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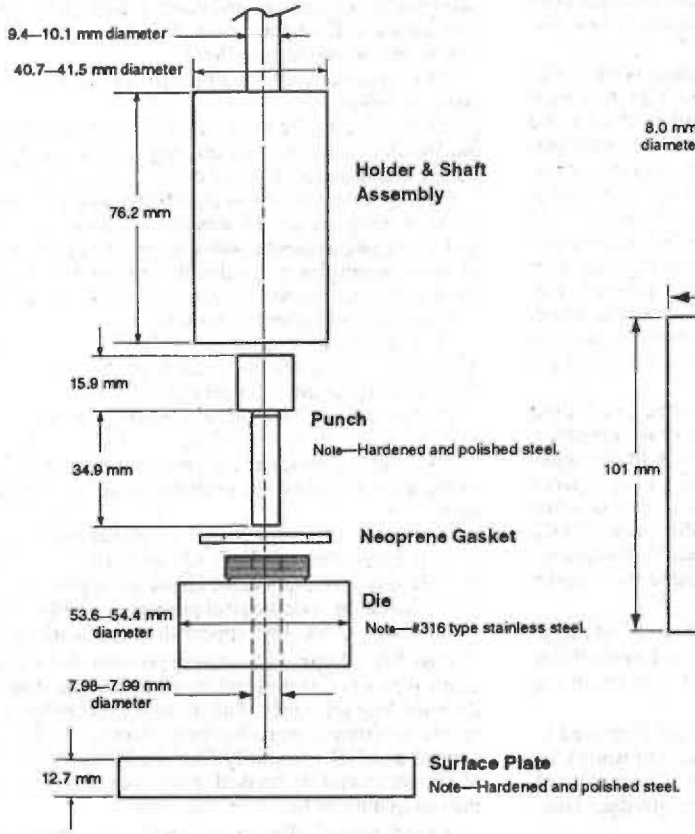
such as hydrodynamics (e.g., test apparatus, and disk rotation speed or fluid flow) and test conditions (e.g., temperature, fluid viscosity, pH, and buffer strength in the case of ionizable compounds). By exposing the surface area of a material to an appropriate dissolution medium while maintaining constant temperature, stirring rate, and pH, the intrinsic dissolution rate can be determined. Typically the intrinsic dissolution is expressed in terms of mg per minute per $cm^2$.

**Apparatus**—A typical apparatus consists of a punch and die fabricated out of hardened steel. The base of the die has three threaded holes for the attachment of a surface plate made of polished steel, providing a mirror-smooth base for the compacted pellet. The die has a 0.1-cm to 1.0-cm diameter cavity into which is placed a measured amount of the material whose intrinsic dissolution rate is to be determined. The punch is then inserted in the die cavity and the test material is compressed with a benchtop tablet press. [NOTE—A hole through the head of the punch allows insertion of the metal rod to facilitate removal from the die after the test.] A compacted pellet of the material is formed in the cavity with a single face of defined area exposed on the bottom of the die (see accompanying figure). The bottom of the die cavity is threaded so that at least 50% to 75% of the compacted pellet can dissolve without its falling out of the die. The top of the die has a threaded shoulder that allows it to be attached to a holder. The holder is mounted on a laboratory stirring device, and the entire die, with the compacted pellet still in place, is immersed in the dissolution medium and rotated by the stirring device (see *Dissolution* ⟨711⟩).




Apparatus for Intrinsic Dissolution

**Test Preparation**—Weigh the material to be tested onto a piece of tared weighing paper. Attach the surface plate to the underside of the die, and secure it with the three screws provided. Transfer the accurately weighed portion of the material under test into the die cavity. Place the punch into the chamber, and secure the metal plate on top of the assembly. Compress the powder on a hydraulic press for 1 minute at the minimum compression pressure necessary to form a nondisintegrating compacted pellet. Detach the surface plate, and screw the die with punch still in place into the holder. Tighten securely. Remove all loose powder from the surface of the die by blowing compressed air or nitrogen.

**Procedure**—Slide the die-holder assembly into the dissolution test chuck, and tighten. Position the shaft in the spindle so that when the tested head is lowered, the exposed surface of the compacted pellet will be 3.8 cm from the bottom of the vessel. The disk assembly should be aligned to minimize wobble, and air bubbles should not be allowed to form on the compacted pellet or die surface as this could alter fluid flow. [NOTE—Air bubbles may be avoided by using an apparatus with a different configuration, such as a die holder that holds the compacted pellet in a fixed vertical position with agitation provided by a paddle positioned 6 mm from the surface of the pellet.] Perform the analysis as directed in the individual monograph. If possible, sink conditions should be maintained throughout the test. The area of the compacted pellet against time until 10% is dissolved. The cumulative amount dissolved per unit area is given by the cumulative amount dissolved at each time point divided by the surface area exposed (0.5 $cm^2$). Linear regression should then be performed on data points up to and including the time point beyond which 10% is dissolved. The intrinsic dissolution rate of the test specimen, in mg per minute per $cm^2$, is determined from the slope of the regression line.

