U.S. FOOD & DRUG ADMINISTRATION

FDA's Perspective on QC Dissolution Testing for Oral Drug Products Containing ASD

Kevin Wei, Ph.D.
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality
CDER, US-FDA

FDA-MCERSI Workshop
May 24th, 2023
University of Maryland, Baltimore

Disclaimer

This presentation reflects personal opinions of the speaker and should not be construed to represent any Agency determination or policy. The mention of commercial products, their sources or their use in connection with material reported herein is not to be construed as either an actual or implied endorsement of such products by the Department of Health and Human Services.

Outline

- Biopharmaceutics
- Dissolution testing
- Amorphous Solid Dispersion (ASD)
  - Quality considerations
  - Case study
  - Summary and reminders

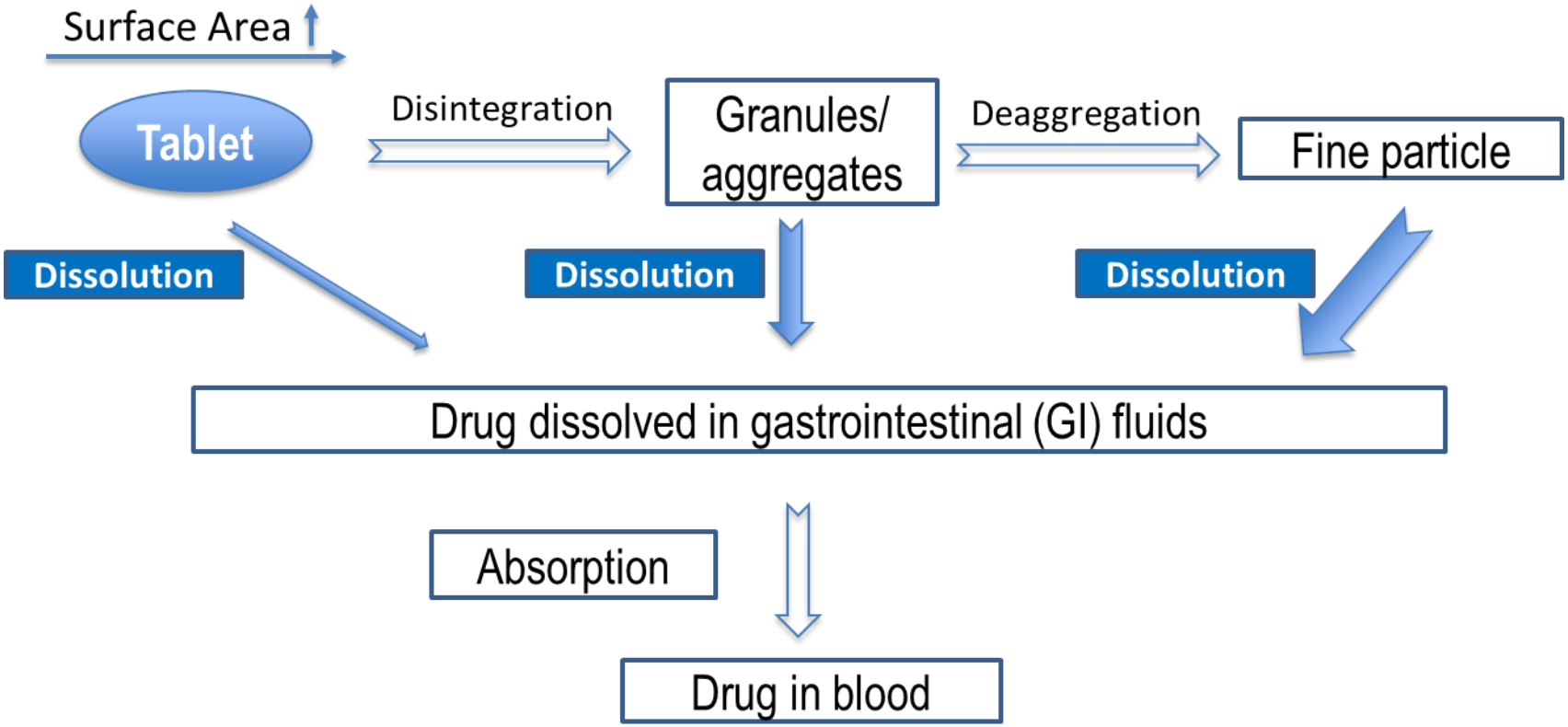
Biopharmaceutics

- The study* of the physical and chemical properties of a drug, its dosage form, and formulation, as related to the onset, duration, and intensity of drug action.
- An important discipline bridging the drug product's quality to its in vivo clinical performance.
- **Tools (oral)**: disintegration, dissolution (quality control (QC), biorelevant*), BA/BE studies, IVIVC/R, PBBM, etc.
- **Ultimate Goal**: each drug product can consistently deliver its clinical performance as described in its label, in terms of safety and efficacy.

