Case Studies of Enteral Feeding Tubes

Pharmaceutical Quality Symposium 2021: Innovations in a Changing World

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Overview

A. Enteral Feeding Tube Background

B. In Vitro Testing Development Considerations

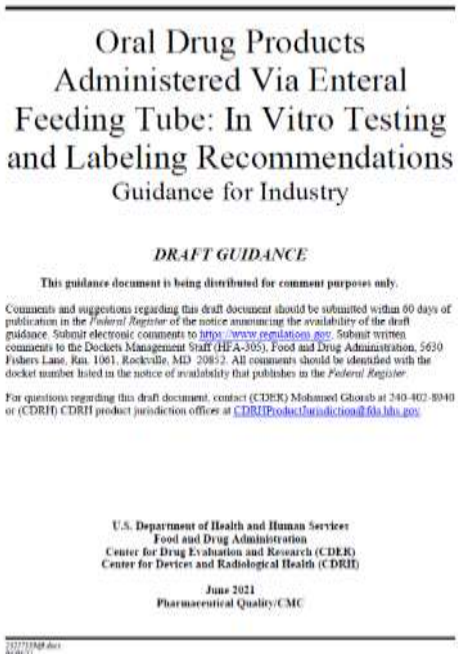
C. Two Proton Pump Inhibitor Case Studies

   i. Esomeprazole Delayed-Release Capsules

   ii. Lansoprazole orally disintegrating tablets (ODTs)

D. Testing Type Recommendations

E. Data Submission



Oral Drug Products Administered Via Enteral Feeding Tube: In Vitro Testing and Labeling Recommendations

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Mohamed Ghonim at 240-402-8040 or (CDRH) CDRH product jurisdiction offices at CDRHProductJurisdiction@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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Pharmaceutical Quality/CMC

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/oral-drug-products-administered-enteral-feeding-tube-in-vitro-testing-and-labeling-recommendations

Background

Enteral tubes are a medical device that allow for the delivery of food and medicine for patients who are unable to swallow oral dosage forms due to a variety of medical conditions

Type	Outer Tube Diameter (Fr*,**)
Nasogastric	5-18
Nasoduodenal	3.5-12
Nasojejunal	3.5-12
Gastrostomy	12-30
Gastrojejunal	12-22
Jejunostomy	12-18

* Fr = French
** 3 Fr = 1 millimeter

http://www.feedingtubeawareness.org/tube-feeding-basics/tubetypes/nasal-tubes/

Enteral Tube Administration

Considerations/Risk Factors:

- Size and composition of tube
  - -Polyurethane, Silicone, PVC
- Enteric Coating
- Dispersion media used for delivery
- Geometry of Tube
  - -Distal tip, number of eyes, gastric balloon

	I.D./O.D. RATIO
Polyurethane	
Polyvinylchloride (PVC)	
Silicone	

Proton Pump Inhibitors (PPIs)

- Proton pump inhibitors are commonly used to manage acid-related disorders by irreversibly inhibiting the proton pump (H+/K+/ATPase) function.