# ⟨1088⟩ IN VITRO AND IN VIVO EVALUATION OF DOSAGE FORMS

The Pharmacopeia provides for dissolution and drug release testing in the majority of monographs for solid oral and transdermal dosage forms. In recognition of the sensitivity of dissolution tests, where a valid bioavailability-bioequivalence (BA-BE) study is in hand, the

of clinically successful formulations. Similarity in dissolution behavior has long been sought from the perspectives of both bioavailability and quality control considerations.

It is the goal of the pharmaceutical scientist to find a relationship between an in vitro characteristic of a dosage form and its in vivo performance. The earliest achievable in vitro characteristic thought to portend an acceptable in vivo performance was tablet and capsule disintegration. A test for disintegration was adopted in *USP XIV* (1950). At that time, no quantitative work was done in attempting to demonstrate such a relationship, especially in regard to in vivo product performance. However, advances in instrumental methods of analysis ultimately opened up prospects for this work. The disintegration test was recognized as being insufficiently sensitive by the USP-NF Joint Panel on Physiologic Availability, and in 1968 the Panel directed the identification of candidate articles for the first twelve official dissolution tests that used *Apparatus 1*.

The state of science is such that conduct of in vivo testing is necessary in the development and evaluation of dosage forms. Also, no product, including suspensions and chewable tablets, should be developed without dissolution or drug release characterization where a solid phase exists. This chapter sets forth, for products intended for human use, guidelines for characterizing a drug that include: (1) developing in vitro test methods for immediate-release and modified-release dosage forms, (2) designing in vivo protocols, and (3) demonstrating and assessing in vitro-in vivo correlations for modified-release dosage forms.

## IN VITRO EVALUATION

### Dissolution and Drug Release Testing—Method Development for Immediate-release Dosage Forms

Dissolution testing is required for all solid oral Pharmacopeial dosage forms in which absorption of the drug is necessary for the product to exert the desired therapeutic effect. Exceptions are for tablets meeting a requirement for completeness of solution or for rapid (10 to 15 minutes) disintegration for soluble or radiolabeled drugs. The apparatus and procedure conform to the requirements and specifications given in the general chapter *Dissolution* ⟨711⟩. Generally, experiments are conducted at 37°.

The dissolution medium preferably is deaerated water or, if substantiated by the solubility characteristics of the drug or the formulation, a buffered aqueous solution (typically pH 4 to 8) or a dilute acid (0.001 *N* to 0.1 *N* hydrochloric acid) may be used. The usual volume of the medium is 500 to 1000 mL, with the use of greater volumes (up to 2000 mL) allowed for drugs having limited solubility. The quantity of medium used should be not less than 3 times that required to form a saturated solution of the drug substance. The significance of deaeration of the medium should be determined. Addition of solutes (i.e., surfactants) and electrolytes to aid in solubilization of the drug must be balanced against the loss of the discriminatory power of the test. The use of hydroalcoholic media is generally not favored. The use of such media should be supported by a documented in vitro-in vivo correlation. Conversely, it should be recognized that this discriminatory power could in some circumstances be excessive in that it may result in detection of differences in dissolution that are not clinically significant.

The choice of apparatus should be based on knowledge of the formulation design and actual dosage form performance in the in vitro test system. Since dissolution apparatuses tend to become less discriminating when operated at faster speeds, lower stirring speeds should be evaluated and an appropriate speed chosen in accordance with the test data. The most common operating speeds are 100 rpm for *Apparatus 1* (basket) and 50 rpm for *Apparatus 2* (paddle) for solid-oral dosage forms and 25 rpm for suspensions. A 40-mesh screen is used in almost all baskets, but other mesh sizes may be used when the need is documented by supporting data.

*Apparatus 2* is generally preferred for tablets. *Apparatus 1* is generally preferred for capsules and for dosage forms that tend to float or that disintegrate slowly. A sinker, such as a few turns of platinum wire, may be used to prevent a capsule from floating. Other types of sinker devices that achieve minimal coverage of dosage form surface are commercially available. Where the use of a sinker device is employed, it is incumbent on the analyst to assure that the device used does not alter the dissolution characteristics of the dosage form.

