In Vitro BE Case Studies

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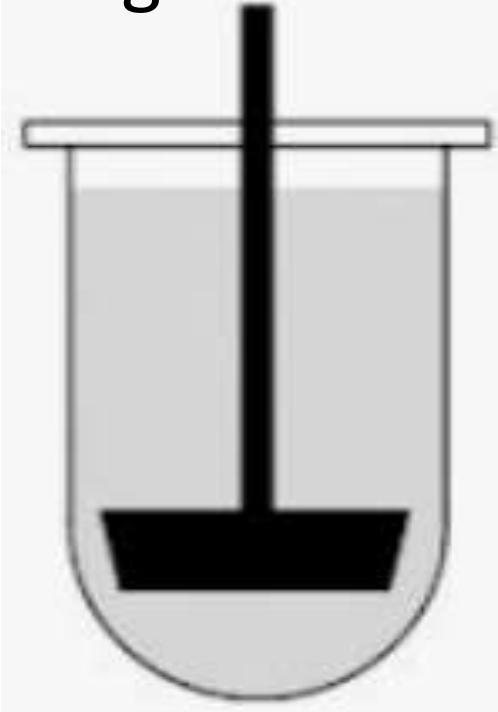
Case Study #1

In Vitro Drug Release Rate Study



In Vitro Drug Release Rate Study

Expectations for the comparative in vitro drug release rate study:

- At least three exhibit batches of the test and reference drug products.
- Testing of 12 units of each of the test and reference drug products.
- Use of acceptable test method for comparative in vitro drug release rate.
- Use of validated method for the study.
- Meets regulation 21 CFR Part 320 requirements
  - Comparative in vitro drug release rate study is a bioequivalence study subject
- Bioequivalence reserves per regulations 21 CFR Part 320.38 and 21 CFR Part 320.63.
- Accountability of investigational drug products used in the study.

In Vitro Drug Release Rate Study

An in vitro drug release test using USP Apparatus was developed and validated in a contract research organization (CRO) for an injectable drug product for comparative in vitro drug release rate to support a bioequivalence study. The drug product was an oil in water emulsion, and the surfactant was used to enhance drug release. The dissolution method was validated with various percentages (0.1, 0.2. 0.3, 0.5. 1.0, and 1.5%) of surfactant to test the drug release from investigational drug products. The site used 2.5% surfactant during the comparative drug release testing of three batches, each of test and reference drug products. Pre-study validation was not demonstrated at control conditions (0% surfactant). Use of 2.5% surfactant was not part of the pre-study validation nor was a justification provided.

In Vitro Drug Release Rate Study

Dissolution Conditions:

- USP Apparatus: Type II (Paddle)
- Temperature: 37°C
- RPM: 50
- Sample weight: 1.0g
- Dissolution medium: Phosphate buffer pH 7.4
- Dissolution volume: 500 mL
- Sample collection volume: 5 mL

In Vitro Drug Release Rate Study

Dissolution studies were performed with 12 units of each of the three batches of test and reference drug products. Dissolution samples were collected at five-minute time intervals for six time points: 5, 10, 15, 20, 25, and 30 minutes. The collected study samples were analyzed using validated HPLC method with UV detector. The percentage of drug release for each sample was calculated.

In Vitro Drug Release Rate Study

Question #1: Based on the provided information in Slides 5-7 for the in vitro comparative drug release study, if you were assigned to conduct an inspection of the study at the site, what are elements you find deficient and why?

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Pause for Discussion

Answer to Question #1

- Answers to questions will be discussed

In Vitro Drug Release Rate Study

Investigational drug products receipt information:

- Test products (Lot #s Test-1, Test-2, and Test-3) used in the study were shipped to the CRO from sponsor in three shipments on March 10, 2021; March 17; and March 24, 2021.
- Reference products (Lot #s Ref-1, Ref-2, and Ref-3 used in the study were shipped to the CRO from sponsor in one shipment on March 31, 2021.

In Vitro Drug Release Rate Study

Accountability records of investigational drug products

Investigational Drug Products	Shipment Dates	Lot Numbers	Number of Units Received	Numb of Units Used	Number of Units Remaining
Test Product	March 10, 2021	Test-1	26	24	2
	March 17, 2021	Test-2	24	24	0
	March 24, 2021	Test-3	24	24	0
Reference Product	March 31, 2021	Ref-1	24	24	0
		Ref-2	24	24	0
		Ref-3	24	24	0

In Vitro Drug Release Rate Study

Question #2: An FDA investigator observed objectionable conditions during the inspection and issued a Form FDA 483 to the management at the inspection close-out. Based on the information provided in Slides 11-12, what are the likely findings for the observation?

