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Current Regulatory Expectations of Assessing In-Use Stability of Solid Oral Dosage Forms to be Mixed with Foods and other Vehicles for Product Labeling

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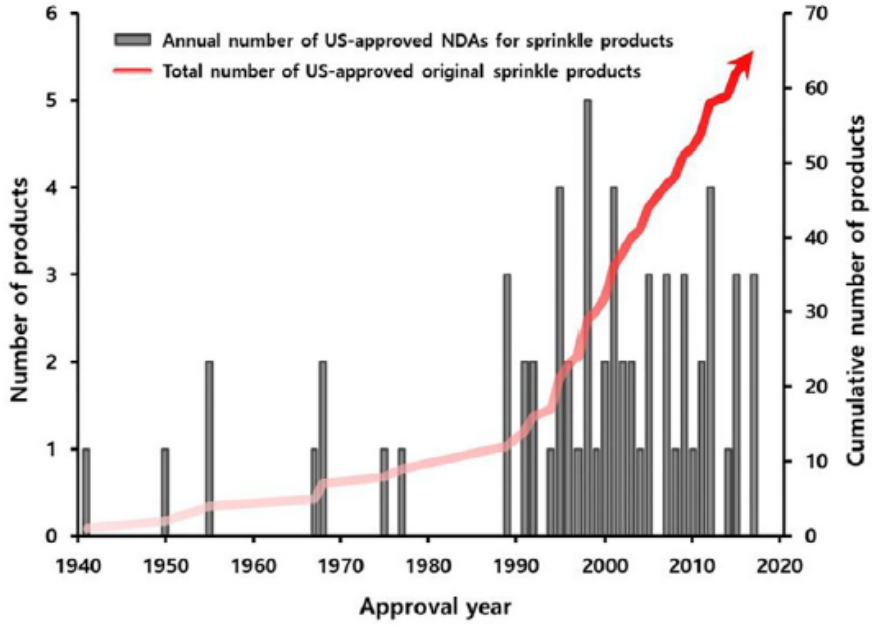
Preparation of Pediatric Formulations

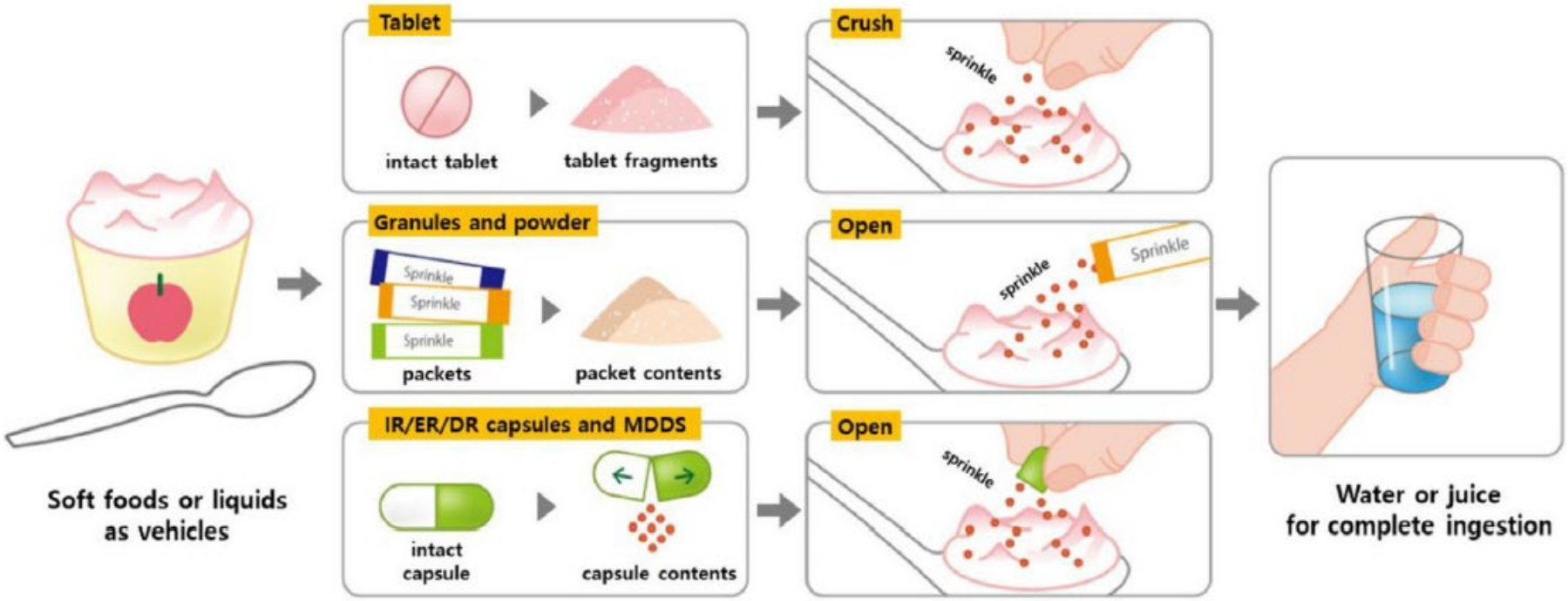
- Extemporaneous preparations using approved adult drug product for pediatric use
- Compounding of approved adult drug product for pediatric use
- Development and manufacture of drug products for Pediatric patients.