Esomeprazole Delayed-Release Capsules

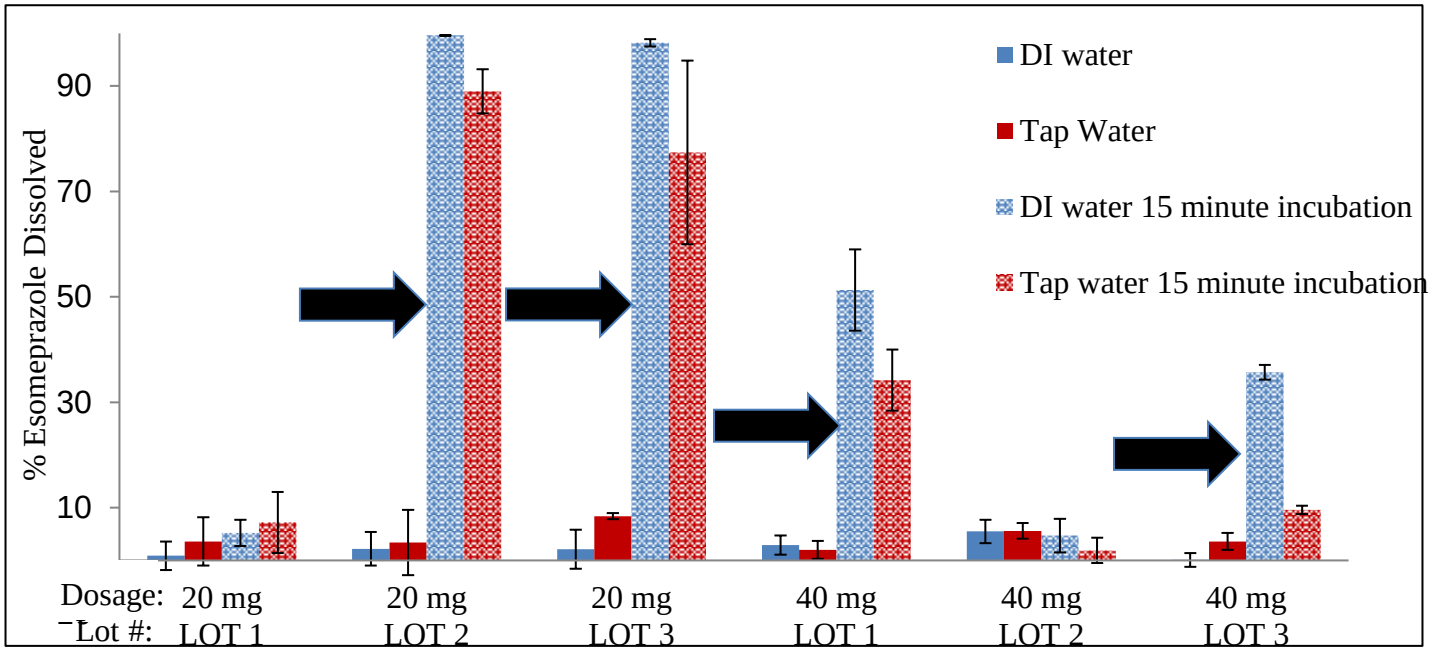
Lansoprazole Delayed-Release Orally Disintegrating Tablets (ODT)

- Can be administered using oral syringe and ≥8 French nasogastric tube
- Formulated with an enteric coating to prevent degradation in stomach acid

Analytical Methods: Esomeprazole

1) Dispersion in media
    - Disintegration
    - Sedimentation
    - pH
2) Percent Recovery through Feeding Tube and Syringe Combination
3) Acid Resistance Stability
4) Particle Size Distribution (PSD)

