U.S. FOOD & DRUG ADMINISTRATION

How to Resolve Current Challenges with ANDAs for Topical Products: Common Deficiencies-OPQ Considerations

Complex Generic Product Development Workshop
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Disclaimer

This presentation reflects only the views of the author and should not be construed to represent FDA's views or policies.

Reminders for All Topical DPs

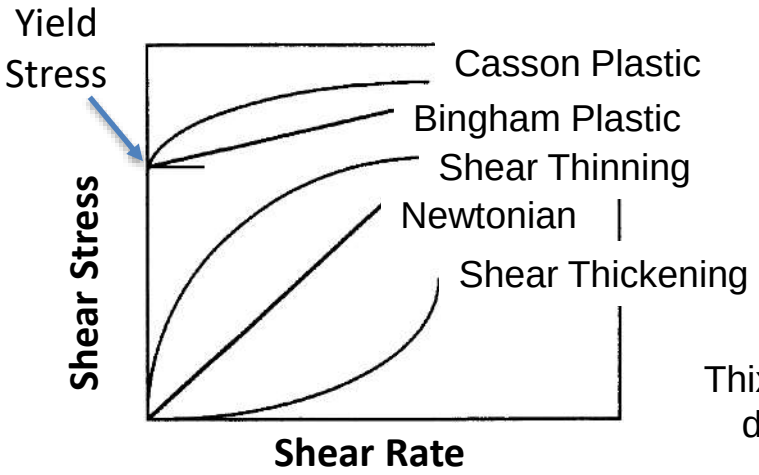
Module	Recommended Items
S.4, P.5	• Tests at retest indicated on specifications • Analytical methods, validation/verification reports, transfer reports if appropriate, name and address of test facility on each report • Forced degradation data with mass balances
S.5, P.6	COAs or analysis for all reference standards (all identified related substances and residual solvents)
P.1	Detailed description of DP, e.g. no phase separation, homogeneous, free of foreign matter, free of lumps, package appearance
P.7	• Horizontal and vertical (cap down) configurations on stability • Thermal cycling and freeze thaw data

1. Check for product-specific guidance
(https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm)
2. Critical functional excipient?
Include assay in specifications, justify range, provide analytical information

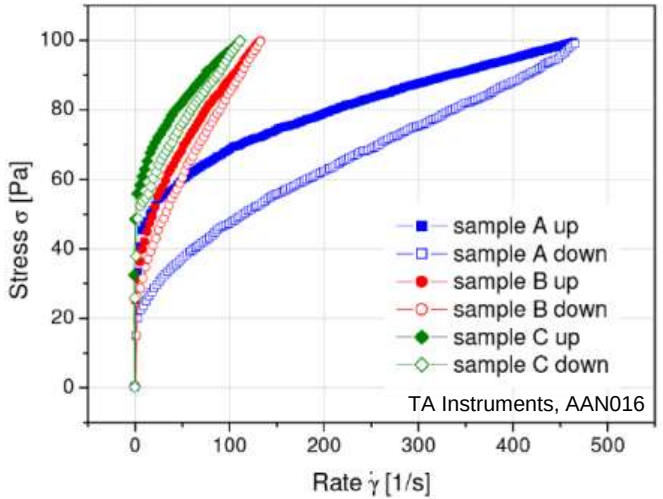
Rheology Studies

What kind of fluid is your DP?

Loading and Unloading Curves, Yield Stress for Plastic Fluids



Thixotropic (time dependent)?



Provide? Comparative data to RLD, loading and unloading (up/down) curves over attainable shear rates, i.e. shear stress (or viscosity) vs. shear rate until low or high plateaus identified

Why? Demonstrate similarity to RLD

Tips:

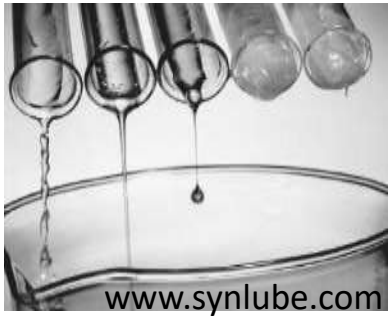
- Use exact same measurement method
- Generic and RLD data on same plot is helpful
- Explain any shifts or differences compared to RLD and implications for DP

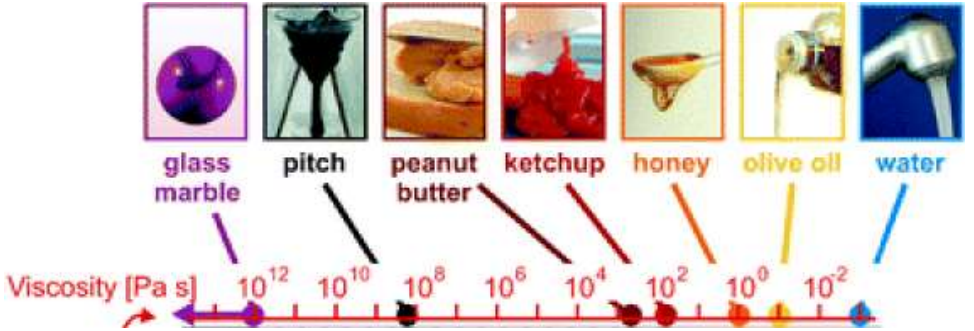
Rheology provides evidence of microstructural similarity

Viscosity Study

Common rheological attribute in DP specifications

Viscosity or Apparent Viscosity: Measure of flowability





Koop et al, Phys Chem Phys, 2011

Provide? Comparative data to RLD (multiple measurements), data table with values, analytical method information