*FDA draft Guidance for Industry: *The Use of Physiologically Based Pharmacokinetic Analyses — Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls* (2020)

Dissolution

- Dissolution is a process or action of a solid dissolving into a solution.
- Dissolution is a prerequisite to drug absorption and in vivo performance for almost all solid oral drugs.



Dissolution Test (Regulatory Submission)

- **Quality Control (QC) (ICH Q6A):**
  - Drug product quality over shelf life
  - Batch to batch consistency

- **Bridging:**
  - Minor/moderate CMC changes during product's development and life cycle management (*as per SUPAC*)

- **BA/BE Waiver (Biowaiver):**
  - Additional strength(s)
  - BCS-Class 1/3-based

Amorphous Solid Dispersion (ASD)

- ASD is a solid solution in which drug molecules are dispersed in an amorphous form within an excipient matrix.

- ASD is used to convert poorly water-soluble crystalline drug substance into its amorphous form with higher solubility.

- Purpose of using ASD formulation:
  - Bioavailability (supersaturation/enhanced dissolution and absorption)
  - Non-Bioavailability: stability, content uniformity, taste masking etc.

Biopharmaceutics Risk Assessment

- Biopharmaceutics Risk Assessment* is a regulatory framework for us to determine how much bioavailability risk associated with the drug product and decide how much effort should be made to mitigate the risk.

- Initial Biopharmaceutics Risk (ASD-based products): **Medium**

- Risk Mitigation: discriminating ability of dissolution test towards **Critical Bioavailability Attributes (CBAs)**
  - Formulation or process attributes which are expected to critically impact the bioavailability (absorption rate and extend) of a drug product.
  - Critical material attributes (e.g., API particle size, polymorphic form etc.); critical formulation variables (CFVs) (e.g., release rate controlling excipients); critical process parameters (CPPs) (e.g., granule particle size, coating parameters and compression force etc.);

*Dr. Min Li's presentation *"Biopharmaceutics Risk Assessment to Guide Dissolution Method Development for Solid Oral Dosage Forms"* - YouTube

Thermodynamic Stability

The most significant quality concern: lack of thermodynamic stability

- High tendency for crystallization due to higher free energy
- Crystallization during manufacturing process and storage (shelf-life)

Impacts on clinical performance: inadequate bioavailability and sub-therapeutic dosing →**High risk**

Risk mitigation: adequate controls for crystalline content

- Discriminating ability demonstrated by dissolution profiles as a function of crystalline content (e.g., target product spiked with 5%, 8%,10%, 15%, 20% crystalline drug substance)
- Orthogonal analytical methods: XRD, Raman, NIR, NMR, etc.

Critical Formulation Variables

Polymer is the most important excipient of ASD:

- Attain/maintain supersaturation
- Maintain amorphous solid-state
- Impact dissolution rate

Low polymer level (high drug/polymer ratio):

- Lead to crystallization within ASD
- Fail to achieve supersaturation
- Impair physical stability

Other excipients may also impact dissolution and bioavailability

→ **To be evaluated:** the level (and grade) of polymer, disintegrant, surfactant, etc.

Critical Process Parameters

- ASD preparation :
  - Solvent-based methods: Spray Drying (SD), Co-precipitation
  - Melting-based methods: Hot Melt Extrusion (HME)

- Downstream process: milling/sieving, granulation, encapsulation/tableting etc.