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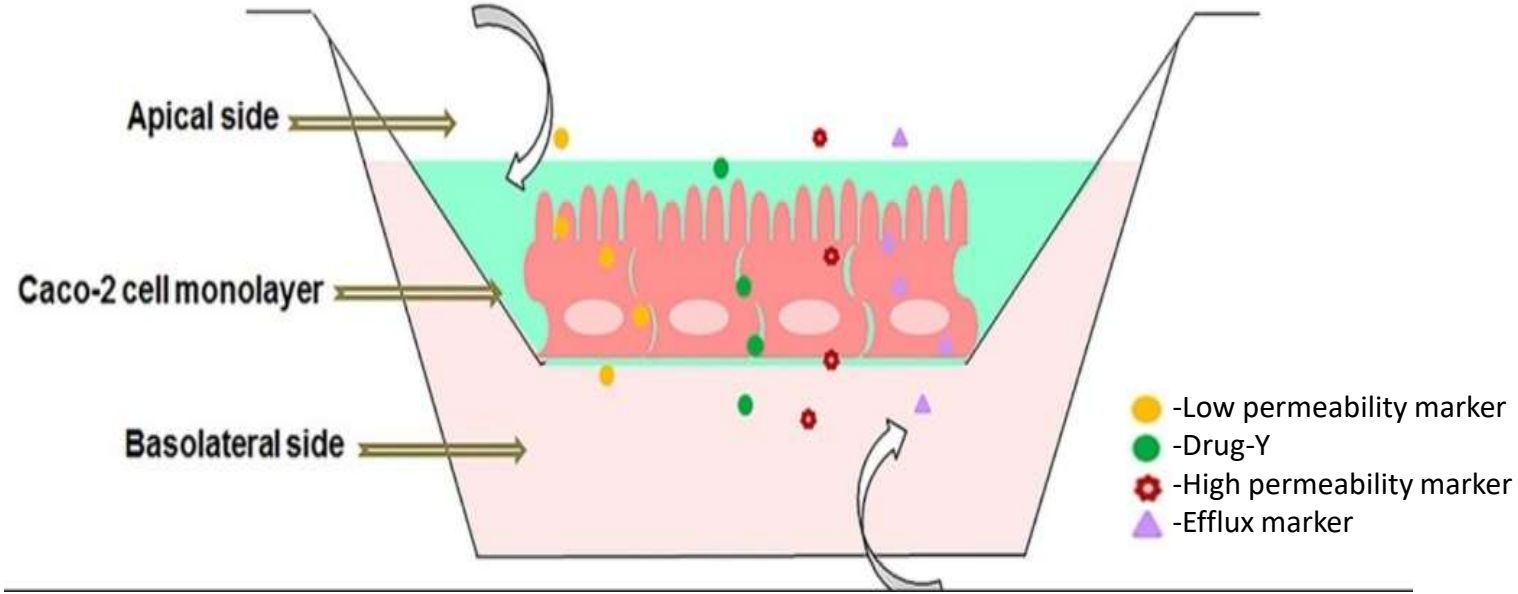
Pause for Discussion

Answer to Question #2

- Answers to questions will be discussed

Case Study #2

In Vitro Permeability Testing



In Vitro Permeability Testing

Expectations for the study:

- Assessment of Caco2 monolayer integrity before and after an experiment.
- Use of low and high permeability markers
- Use of efflux marker
- Selected markers (permeability and efflux) should be compatible with study drug.
- Validated analytical method should be used for the sample analysis.
- Efflux ratio
- Apparent permeability

In Vitro Permeability Testing

Drug and Study Information:

- Drug-Y was a BCS Class I drug.
- Bidirectional Caco2 assay performed.
- BCS-based biowaiver submitted for an Abbreviated New Drug Application.
- No clinical bioequivalence studies conducted.
- This was not a bioequivalence study.

In Vitro Permeability Testing

In vitro permeability studies were conducted using Caco-2 cell monolayers for Drug-Y to support biowaiver for a drug product. The bidirectional (apical-to-basolateral and basolateral-to-apical) permeability of Drug-Y was determined. Caco2 cell monolayer integrity was assessed by transepithelial electrical resistance (TEER). Permeability of low and high permeability markers and an efflux marker were determined in the study. The site conducted analytical method validation for Drug-Y and not for the controls (permeability and efflux markers) used in the study.

In Vitro Permeability Testing

Study samples from donor site were collected for two points: 60 and 120 minutes. Study samples from receiver side were collected for four time points: 30, 60, 90, and 120 minutes. The collected study samples were analyzed by HPLC-MS/MS. The concentration of markers and the study drug were quantified for subsequent calculation of the apparent permeability coefficient.

In Vitro Permeability Testing

Question #3: Based on the provided information in Slides 20-21 for the in vitro permeability study, if you were assigned to conduct an inspection of the study at the site, what are elements you find deficient and why?

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Pause for Discussion

Answer to Question #3

- Answers to questions will be discussed

In Vitro Permeability Testing

Question #4: Do you think not conducting pre-study validations for the permeability and efflux markers in Slide 20 has an impact on accuracy of the analytical results? Why?

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Pause for Discussion

Answer to Question #4

- Answers to questions will be discussed

Resources

- FDA Dissolution Methods:
https://www.accessdata.fda.gov/scripts/cder/dissolution/

- FDA Guidances (Drug):
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

- FDA Product Specific Guidance for Generic Drug Development:
https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development

- Guidance for Biopharmaceutics Classification System:
M9 Biopharmaceutics Classification System-Based Biowaivers | FDA


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