Dissolution testing should be conducted on equipment that conforms to the requirements in the chapter *Dissolution* ⟨711⟩ and that has been calibrated with both the USP Salicylic Acid and Prednisone Calibrator Tablets. The method of analysis should be validated in accordance with the procedures given in the chapter *Validation of Compendial Methods* ⟨1225⟩.

The test time is generally 30 to 60 minutes, with a single time point specification for pharmacopeial purposes. To allow for typical disintegration times, test times of less than 30 minutes should be based on demonstrated need. Industrial and regulatory concepts of product comparability and performance may require additional time points, and this may also be a feature required for product registration or approval. For registration purposes, a plot of percentage of drug dissolved versus time should be determined. Enough time points should be selected to characterize adequately the ascending and plateau phases of the dissolution curve.

Dissolution test times and specifications usually are established on the basis of an evaluation of dissolution profile data. Typical specifications for the amount of active ingredient dissolved, expressed as a percentage of the labeled content ($Q$), are in the range of 70% to 80% $Q$ dissolved. A $Q$ value in excess of 80% is not generally used, as allowance needs to be made for assay and content uniformity ranges.

For products containing more than a single active ingredient, dissolution normally should be determined for each active ingredient. Where a dissolution test is added to an existing monograph, the disintegration test is deleted. However, in the case of sublingual preparations, a short disintegration time may be retained as a monograph specification in addition to a dissolution requirement.

### Dissolution and Drug Release Testing—Method Development for Modified-release Dosage Forms

Drug release testing is required for all modified-release dosage forms in which absorption of the drug is necessary for the product to exert the desired therapeutic effect. The apparatus and procedure conform to the requirements and specifications given in the general chapter *Drug Release* ⟨724⟩.

The dissolution medium preferably is deaerated water or, if substantiated by the solubility characteristics of the drug or the formulation, buffered aqueous solutions (typically pH 4 to 8) or dilute acid (0.001 *N* to 0.1 *N* hydrochloric acid) may be used. (See above under *Dissolution and Drug Release Testing—Method Development for Immediate-release Dosage Forms.*) For modified-release dosage forms, the pH- and surfactant-dependence of the dosage form should be evaluated by in vitro testing in media of various compositions. The volume of medium will vary depending on the apparatus used and the formulation under test.

The choice of apparatus should be based on knowledge of the formulation design and actual dosage form performance in the in vitro test system. *Apparatus 1* (basket) or *Apparatus 2* (paddle) may be more useful at higher rotation frequencies (e.g., the paddle at 100 rpm). *Apparatus 3* (reciprocating cylinder) has been found to be especially useful for bead-type modified-release dosage forms. *Apparatus 4* (flow cell) may offer advantages for modified-release dosage forms that contain active ingredients having very limited solubility. *Apparatus 7* (reciprocating disk) has been shown to have application to nondisintegrating oral modified-release dosage forms, as well as to transdermal dosage forms. *Apparatus 5* (paddle over disk) and *Apparatus 6* (cylinder) have been shown to be useful for evaluating and testing transdermal dosage forms.

At least three test times are chosen to characterize the in vitro drug release profile for Pharmacopeial purposes. Additional sampling times may be required for drug approval purposes. An early time point, usually 1 to 2 hours, is chosen to show that potential dose dumping is not probable. An intermediate time point is chosen to define the in vitro release profile of the dosage form, and a final time point is chosen to show essentially complete release of the drug. Test times and specifications are usually established on the basis of an evaluation of drug release profile data. For products containing more than a single active ingredient, drug release should be determined for each active ingredient.

Where a single set of specifications cannot be established to cover multisource monograph articles, application of a Case Three standard is appropriate. In Case Three, multiple drug release tests are included under the same monograph heading, and labeling requirements are

included to indicate with which drug release test a specific product complies and, in some cases, the biological performance to be expected.

Drug release testing should be conducted on equipment that conforms to the requirements in the chapter *Drug Release* ⟨724⟩ and that has been calibrated with the appropriate USP calibrators. The method of analysis should be validated in accordance with the procedures given in the chapter *Validation of Compendial Methods* ⟨1225⟩.

## IN VIVO EVALUATION OF MODIFIED-RELEASE DOSAGE FORMS

In evaluating a modified-release product, a fundamental issue is the types of studies that should be performed to give reasonable assurance of safety and efficacy. While providing important information concerning the release characteristics of the drug from the dosage form, at present in vitro studies are most useful for such purposes as monitoring drug product stability and manufacturing process control. The assessment of safety and efficacy of a modified-release dosage form is best achieved through observing in vivo pharmacodynamics or pharmacokinetics. Moreover, where there is a well-defined, predictive relationship between the plasma concentrations of the drug or active metabolites and the clinical response (therapeutic and adverse), it may be possible to use plasma drug concentration data alone as a basis for the approval of a modified-release preparation that is designed to replace an immediate-release preparation.