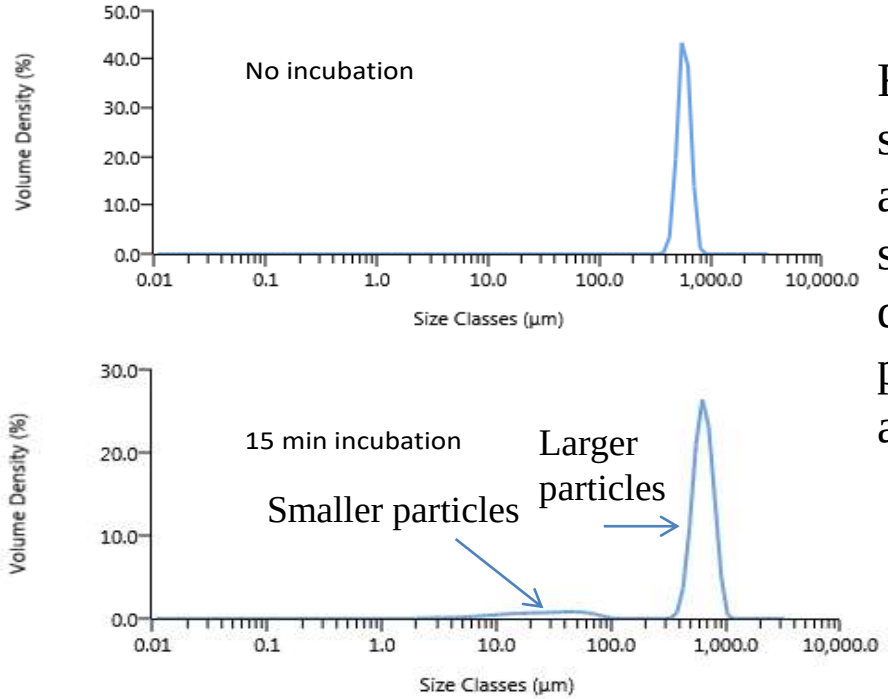
Esomeprazole Delayed-Release Capsules



Four out of six lots had >10% drug release when the granules were delivered after a 15 min incubation time.

 Hoover, A.; Sun, D.; Wen, H.; Jiang, W.; Cui, M.; Jiang, X.; Keire, D.; Guo, C. J. Pharm. Sci 2017; 106(7):1859-1864.

Esomeprazole Delayed-Release Capsules



For the particle size distribution analysis, smaller and larger particles are observed after a 15-minute incubation in water. The smaller particles may be debris from damaged enteric coating and the larger particles may be a result of particle agglomeration.

Hoover, A.; Sun, D.; Wen, H.; Jiang, W.; Cui, M.; Jiang, X.; Keire, D.; Guo, C. J. Pharm. Sci 2017; 106(7):1859-1864.

Lansoprazole ODTs

- According to product instructions, Lansoprazole ODTs can be dispersed in water and delivered through an ≥8 French NG tube.
- Many adverse events have been reported for Gastrostomy (G) and Jejunal (J) tubes, which are off-label uses.
  - Testing methods were performed with 2 sets of tubes of each type (NG, G, and J)
  - Two drug products (A, B) were selected for analysis.

Hoover et al. *In vitro* evaluation of enteral tube administration of lansoprazole orally disintegrating tablets. Pharm Dev Technol. 2021 Oct;26(8):846-851.

Analytical Methods: Lansoprazole

1) Dispersion in media
    - Disintegration
    - Sedimentation
    - pH

2) Percent Recovery through Feeding Tube and Syringe Combination

3) Acid Resistance Stability

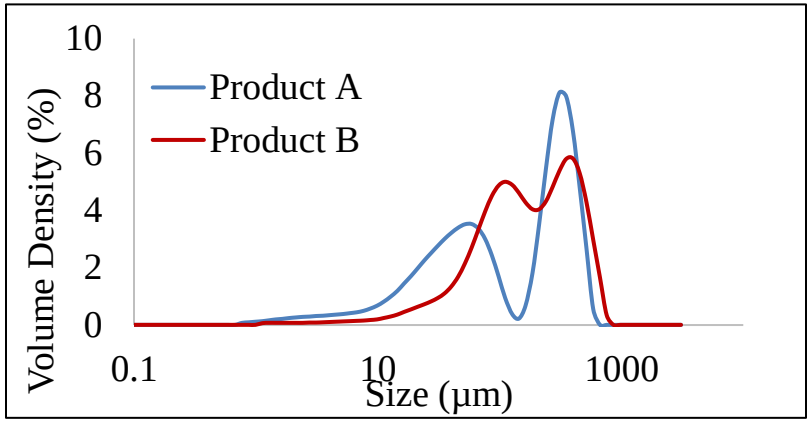
4) Particle Size Distribution (PSD)

Hoover et al. *In vitro* evaluation of enteral tube administration of lansoprazole orally disintegrating tablets. Pharm Dev Technol. 2021 Oct;26(8):846-851.

Lansoprazole Particle Size Distribution

	D(10), µm	D(50), µm	D(90), µm
Product A	17.5 ± 1.5	129.9 ± 44.0	425.0 ± 20.0
Product B	44.0 ± 6.4	170.0 ± 28.6	503.0 ± 40.0

Particle size distribution of lansoprazole after enteral tube delivery.



Particle size distribution of 30 Product A and B.

