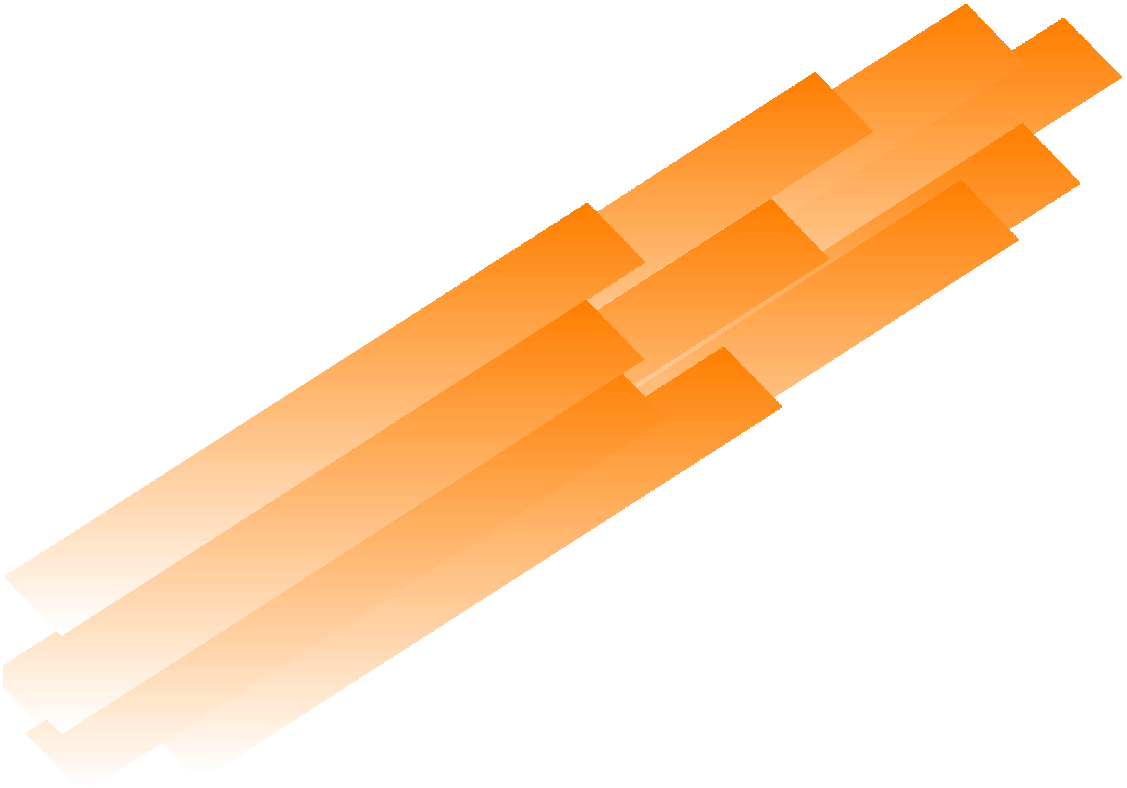
Guidance for Industry

Dissolution Testing of Immediate Release Solid Oral Dosage Forms



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
August 1997

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Dissolution Testing of Immediate Release Solid Oral Dosage Forms

I. INTRODUCTION

This guidance is developed for immediate release (IR) dosage forms and is intended to provide (1) general recommendations for dissolution testing; (2) approaches for setting dissolution specifications related to the biopharmaceutic characteristics of the drug substance; (3) statistical methods for comparing dissolution profiles; and (4) a process to help determine when dissolution testing is sufficient to grant a waiver for an in vivo bioequivalence study. This document also provides recommendations for dissolution tests to help ensure continuous drug product quality and performance after certain postapproval manufacturing changes. Summary information on dissolution methodology, apparatus, and operating conditions for dissolution testing of IR products is provided in summary form in Appendix A. This guidance is intended to complement the SUPAC - IR guidance for industry: *Immediate Release Solid Oral Dosage Forms: Scale-up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation*, with specific reference to the generation of dissolution profiles for comparative purposes.

II. BACKGROUND

Drug absorption from a solid dosage form after oral administration depends on the release of the drug substance from the drug product, the dissolution or solubilization of the drug under physiological conditions, and the permeability across the gastrointestinal tract. Because of the critical nature of the first two of these steps, in vitro dissolution may be relevant to the prediction of in vivo performance. Based on this general consideration, in vitro dissolution tests for immediate release solid oral dosage forms, such as tablets and capsules, are used to (1) assess the lot-to-lot quality of a drug product; (2) guide development of new formulations;

[1]This guidance has been prepared by the Immediate Release Expert Working Group of the Biopharmaceutics Coordinating Committee in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on the dissolution testing of immediate release solid oral dosage forms. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

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and (3) ensure continuing product quality and performance after certain changes, such as changes in the formulation, the manufacturing process, the site of manufacture, and the scale-up of the manufacturing process.

Current knowledge about the solubility, permeability, dissolution, and pharmacokinetics of a drug product should be considered in defining dissolution test specifications for the drug approval process. This knowledge should also be used to ensure continued equivalence of the product, as well as to ensure the product's *sameness* under certain scale-up and postapproval changes.

New drug applications (NDAs) submitted to the Food and Drug Administration (FDA) contain bioavailability data and in vitro dissolution data, that, together with chemistry, manufacturing, and controls (CMC) data, characterize the quality and performance of the drug product. In vitro dissolution data are generally obtained from batches that have been used in pivotal clinical and/or bioavailability studies and from other human studies conducted during product development. Acceptable bioequivalence data and comparable in vitro dissolution and CMC data are required for approval of abbreviated new drug applications (ANDAs) (21 CFR 314.94). The in vitro specifications for generic products should be established based on a dissolution profile. For new drug applications, as well as generic drug applications, the dissolution specifications should be based on acceptable clinical, bioavailability, and/or bioequivalence batches.

Once the specifications are established in an NDA, the dissolution specifications for batch-to-batch quality assurance are published in the *United States Pharmacopeia* (USP) as compendial standards, which become the official specifications for all subsequent IR products with the same active ingredients. In general, these compendial dissolution standards are single-point dissolution tests, not profiles.

III. BIOPHARMACEUTICS CLASSIFICATION SYSTEM

Based on drug solubility and permeability, the following Biopharmaceutics Classification System (BCS) is recommended in the literature (Amidon 1995):

Case 1:	High Solubility - High Permeability Drugs
Case 2:	Low Solubility - High Permeability Drugs
Case 3:	High Solubility - Low Permeability Drugs
Case 4:	Low Solubility - Low Permeability Drugs

This classification can be used as a basis for setting in vitro dissolution specifications and can also provide a basis for predicting the likelihood of achieving a successful in vivo-in vitro correlation (IVIVC). The solubility of a drug is determined by dissolving the highest unit dose of the drug in 250 mL of buffer adjusted between pH 1.0 and 8.0. A drug substance is considered highly soluble when the dose/solubility volume of solution are less than or equal to 250 mL. High-permeability drugs are generally those with an extent of absorption that is greater than 90% in the absence of

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