Process parameters that may impact dissolution: → **To be evaluated:**

- ASD Particle Size/Particle Size Distribution
- Compression force (Tableting)

Case Study

- Immediate Release (IR) Tacrolimus Capsules

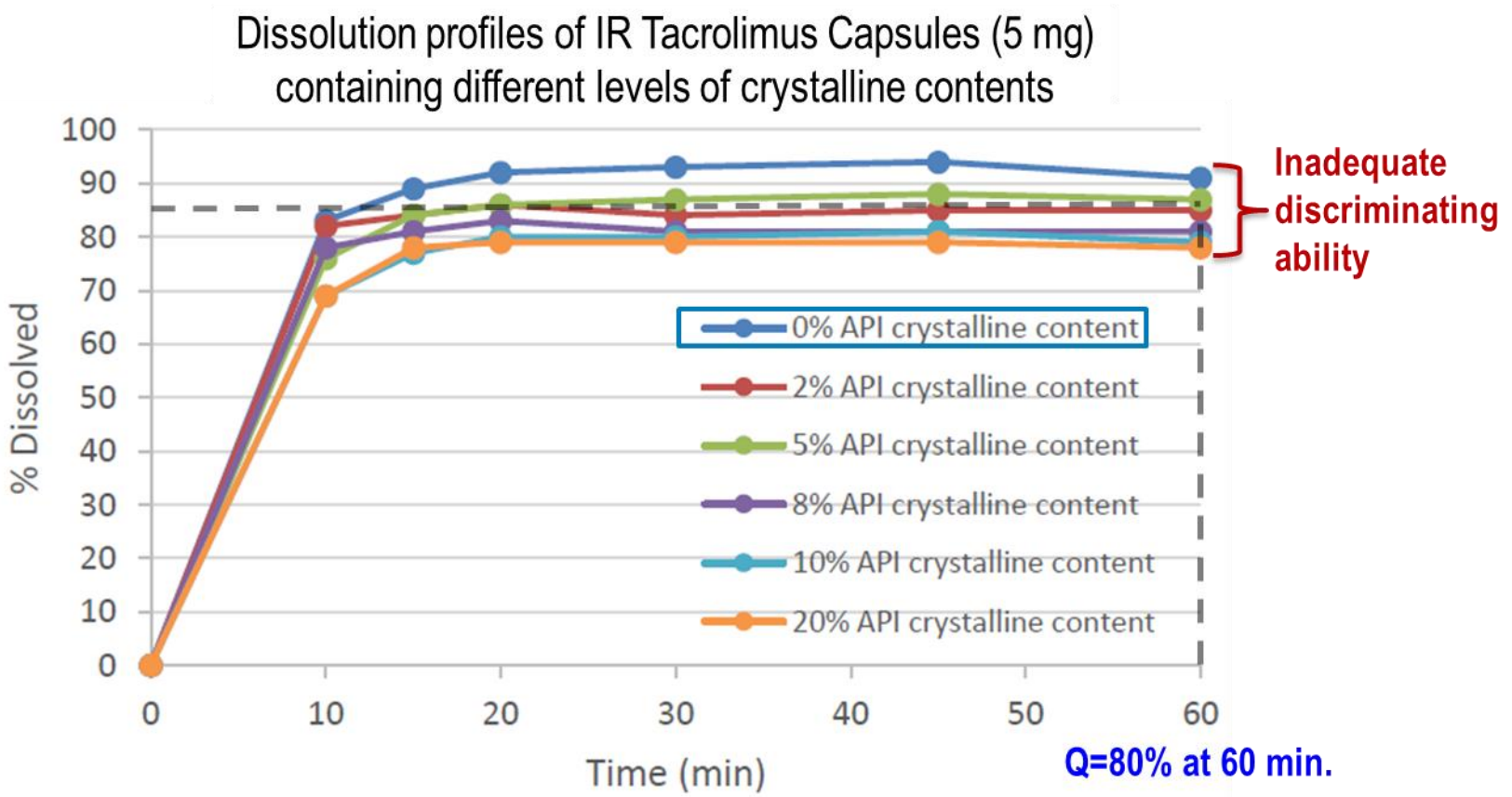
- Indication:
  - Immunosuppressant
  - Prophylaxis of rejecting a transplanted organ

- Doses:
  - Based on body weight (individual dose titration)
  - Narrow-Therapeutic-Index (**NTI**) drug

- Product Design and Manufacturing Process:
  - ASD (solvent evaporation method)