- A bimodal particle size distribution was observed for both lansoprazole products after suspension in water.
- Larger particles as well as an increased amount of insoluble excipients are observed for Product B.

Hoover et al. *In vitro* evaluation of enteral tube administration of lansoprazole orally disintegrating tablets. Pharm Dev Technol. 2021 Oct;26(8):846-851.

Clogging Behavior of Lansoprazole ODTs

NG tube that is partially clogged

Clogged G tube following lansoprazole administration.

- An irreversible clog was an obstruction where the drug product could no longer be delivered through the tube.
- A push-pull motion of the syringe plunger was unsuccessful in removing these obstructions.

	NG tube 1	NG tube 2	G tube 1	G tube 2	J tube 1	J tube 2
15 mg Product A	0	0	0	4	0	0
15 mg Product B	0	0	0	5	0	0
30 mg Product A	0	1	0	8	0	0
30 mg Product B	0	2	1	9	0	0

Irreversible clogs observed during administration (n=48).

Hoover et al. *In vitro* evaluation of enteral tube administration of lansoprazole orally disintegrating tablets. Pharm Dev Technol. 2021 Oct;26(8):846-851.

Summary

- Dispersion in water can affect the integrity of the enteric coating on PPI drug products.
- Tube geometry and design can affect drug delivery through enteral feeding tubes.
- The methods developed in these studies assessed the risks associated with enteral feeding tube drug administration.

Challenge Question #1

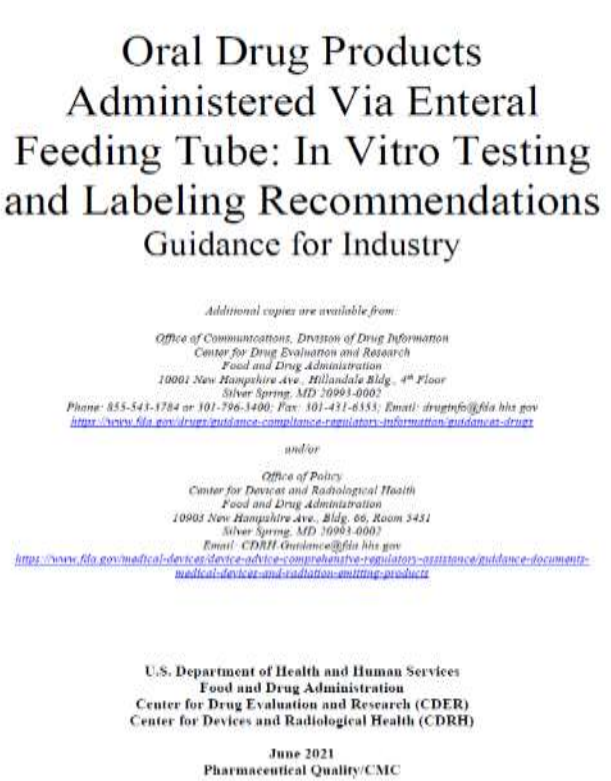
Which is NOT an example of a material that feeding tubes are made of?