Why? Demonstrate similarity to RLD, justify specification range

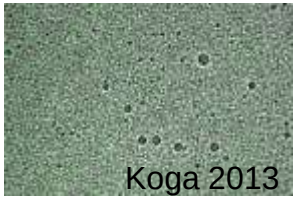
Tips:

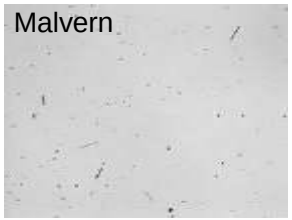
- Use exact same measurement method
- Reduce variability due to method so that any real trends are observable
- Typical range is ≤ 1 order of magnitude

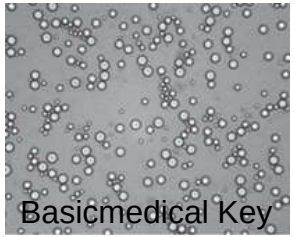
API Particle and Globule Studies

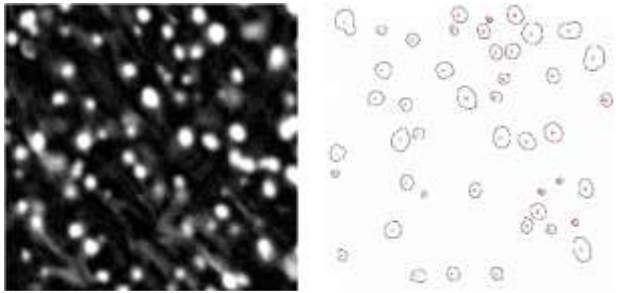
Common attributes in DP specifications for solid APIs and emulsions

Particle/Globule Size Distribution

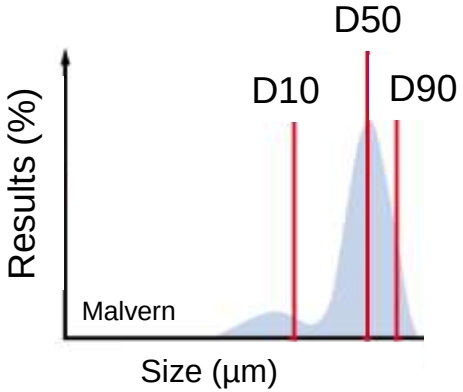








Underwood and Gorham NIST SP 1200-22



Provide? Comparative data to RLD, photomicrographs, data tables, particle size distribution plots, analytical method information, calibration, resolution, sample size

Why? Demonstrate similarity to RLD, justify specification range

Meaningful metrics

Tips:

- Technique—Appropriate for particle and sample type, validated to demonstrate suitability
- Photomicrographs—Same magnification when comparing, different magnification to highlight attributes of different scale, scale bars, labels, raw and thresholded images
- Results—Define measure, explain why it is appropriate and representative of sample

Tips to Improve Submission Quality

- Label figures: what it is, sample information
- Identify age of sample at time of testing (i.e. how close to expiry); try for age-matched comparisons
- Provide complete test reports, especially when asked
- Explain what your data mean
- Justify ranges chosen for specifications and processing conditions
- If trends are apparent on stability, discuss them and what they mean for DP quality

Resources: Part 1

Literature Articles

- A. Srinivasan and R. Iser, “Common Deficiencies in Abbreviated New Drug Applications (Part 1): Drug Substance”, Pharm. Technol. 34(1), 50-59 (2010)
- A. Srinivasan, R. Iser and D. Gill, “Common Deficiencies in Abbreviated New Drug Applications (Part 2): Description, Composition, and Excipients”, Pharm. Technol. 34(8), 45-51 (2010)
- A. Srinivasan, R. Iser and D. Gill, “Common Deficiencies in Abbreviated New Drug Applications (Part 3): Control of Drug Product and Stability”, Pharm. Technol. 35(2), 58-67 (2011)
- A. Srinivasan and R. Iser, “Common Deficiencies in Abbreviated New Drug Applications (Part 4): Manufacture and Container Closure”, Pharm. Technol. 35(4), 62-68 (2011)
- R.K. Chang, P. Simamora, B. Cai, A. Raw and S. Rosencrance, “Common Deficiencies in ANDAs for Dermatologic Drug Products”, Pharm. Tech., 68-76, September 2016
- R.K. Chang, A. Raw, R. Lionburger and L. Yu, “Generic Development of Topical Dermatologic Products: Formulation Development, Process Development and Testing of Topical Dermatologic Products”, AAPS Journal, 16(1), 41-52 (2013)
- R.K. Chang, A. Raw, R. Lionburger and L. Yu, “Generic Development of Topical Dermatologic Products, Part II: Quality by Design for Topical Semisolid Products”, AAPS Journal, 15(3), 674-83, (2013)

Presentations

- P. Simamora, “In Vitro Bioequivalence Data for a Topical Product: Chemistry Review Perspective”, FDA Public Workshop on Topical Dermatological Generic Drug Products: Overcoming Barrier to Development and Improving Patient Access, October 20, 2017, https://www.fda.gov/drugs/newsevents/ucm557252.htm

Resources: Part 2

Standards

- USP <912> Rotational Rheometer Methods
- USP <429> Light Diffraction Measurement of Particle Size
- USP <776> Optical Microscopy
- ISO 13322-1 and -2 Particle Size Analysis—Image Analysis Methods—Part 1: Static Image Analysis Methods and Part 2: Dynamic Image Analysis Methods
- ISO 9276 Series, Representation of Results of Particle Size Analysis

Guidance Documents

- Drug Guidance Webpage (https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm)
- ANDA Submissions—Refuse-to-Receive Standards Rev. 2 (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM370352.pdf)

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