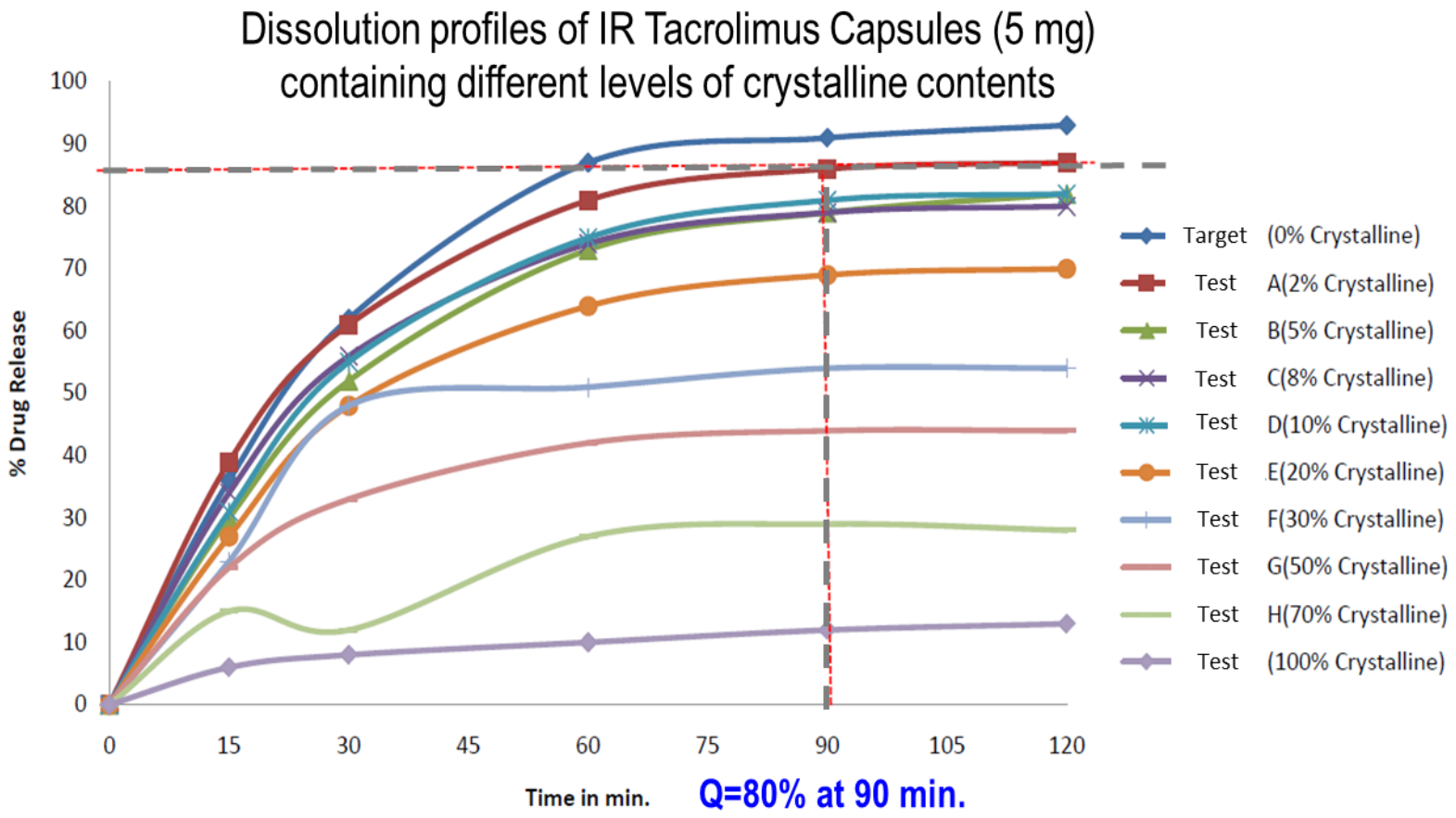
Product A: Crystalline Content

USP 2 (paddle), 50 rpm, 900 mL of pH 7.0 phosphate buffer with 0.1% SDS



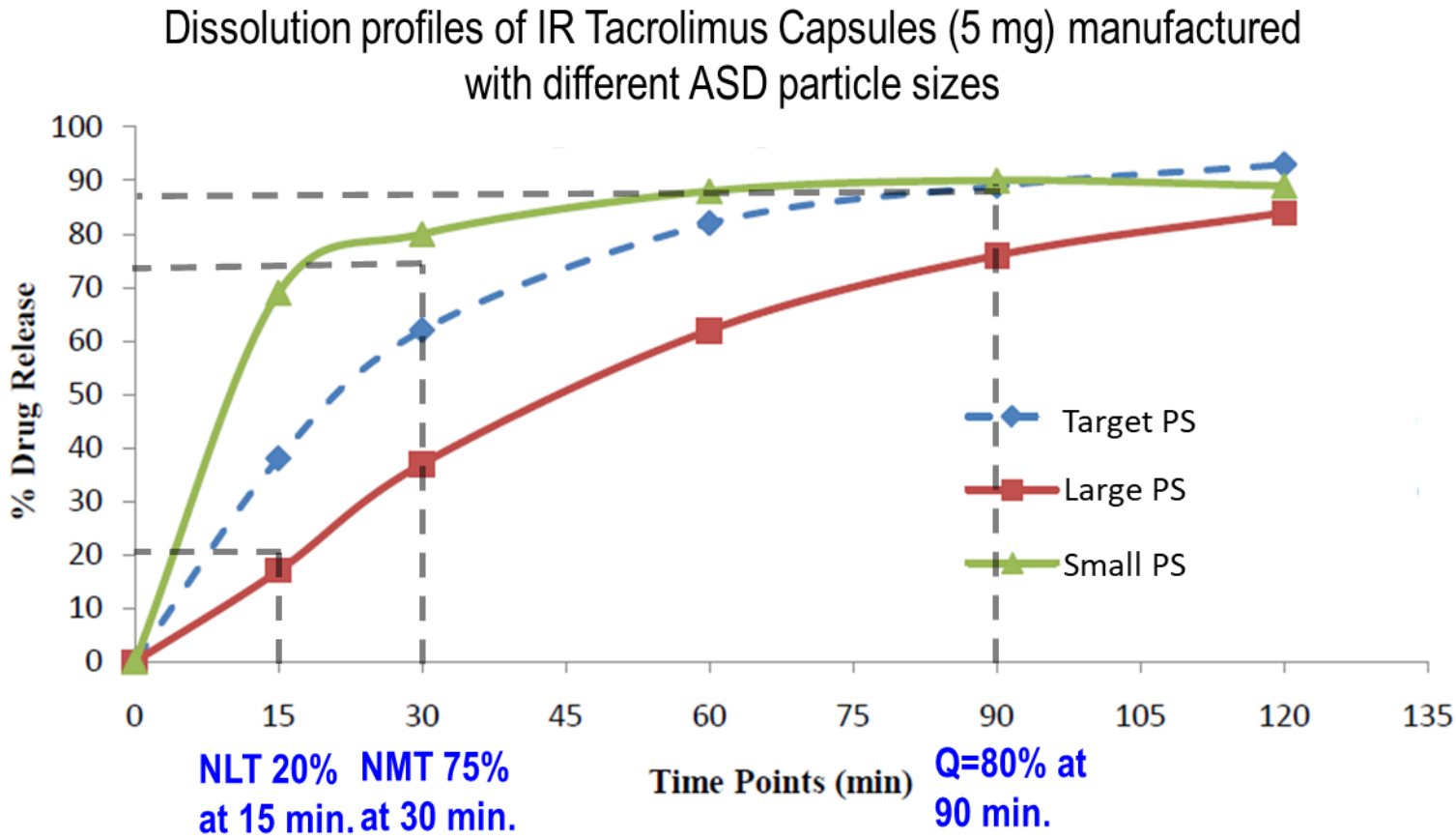
Product B: Crystalline Content

USP 2 (paddle), 75 rpm, 500 mL of aq. hydroxypropyl cellulose (HPC) , pH 4.5



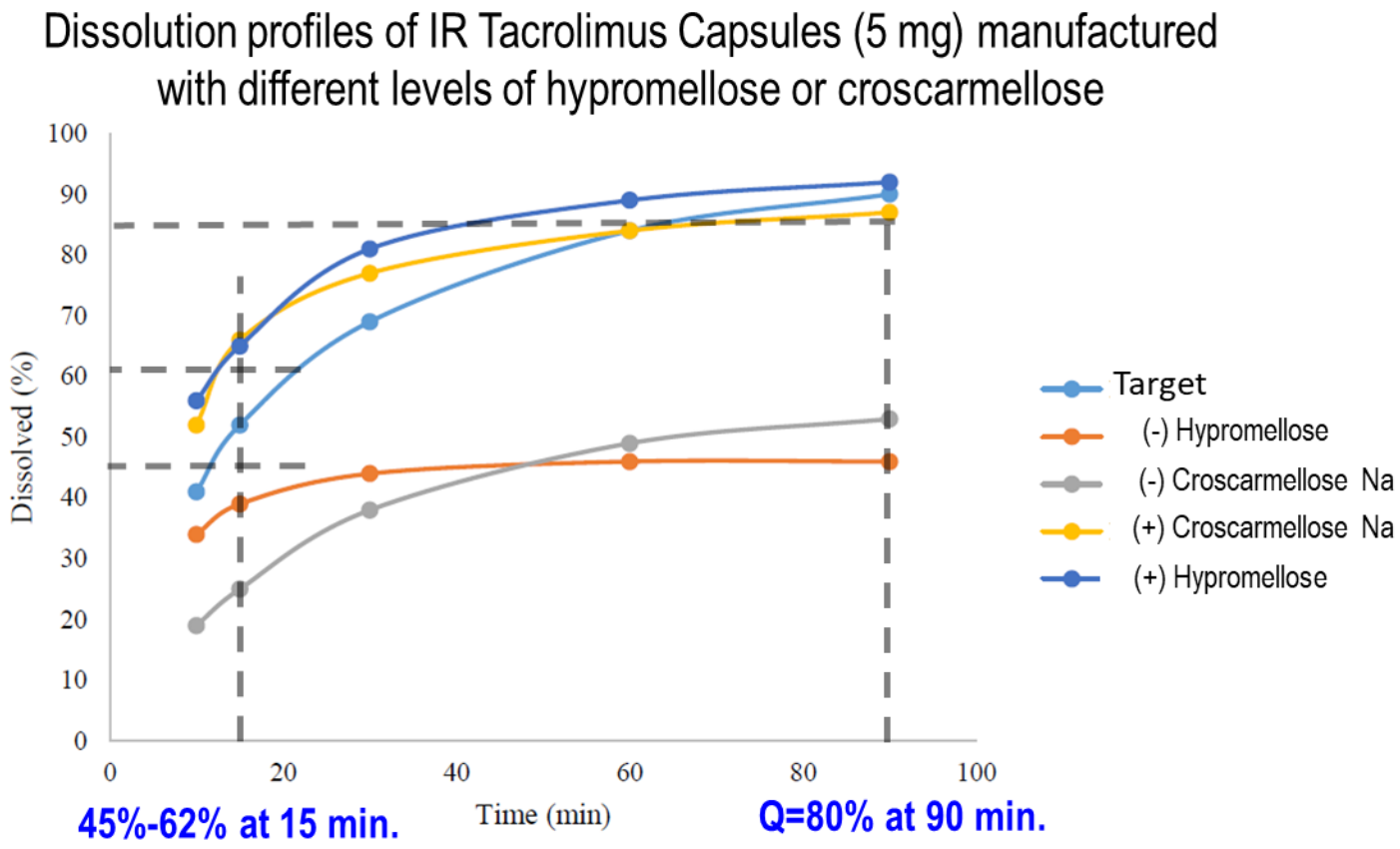
Product B: ASD Particle Size

USP 2 (paddle), 75 rpm, 500 mL of aq. HPC, pH 4.5



Product C: Critical Formulation Variables

USP 3 (reciprocating cylinder), 50 dpm, 1000 mL of aq. HPC, pH 4.5



Summary

- The main quality concern for ASD-based drug product is thermodynamic stability and re-crystallization may pose a high risk to patient.

- Adequate quality controls should be implemented to ensure that the level of crystalline content in the drug product does not impact the bioavailability and clinical performance.

- Dissolution method should show adequate discriminating ability towards critical bioavailability attributes (e.g., crystalline content, ASD particle size, level of polymer and other critical excipients etc.)

- Dissolution method development and validation report(s) are required for regulatory submission.

Reminders

Do not forget :

- Start the development and validation of the dissolution method for QC testing as early as possible during product development.
- Submit the dissolution method development report and seek FDA's feedback (Div. of Biopharmaceutics) prior to NDA submission (i.e., IND Amendment).
- Use modeling and simulation approaches (e.g., PBBM) to support the development of a biopredictive dissolution method and the establishment of clinically relevant dissolution specifications.
- Attend our next workshop in this August ☺

Acknowledgments

Bhagwant Rege, Ph.D.
Angelica Dorantes, Ph.D.
Elsbeth G. Chikhale, Ph.D.
Kimberly (Kim) Raines, Ph.D.
Division of Biopharmaceutics/ONDP/OPQ/CDER/FDA

Thank you for Attending

Q&A


FDA
U.S. FOOD & DRUG
ADMINISTRATION