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▲⟨1711⟩ ORAL DOSAGE FORMS—PERFORMANCE TESTS

INTRODUCTION

This general information chapter provides approaches for the development of performance tests, mainly dissolution and disintegration procedures for oral dosage forms intended for human and animal applications, which are not covered by *Disintegration* ⟨701⟩, *Dissolution* ⟨711⟩, *Drug Release* ⟨724⟩, *The Dissolution Procedure: Development and Validation* ⟨1092⟩, *Capsules—Dissolution Testing and Related Quality Attributes* ⟨1094⟩, and *Disintegration and Dissolution of Dietary Supplements* ⟨2040⟩.

The oral dosage forms referred to, but not restricted to, in this chapter are: effervescent tablets, chewable tablets, sublingual tablets, orally disintegrating tablets, gastroretentive tablets, delayed-release dosage forms, granules or pellets that are administered with food or beverages, suspensions, powder for suspension, granules for suspensions, tablets for suspension, lozenges, oral pastes, oral gels, chewable gels, Type A medicated articles, and Type B and Type C medicated feeds that deliver animal drugs and drug products in animal feeds.

PRODUCT PERFORMANCE PROCEDURE DEVELOPMENT

The dissolution test should be, in most cases, discriminative for the critical quality attributes of the product. The FDA Guidance for Industry *Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances* (*1*) discusses the cases in which the dissolution test does not need to be discriminative. The test conditions (media, apparatus, tolerances/acceptance criteria) are typically defined in a case-by-case approach, supported and justified by data obtained with samples from the formulation(s) under evaluation. Generally, the compendial apparatus and procedures that can be used are described in ⟨711⟩, ⟨724⟩, and ⟨2040⟩. Any deviations from or modifications to the conditions stated in these chapters are acceptable with appropriate justification. For additional information see also ⟨1092⟩ and *In Vitro and In Vivo Evaluation of Dosage Forms* ⟨1088⟩. Other useful documents are FDA Guidance for Industry *Dissolution Testing of Immediate-Release Solid Oral Dosage Forms* (*2*) and FDA Guidance for Industry *Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations* (*3*).

The dissolution media to be evaluated should have pH values within the physiological range, e.g. from 1.2–6.8. Dissolution media with pH values outside this range can be used with appropriate justification. The dissolution media for animal applications may be animal species specific.

Examples of dissolution tests can be found at the FDA Dissolution Methods database (*4*) and at the USP Dissolution Methods database (*5*).

Solid Oral Dosage Forms

The general descriptions of and definitions for solid oral dosage forms can be found in *Pharmaceutical Dosage Forms* ⟨1151⟩.

TABLETS

Effervescent tablets: Effervescent tablets that result in a solution when handled according to the instructions to the patient do not require a dissolution test. In this case, a disintegration test is to be conducted.

For effervescent tablets that result in a suspension after being handled according to the instructions to the patient, a dissolution test should be developed. Depending on the size of the tablet, it may be necessary to position the paddles of USP *Apparatus 2* described in ⟨711⟩ at a distance higher than 2.5 cm, to avoid having the dosage form being hit by the paddle.

Chewable tablets: The dissolution test should be conducted using intact tablets. Since these types of tablets may be harder or more elastic than the regular immediate-release tablets, the dissolution procedure may require more aggressive conditions such as higher agitation speed and longer test time.

In the case of chewable tablets for use in animals, when developing a disintegration test, it is important to consider their size as they may be too big to fit in the equipment described in ⟨701⟩. An alternative is *Apparatus B* described in ⟨2040⟩. When developing a dissolution test, depending on the size of the tablet, it may be necessary to position the paddles of USP *Apparatus 2* described in ⟨711⟩ at a distance higher than 2.5 cm, to avoid having the dosage form being hit by the paddle.

In addition to dissolution testing, a disintegration test should be conducted using intact tablets in an appropriate medium using the appropriate equipment described in ⟨701⟩ or ⟨2040⟩ [see FDA Guidance for Industry *Quality Attribute Considerations for Chewable Tablets* (*6*)].

Sublingual tablets: Typically, sublingual tablets are immediate-release formulations which disintegrate very rapidly and contain a drug substance that has a good solubility at the pH value representing the pH of the buccal cavity. A dissolution test should be developed for this type of dosage form. However, the dissolution test may be replaced by a disintegration test, when justified. It may be advantageous to use a dissolution medium with a pH close to the saliva pH. Normal, healthy, human saliva in the oral cavity has, typically, a pH between 6.7 and 7.4. Other media may be used with appropriate justification.

Orally disintegrating tablets: The technological concept and manufacturing process have a great influence on the disintegration behavior of orally disintegrating tablets. The tablets manufactured by lyophilization will have a very short disintegration time, typically 1–3 s, when compared to orally disintegrating tablets manufactured by conventional means that have a disintegration time of around, or more than, 30 s.

Products labeled as orally disintegrating tablets require disintegration and dissolution tests [see FDA Guidance for Industry *Orally Disintegrating Tablets* (*7*)].

The evaluation of the amount of drug dissolved at early time points (less than 5 min) may be useful.

Gastroretentive tablets: Gastroretentive tablets are tablets intended to be retained in the stomach for a sufficient time while withstanding gastric mobility, and releasing the drug substance in a controlled manner. The advantages of this type of dosage form are the enhanced bioavailability of drugs having a narrow absorption window at the upper part of the gastrointestinal tract or drugs showing a higher solubility, stability, or absorption at an acidic pH. They can also be advantageous for drugs which are locally active in the gastric mucosa.