Marketed Pediatric Dosage Forms

- Solution/Syrups/Elixir
- Suspension
- Powders for Reconstitution as Suspension
- Dispersible/Effervescent Tablets
- Chewable Tablets
- Orally Disintegrating Tablets
- Tablets/Coated Tablets
- Sprinkle Oral Powder/Granules
- Capsules



Han Sol Lee, et.al. Asian Journal of Pharmaceutical Sciences, 2020, Vol 15, pp 292-310.



Taken From
Han Sol Lee, et.al. Asian Journal of Pharmaceutical Sciences, 2020, Vol 15, pp 292-310.

FDA Expectations for In-Use Stability Studies to Support labeling instructions for preparation and use time

- Food/Vehicle Selection
- Sampling Plan
- Appropriate Time Points
- Test Parameters
- Analytical Method Development and Validation

In-Use Stability Critical Quality Attributes

Properties	Attribute
Physical (Homogeneity)	Color; Clarity; Homogeneity
	Particulate matter
Chemical	Assay
	Impurity/Degradation profile
	pH
	Dissolution (Drug Release)
Microbial (liquid preparations)	Preservative/antioxidant effectiveness
	Antimicrobial testing

Common Soft Foods and Liquid Vehicles

Soft Food / Liquids	pH range
Apples (puree)	3.34 – 3.90
Apple juice	3.35 – 4.00
Applesauce	3.10 – 3.60
Baby food, unstrained	5.95 – 6.05
Bananas (puree)	4.5 – 5.2
Buttermilk	4.41 – 4.83
Carrots (puree)	5.88 – 6.40
Chocolate pudding	5.5 – 6.0
Coconut milk	6.1 – 7.0
Cranberry juice	2.30 – 2.52
Drinking water	6.5 – 8.5
Fruit jellies	3.0 – 3.5
Fruit jam	3.5 – 4.5
Grapefruit juice	2.90 – 3.25

Table source: FDA Guidance for Industry Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In-vitro Methods for Product Quality Assessments (July 2018)

Soft Food / Liquids	pH range
Honey	3.70 – 4.20
Infant formula	5.7 – 6.0
Maple syrup	4.6 – 5.15
Milk	6.4 – 6.8
Orange juice	3.30 – 4.19
Orange marmalade	3.00 – 3.33
Peanut butter	6.28
Pineapple juice	3.30 – 3.60
Rice pudding	4 – 5
Soybean milk	7
Strawberries	3.00 – 3.90
Strawberry jam	3.00 – 3.40
Yogurt	4.4 – 5.0

Table source: FDA Guidance for Industry Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In-vitro Methods for Product Quality Assessments
(July 2018)

Other Criteria

- Sampling should be under normal conditions of use
- Preferably using aged drug product stability batches
- In-Use study is a one-time study
- Time period for in-Use study usually 2 hr to 12 hours
  Time intervals e.g. 0, 1, 2, 4, 8 and 12 hours
  [one time use (immediately) or multiple uses]
- Analytical Methods should be validated for assay
  If degradation observed, then degradants/impurities should also be analyzed using validated methods

Dissolution

In cases wherein the drug product is not dissolved in the vehicle/food, then dissolution testing of the drug product-food mixture is needed.

Comparative dissolution profile of the drug product and the drug product-vehicle mixture should meet the similarity factor (f2) acceptance criteria

Labeling Recommendations

i. In-Use Time Period should be established
ii. Identification of foods/vehicles that can be used and those that should NOT be used
iii. Special Instructions for preparation and administration

Drug A: sprinkles within a capsule

Time Interval: 0, 30min, 1 hour, 2, hr, 12 hr and 24 hr

Food	pH range
Yogurt	4.0 to 5.0
Apple Sauce	3.1 to 3.6
Pudding	4.0 to 5.0
Vehicle 1	6.8
Vehicle 2	1.2

Sample Prep included Shaker/Sonication followed by extraction of the drug from the food, dilution, filtration and analysis.
HPLC method developed to separate drug peak from food peaks

Drug A outcome

Drug is stable in soft foods
With pH 1.2 to 5.0 up to 24 hours.

Significant degradation in vehicles
With a pH of 6.8

Labeling instructions: sprinkle into 1 tablespoon of applesauce, pudding or yogurt.
Can store food and drug mixture for up to 2 hours

Drug B: powder for oral suspension

Mixed in water only
Tested with aged batches (24 months)
5ml samples, tested at 0, 1 and 2 hours.
Degradation observed at 2 hours.

Labeling : administer within one hour of preparation.
Discard any unused portion after one hour.

Drug C: delayed release granules for oral suspension

Only applesauce and apple juice were tested.

Time Intervals at 1, 2 and 3 hours

Degradation and dissolution were within specifications

Labeling Instructions: Mix in 1 teaspoon of applesauce or apple juice only. **Do not mix with other foods or liquids**. Swallow mixture with granules within 10 minutes after preparation

Conclusions

- Compatability of the drug substance and drug product with food/vehicles should be assessed for assay, dissolution, homogeneity

- Food/vehicle selection based on acidity (pH)

- Aged batches should be used for testing

- Time period for testing should be at least 2 hours

- Results inform labeling instructions for administration
  Only foods tested should be included in the label

Use of Liquids and /or Soft Foods for drug administration guidance (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-liquids-andor-soft-foods-vehicles-drug-administration-general-considerations-selection-and-vitro)

THANK YOU!