A. Polyurethane

B. Polyvinylchloride

C. Polyethylene

D. Silicone



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Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
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Silver Spring, MD 20993-0002
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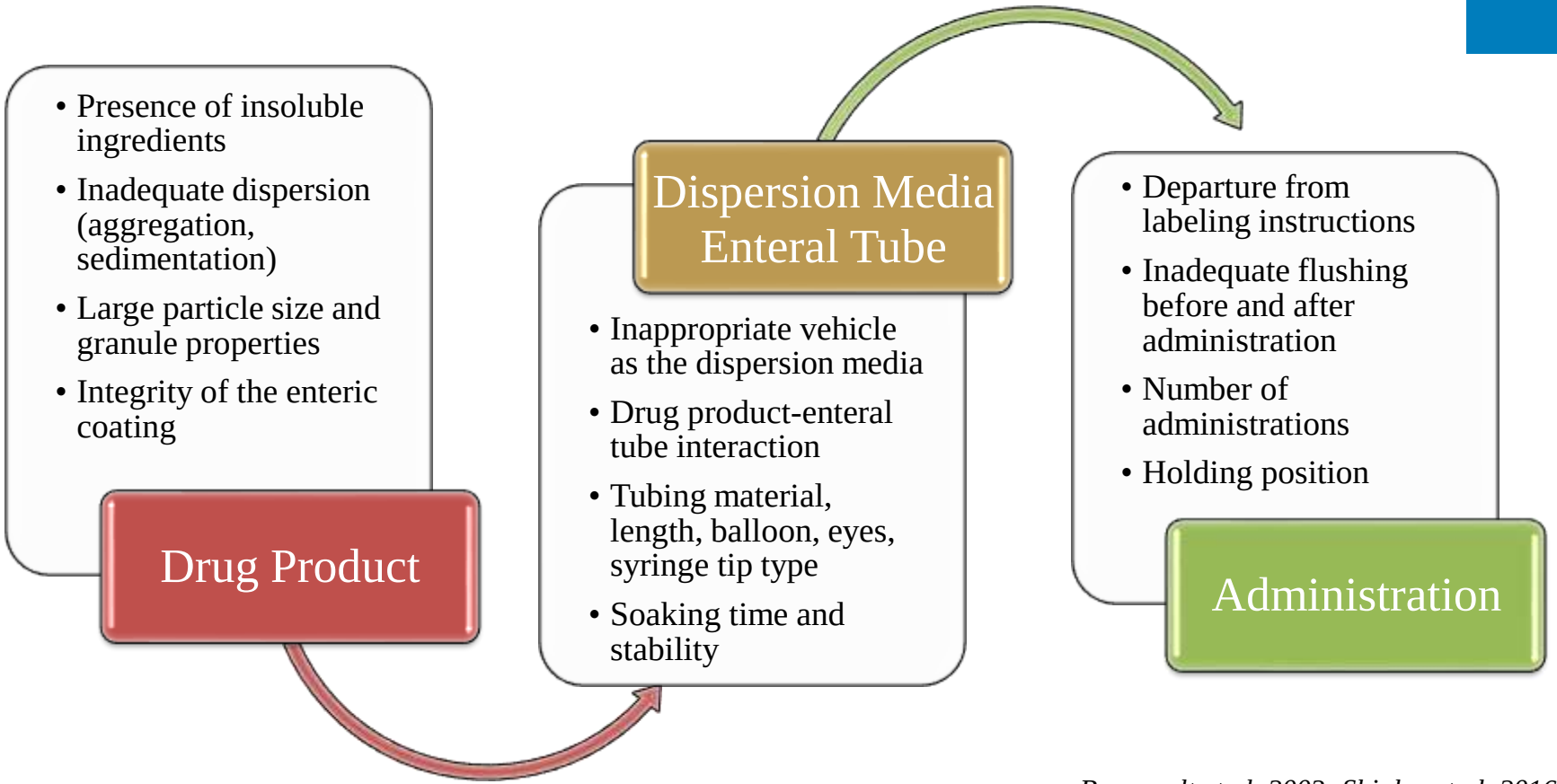
Testing Type Recommendations

- Case studies

Data Submission

Risk Factors



Bourgault et al. 2003; Shipley et al. 2016

Testing Type Recommendations

Recovery testing

- Water with different pH 5.5, 7.0, 8.5
- Repeat administration study
- Different tubing materials (three different tubing configurations)
- Intended Soaking times (0 to 15min or longer)

Sedimentation Redispersibility

- Sedimentation potential and risk of clogging
- Redispersibility – Qualitative test
- Routine testing for oral suspension

In-Use Stability

- Drug product dispersion chemical and physical stability
- Drug content and degradation products during the proposed soaking time
- Microbial testing for >4 hours holding times

