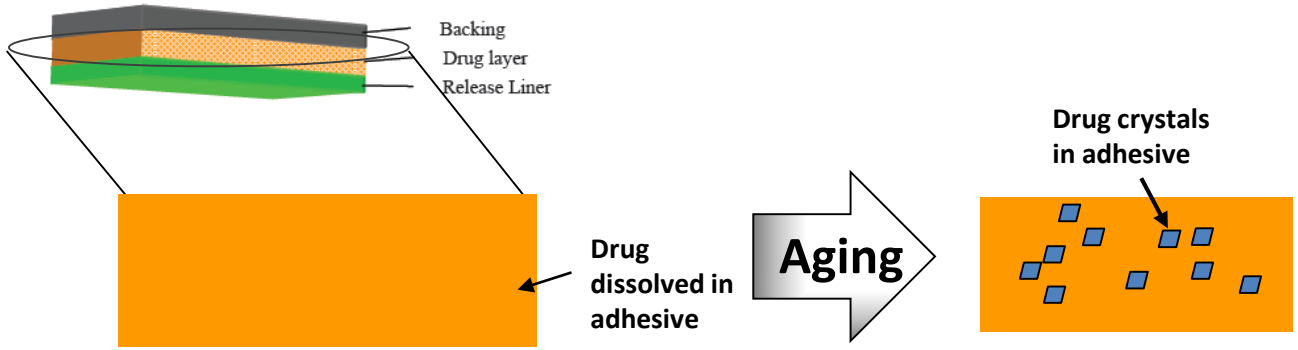


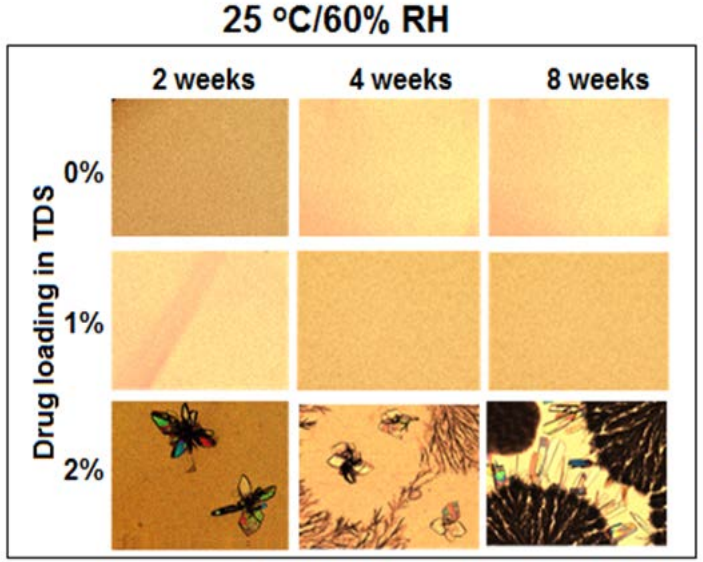
MDRS: Morphologically-Directed Raman Spectroscopy:

Distinguish chemically different particles and measure size and morphology information.

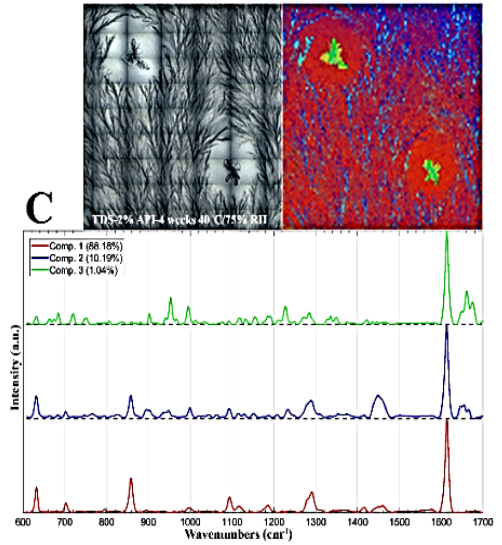
MDRS data supported first generic approval for mometasone furoate nasal suspension

A.2. Case Study: Raman Microscopy of Drug Crystallization in Transdermal Systems



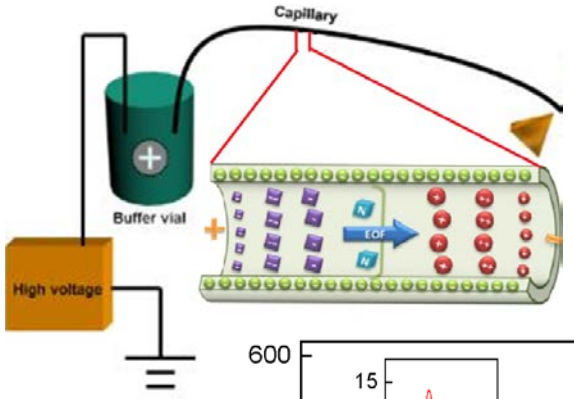


- Drug crystals can form in TDS products affecting drug release, peel adhesion, and cohesive strength.
- Optical and Raman imaging can monitor drug crystal formation to help guide drug product development, manufacturing process conditions, and assessment of appropriate product shelf-life.