Different strategies have been proposed to prolong the gastric residence time, including floating, expanding, high density and bioadhesive systems. Floating formulations should float on the gastric contents preventing its passage through the pylorus. Floating hydrodynamically balanced systems or effervescent matrix systems are the most common approaches for floating dosage forms. Depending on the formulation, a lag time may precede the dosage form floating. Gas-generating coated floating tablets, which form balloon-like floating devices upon hydration, can have a shorter floating lag time independent from surrounding pH (*8*).

The dissolution medium should be hydrochloric acid in the concentration of 0.1 N or 0.01 N. Other dissolution media can be used with appropriate justification.

Besides the dissolution test, floating tablets may also require a buoyancy or a floating strength test.

Delayed-Release Dosage Forms

Delayed-release dosage forms are, typically, formulated with acid-resistant, or enteric or gastro-resistant coatings or matrices to protect acid-labile drug substances from the gastric environment, to avoid absorption in the proximal segment of the gastrointestinal tract, to prevent local adverse effects such as irritation, or to target drug release at the site of action or where the absorption is desired (i.e., in the colon region).

If the release of the drug substance is intended to occur in the proximal portion of the intestine, the procedures described in ⟨711⟩, with one acid stage and one buffer stage, should be followed. If the release of the drug substance is intended for the distal portion of the intestine (colon), the dissolution test consists of up to three stages—one acid stage and one or two buffer stages.

For non-pH-dependent delayed-release dosage forms the onset of dissolution is not intended to occur in a specific segment of the gastrointestinal tract but at a defined time point. The release mechanism is usually not pH dependent but driven by the propagation rate of a moisture front within the dosage form. The medium pH switch from acid to base may not be applicable. Instead, the dissolution procedure is similar to that used for immediate-release dosage forms, with the use of only one dissolution medium. It may require multivariate specifications for the time of the onset of the dissolution and the amount dissolved. The sampling time points have to be defined to include the pivotal time point of the onset of drug release.

Granules, Powders, or Pellets That Are Administered with Food or Beverages

These granules, powders, or pellets are sprinkled, according to the instructions to the patient, into a small amount of soft food (e.g., applesauce, fruit- or vegetable-based baby food, or yogurt) or into a small amount of liquid (e.g., infant formula, apple juice, or pediatric electrolyte solution).

Granules or pellets that result in a solution when used according to the instructions to patients do not require a dissolution test. In this case, a disintegration test is to be conducted.

For granules or pellets that result in a suspension when used according to the instructions to the patient, a dissolution test should be developed. In this case, the amount of sample to be transferred to the dissolution equipment should be equivalent to 1-unit dose. If the product has different doses according to body weight or age, the amount of sample to be transferred to the dissolution equipment should correspond to the highest unit dose that can be administered. If labeled for single use, each sample should come from a different container/packet.

Sometimes, such granules or pellets are filled in capsules, which are then opened prior to being administered by the patient. In this case, the dissolution test needs to be conducted only with the capsule contents.

Food and beverages may influence the bioavailability of the drug substance(s) incorporated into the granules or pellets. However, adding food or beverage to the dissolution media is typically not required. See FDA Draft 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* (*9*).

Suspensions

The product needs to be re-suspended according to the instructions to the patient before the test. The sample agitation procedure should be defined in order to ascertain a homogeneous and representative sample and to avoid introducing too many bubbles into the sample to ensure the precision of dosing. The sample preparation procedure should be well described and standardized in the final version of the method.

The amount of sample to be transferred to the dissolution equipment should be equivalent to 1-unit dose. If the product has different doses according to body weight or age, the amount of sample to be transferred to the dissolution equipment should correspond to the highest unit dose that can be administered at one time. If labeled for single use, each sample should come from a different container/packet.

The sample can be transferred to the dissolution apparatus by volume or by weight. Other alternative transferring procedures can be used.

The sample should be introduced into the dissolution medium in a way to be rapidly dispersed. The dispensing point/place and the dispensing time should be evaluated and defined in a case-by-case approach during method development. The evaluation of the amount of drug dissolved at early time points (5–10 min) may be useful. Lower paddle speeds may be appropriate for this type of dosage form.

Powders for Oral Suspension, Granules for Oral Suspension, or Tablets for Oral Suspension

Powders, granules, or tablets for oral suspension are prepared according to the instructions to the patient to constitute a suspension, and the resulting suspension is placed into the dissolution equipment.

For additional information regarding dissolution test conditions for these type of dosage forms, see *Suspensions*.

Lozenges

Lozenges can be, basically, manufactured in two ways: 1) molded, where the drug substance(s) is/are dissolved in a hot mixture of sugars, syrups, and other ingredients, the final mixture is transferred to molds and cooled down; and 2) compressed, where all the formulation components, in the powder form, are compressed together.

In case of molded lozenges, a dissolution or disintegration test may not be required. In the case of compressed lozenges, the development of the dissolution or disintegration test should follow the same steps as any other immediate-release solid oral dosage form.

Oral Pastes and Oral Gels

In addition to the equipment described in ⟨711⟩ and ⟨724⟩, it may be useful to consider the equipment and procedures described in *Semisolid Drug Products—Performance Tests* ⟨1724⟩.

Chewable Gels

The development of the dissolution test for chewable gels should follow the same steps as for any other immediate-release solid oral dosage form.

Type A Medicated Articles and Type B and Type C Medicated Feeds

For definitions and general descriptions of animal drugs and drug products delivered in animal feeds, see *Animal Drugs for Use in Animal Feeds* ⟨1152⟩.

Usually, dissolution testing is not required for Type A medicated articles and Type B and Type C medicated feeds that deliver animal drugs and drug products in animal feeds, but it may be required to support certain formulation changes for approved products or bioequivalence determinations for generic products.

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