Testing Type Recommendations

Particle size

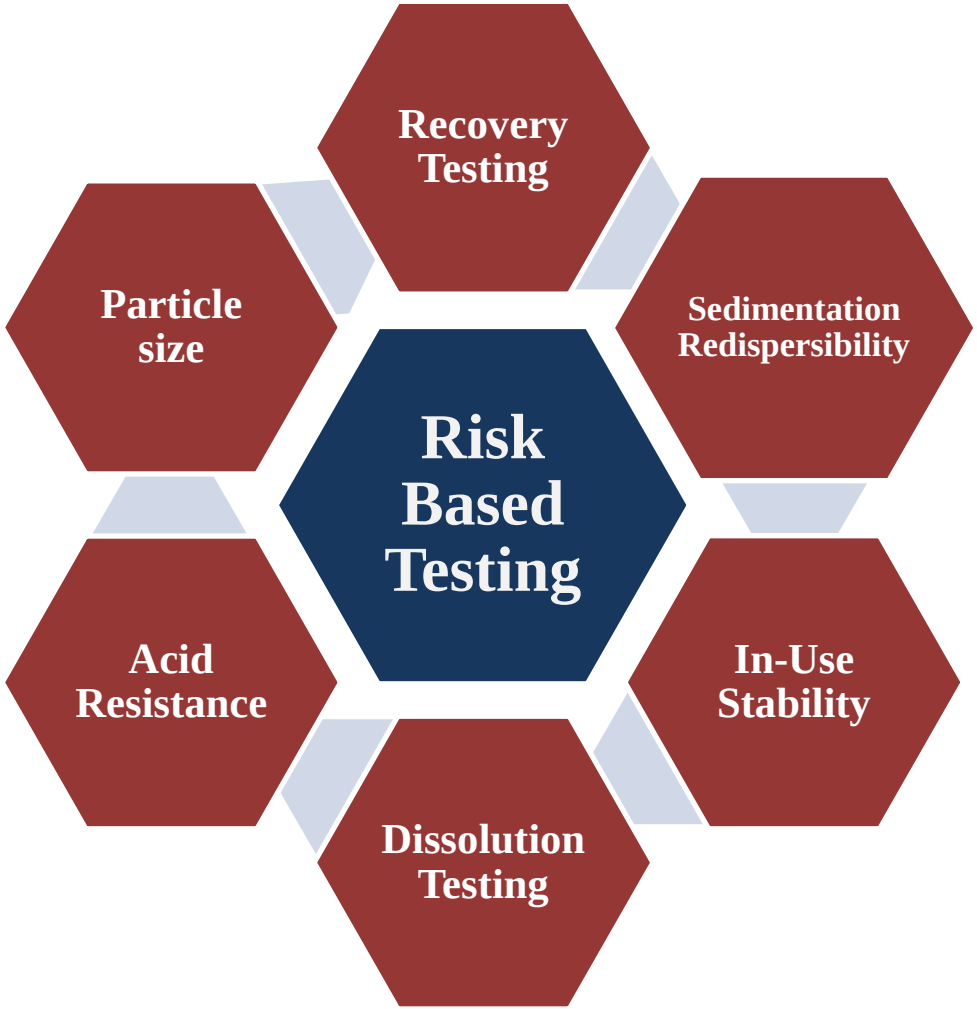
- Key attribute for the passage of the drug product
- Before and after delivery
- Reproducible and sensitive method

Acid Resistance

- Integrity of the enteric coating of dosage form
- Degradation of acid-labile APIs

Dissolution

- Effect of enteral tube passage on timing of drug release


Recovery Testing
Particle size
Sedimentation Redispersibility
Risk Based Testing
Acid Resistance
In-Use Stability
Dissolution Testing

Case study# Drug Product Formulation Factors

Lansoprazole Delayed-Release Orally Disintegrating Tablets, 15mg and 30mg

Layer	Attributes	ANDA Properties compared to RLD And Risk of Enteral Tube Administration
Core	Particle size	3X sphere size larger than RLD
	Amount of spheres	2X more weight than RLD
Coating	Binder polymer	Similar type and amount
	Enteric coating	Similar type and amount
Excipients	Insoluble excipients quantity	More insoluble excipients than RLD
Tablet	Total weight	+200mg more weight than RLD