The following guidelines are intended to provide guidance in drug substance evaluation and the design, conduct, and evaluation of studies involving modified-release dosage forms. While these guidelines will focus on oral drug delivery systems, the principles may be applicable to other routes of drug administration (e.g., transdermal, subcutaneous, intramuscular, etc.).

### Characterization of Drug Substance

#### PHYSICOCHEMICAL PROPERTIES

Physicochemical information necessary to characterize the drug substance in a modified-release dosage form should generally be no less than for the drug substance in an immediate-release dosage form. Additional physicochemical information may be needed on polymorphism, particle size distribution, solubility, dissolution rate, stability, and other release-controlling variables of the active drug entity under conditions that may react to the extremes of the physiologic environment experienced by the dosage form. For purposes of this chapter, *active drug entity* is taken to be the official drug substance.

#### PHARMACOKINETIC PROPERTIES

It is recommended to characterize thoroughly the input absorption profile of the active drug entity from a rapidly available preparation (an intravenous solution or oral solution or a well-characterized FDA-approved immediate-release drug product), which serves in turn as a reference to evaluate the input profile of the modified-release dosage form. This information together with the biological disposition characteristics for the active drug entity can characterize and predict changes in the bioavailability of the drug when input is modified as in the case of the modified-release dosage form. For example, if the active drug entity exhibits saturable first-pass hepatic metabolism, a reduction in systemic availability could result after oral administration if the input rate is decreased.

In designing an oral modified-release dosage form, it may be useful to determine the absorption of the active drug entity in various segments of the gastrointestinal tract (particularly in the colon in the case of dosage forms that may release drug in this region). The effects of food also may be important, and should be investigated.

#### DISPOSITION PROPERTIES

The information required to characterize the processes of disposition of the active drug entity from a modified-release dosage form should include those generally determined for the same drug in an immediate-release dosage form. This may include the following:

(1) Disposition parameters—clearance, volume of distribution, half-life, mean residence time, or model-dependent or noncompartmental parameters.
(2) Linearity or characterization of nonlinearity over the dose or concentration range which could possibly be encountered.
(3) Accumulation.
(4) Metabolic profile and excretory organ dependence, with special attention to the active metabolites and active enantiomers of racemic mixtures.
(5) Enterohepatic circulation.
(6) Protein binding parameters and dialyzability.
(7) The effects of age, gender, race, and relevant disease states.
(8) Plasma/blood ratios.
(9) A narrow therapeutic index or a clinical response that varies significantly as a function of the time of day.

#### PHARMACODYNAMIC PROPERTIES

Prior to developing a modified-release dosage form, information described below should be gathered.

Concentration-response relationships should be available over a dose range sufficiently wide to encompass important therapeutic and adverse responses. In addition, the equilibration time[1] characteristics between plasma concentration and effect should be evaluated. These concentration-response relationships should be sufficiently characterized so that a reasonable prediction of the safety margin can be made if dose-dumping from the modified-release dosage form should occur. If there is a well-defined relationship between the plasma concentration of the active drug entity or active metabolites and the clinical response (therapeutic and adverse), the clinical performance of a new modified-release dosage form could be characterized by plasma concentration-time data. If such data are not available, clinical trials of the modified-release dosage form should be carried out with concurrent pharmacokinetic-pharmacodynamic measurements.

### Characterization of the Dosage Form

#### PHYSICOCHEMICAL PROPERTIES

The variables employed to characterize the physicochemical properties of the active drug entity as it exists or is discernible in the dosage form should be the same as those employed to characterize the drug substance. Solubility and dissolution profiles over a relevant pH range, usually from pH 1 to pH 7.4, should be obtained, with particular attention given to the effect of the formulation (as compared to the active drug entity). Characterization of formulations that are insoluble in aqueous systems may require the addition of sodium lauryl sulfate or other surfactant.

#### PHARMACOKINETIC PROPERTIES

The types of pharmacokinetic studies that should be conducted are a function of how much is known about the active drug entity, its clinical pharmacokinetic and biopharmaceutic properties, and whether pharmacokinetic studies are intended to be the sole basis for product approval. As a minimum, (1) a single-dose crossover study for each strength of a modified-release dosage form and (2) a multiple-dose, steady-state study using the highest strength of a modified-release do-

[1] Equilibration time is a measure of the time-dependent discontinuity between measured plasma concentrations and measured effects. The discontinuity is more often characterized by the degree of hysteresis observed when the effect-concentration plot for increasing concentrations is compared with that for decreasing concentrations. Where the equilibration time is very short

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