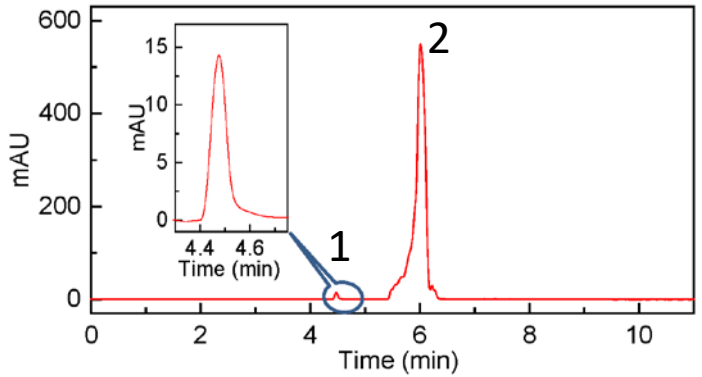


New Methods to Improve Quantification of Encapsulated and Unencapsulated Drug

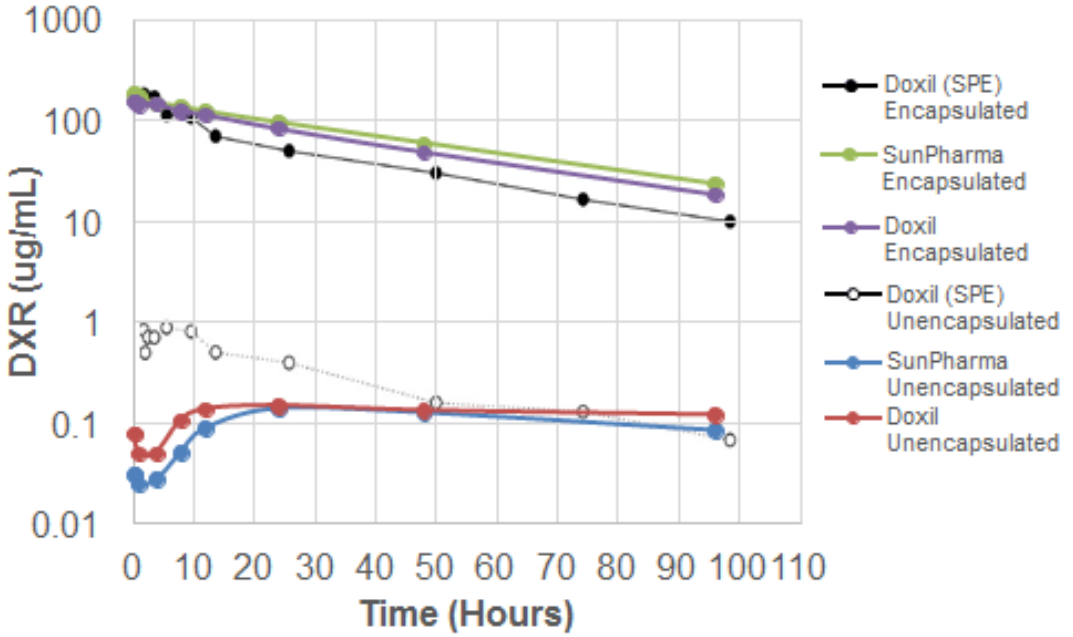
- ## Capillary Electrophoresis
  - Rapid separation (10min) and direct quantification of unencapsulated drug in liposome formulations.



1. Unencapsulated Dox
2. Liposome associated Dox



- ## Doped Stable Isotope Drug
  - Isotopically labeled drug (D*) method indicated that unencapsulated liposomal doxorubicin is lower than measured by solid phase extraction.



Siyam M. Ansar, et. al.. International Journal of Pharmaceutics 2018, 549:109-114

J Control Release, 2015, 220(Pt A):169-74.

Engaging FDA When Using a New Analytical Method

FDA is committed to supporting the latest scientific methods and tools to evaluate generic drug equivalence and for industry to efficiently develop new generic products.

Utilizing a New Method in an ANDA

Discuss new method with FDA via:

- **Pre-ANDA product development meeting**
  - Discuss technical aspects of the method and study design proposed/preliminary data to support generic product development
- **Pre-ANDA pre-submission meeting**
  - Discuss technical aspects of data generated on ANDA batches and rationale/justification how the data supports ANDA approval
  - Guidance for Industry: *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*

Engaging FDA on Developing a New Analytical Method

Developing a New Method

Propose research initiative or project on a new analytical method and/or approach to solve a complex generic drug issue:

- **GDUFA Public Workshop (here / now)**
  - Propose research initiative for OGD to undertake in FY20
  - Regulations.gov, Open Docket FDA-2017-N-6644-0010
- **Broad Agency Agreement (BAA) applications**
  - Propose a research project to undertake that you believe will provide FDA with new tools / understanding to of generic drug development and/or approval.
  - FedBizOpps.gov, Solicitation FDABAA-19-00123
- **Grant Opportunities**
  - Respond to FDA's request for application (RFA) to develop and conduct a specific research project.
  - RFAs posted on NIH Grants & Funding and Generic Drugs Collaboration Opportunities websites

Conclusions

- FDA is committed to supporting the latest scientific methods and tools to evaluate generic drug equivalence and for industry to efficiently develop new generic products.
- FY19 GDUFA research has focused on developing and evaluating new methods for characterizing
  - A.1. Complex ingredients
  - A.2. Complex particle formulations
- Public and industry input directs GDUFA research
- Public, industry, and prospective ANDA applicants using a new analytical method can engage FDA via research project proposals and pre-ANDA meetings.

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