In-vitro testing - Major Tube Clogging

NOT ACCEPTABLE

Reformulation with smaller core, less amount of insoluble excipients

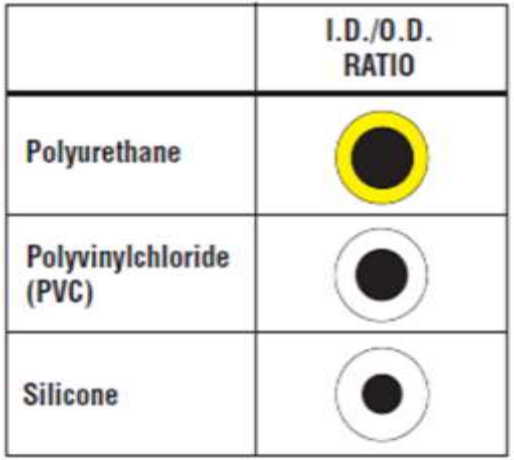
No Clogging

RLD: Reference Listed Drug; ANDA: Abbreviated New Drug Application

Case study# Evaluation of Tubing Materials

Esomeprazole Magnesium Delayed-Release Capsules, 15mg and 30mg

Name/ Brand	Material of Construction	Design	Size	Observations
NG tube - A	Polyurethane	Two ports; Open distal end	6 French Length: 65.4 cm	Clogging observed in all the tested samples
NG tube - B	Polyurethane	Two ports; Open distal end	8 French Length: 95.8 cm	Clogging observed in 1 out of 12 units
NG tube - C	PVC	Four ports; Closed distal end	14 French Length: 120 cm	No Clogging (n=12)
NG tube - D	Silicon	Three ports; Closed distal end	16 French Length: 120 cm	No Clogging (n=12)



Internal diameter (I.D.), Outer diameter (O.D.)

Recommendations

- ✓ The same size tubes made of different materials have very different inner diameter. Perform the study with same size tubing with different material for both test and reference product.
- ✓ If needed, repeat the study with next higher size tubing for both test and reference product.
- ✓ Perform the testing as per RLD PI and PSG.

RLD: Reference Listed Drug; PI: Package Insert/Prescribing Information; PSG: Product-Specific Guidance; NG: Nasogastric;

Case study# Drug Product and Syringe Material Compatibility

Esomeprazole Magnesium Delayed-Release Capsules, 15mg and 30mg

- ❑ The test product beads were found to adhered to the syringes and showed lower recovery
- ❑ The applicant proposed "pre-treatment of syringe and seal ring on the plunger" and labeling change to add pre-treatment of syringe.

	% Recovery from syringe
Without Pre-treatment	~92%
With Pre-treatment	~100%

Not Acceptable

Recommendations

- ✓ The pre-treatment of syringe and labeling changes are not acceptable.
- ✓ Conduct the recovery study of your test product and reference product side by side as per RLD PI and PSG.

RLD: Reference Listed Drug; PI: Package Insert/Prescribing Information; PSG: Product-Specific Guidance

Data Submission and Report

- ✓ Summary Table
- ✓ Test objectives
- ✓ Method and procedures
  - ➢ Details about samples (e.g., tube material, length, diameter, syringe details, dispersion media, volume, flushing volume, etc.
  - ➢ Sample size and rationale to support the number and type of samples
  - ➢ Test protocol, procedures, parameters, acceptance criteria
- ✓ Test results
  - ➢ Data points (min, max, average, standard deviation), side by side comparison of T and R products, observations (additional pressure applied, pre-treatment of syringe etc.)
  - ➢ Data analysis discuss the potential reasons for test failure, identify risk mitigation measure(s); and provide justification for why the testing results should be considered acceptable
  - ➢ Clear pictures with labels and focused video

Summary

- *In vitro* testing is to ensure safe and effective delivery of drug products that may be administered via enteral tube.
- The type and extent of *in-vitro* testing should be a risk-based decision focused on the characteristics of the individual drug product.

Challenge Question #2

Which of the following conditions is possible risk of enteral tube blocking :

A. Presence of insoluble ingredients

B. Drug product-enteral tube interactions

C. Particle size

D. All of the above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