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FIP GUIDELINES FOR DISSOLUTION TESTING OF SOLID ORAL PRODUCTS (FINAL DRAFT, 1995)

JOINT REPORT OF THE SECTION FOR OFFICIAL LABORATORIES AND MEDICINES CONTROL SERVICES AND THE SECTION OF INDUSTRIAL PHARMACISTS

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In 1981 Federation International Pharmaceutique (FIP) published "Guidelines for Dissolution Testing of Solid Oral Products" as a joint report of the Section for Official Laboratories and Medicines Control Services and the Section of Industrial Pharmacists. These guidelines were intended as suggestions primarily directed to compendial committees, working on the introduction of dissolution/release tests for the respective Pharmacopoeias.

During the past decade there have been many developments. Biopharmaceutics has attracted much scientific as well as political interest. Dissolution test methodology has been introduced to many Pharmacopoeias and a number of regulations and guidelines on bioavailability, bioquivalence, and in vitro *dissolution testing have been issued at national and international levels.*

The joint working group on dissolution of the two FIP sections, therefore, decided to establish a new dissolution guideline, taking all these developments into consideration but adding proposals for further harmonization and for definitions and procedures which are not yet covered by international recommendations.

The following guideline is the final draft version elaborated by the FIP working group with contributions from J. M. Aiache, Clermont Ferrant; H. Blume, Eschborn; H. D. Friedel, Leverkusen; L. T. Grady, Rockville; V. Gray, Rockville; B. Hubert, Rockville; J. Krämer, Eschborn; I. McGilveray, Ottawa; F. Langenbucher, Basel; L. Leeson, Montville; L. Lesko, Rockville; H. Möller, Frankfurt; S. Qureshi, Ottawa; V. P. Shah, Rockville; M. Siewert, Frankfurt; R. Süverkrp̈, Bonn; J. O. Waltersson, Uppsala; and E. Wirbitzki, Frankfurt.

The FIP working group decided to publish this final draft version to give colleagues from universities, drug authorities, Pharmacopoeias, and the pharmaceutical industry the opportunity to contribute with their comments to further improvement of the guideline text prior to publication of the final official version. FIP will organize a symposium on all biopharmaceutical aspects of in vitro *dissolution testing of solid oral products in November 1996, where the final guidelines for dissolution testing of solid oral products will be discussed and issued.*

Key Words: Dissolution testing; Solid oral products; FIP; *In vitro–In vivo*

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INTRODUCTORY REMARKS

THE FIRST "GUIDELINES for Dissolution Testing of Solid Oral Products" were published in 1981 (1) as a joint report of the Section for Official Laboratories and Medicines Control Services and the Section of Industrial Pharmacists of the FIP. These guidelines were intended as suggestions primarily directed to compendial committees, working on the introduction of dissolution/release tests for the respective Pharmacopoeias.

During the past decade, there have been many developments. Biopharmaceutics has attracted much interest scientifically as well as regarding drug regulatory policies. Dissolution test methodology has been introduced to many Pharmacopoeias and a number of regulations and guidelines on bioavailability, bioequivalence, and *in vitro* dissolution testing have been issued at national and international levels.

These updated guidelines (second edition) are the result of careful discussions of the joint working group of the two FIP sections and are based on recent developments. Descriptions of test methodology are no longer necessary, because they are already published elsewhere, officially or semi-officially. Differences between the regulations of different countries and compendias were identified and proposals for harmonization are made.

As far as is reasonable for the purpose of these guidelines, technical terms and definitions have been adopted from other harmonized recommendations and mainly correspond to United States Pharmacopeia (USP) terminology. New terms are "*in vitro-in vivo*" comparison," "verification," and "side batches." *In vitro-in vivo* comparison means any study collecting *in vitro*- and *in vivo*-data on the same set of test specimen to obtain information and understanding about how *in vitro* and *in vivo* performance are related to each other. A significant *in vivo-in vitro* association can be a result of an *in vitro-in vivo* comparison study, but valuable information could also be obtained when no correlation in a strict sense (eg, USP levels) is achieved. Verification is used to define the *in vivo* dataset which provides evidence that a chosen *in vitro* test method and the proposed specifications are suitable for the drug formulation in terms of biopharmaceutical performance. Verification is proposed as a new terminus technicus to avoid extending validation also on *in vivo* investigations. Side batches are batches of a given drug formulation which represent the intended upper and lower specification limits. They are preferably to be derived from the defined manufacturing process by setting process parameters within the range of maximum variability expected from process validation studies. The term dissolution itself is used for all dosage forms, that is, immediate-release (such as prompt drug release or conventional dosage forms) as well as controlled/modified-release products (such as controlled, delayed, extended, modified, prolonged, or sustained).

CONCEPTS OF DISSOLUTION TESTING

In vitro dissolution testing serves as an important tool for characterizing the biopharmaceutical quality of a product at different stages in its life cycle. In early drug development *in vitro* dissolution properties are supportive for choosing between different alternative formulation candidates for further development and for evaluation of active ingredients/drug substances. *In vitro* dissolution data are supportive in the evaluation and interpretation of possible risks, especially in the case of controlled/modified-release dosage forms, for example, as regards dose dumping, food effects on bioavailability, or interaction with other drugs, which influence gastrointestinal environmental conditions. Biopharmaceutical aspects are as important for stability concerns as they are for batch release after production, *in vitro* dissolution being of high relevance in quality control and quality assurance. Last but not least, *in vitro* dissolution data will be of great impor-

tance when assessing changes in production site and manufacturing process or formulation, and assist in decisions concerning the need for bioavailability studies.

None of these purposes can be fulfilled by an *in vitro* test system without sufficient reliability. Reliability here would be defined as the system being experimentally sound, yielding precise, accurate, repeatable results and with sufficient knowledge of the *in vivo* relevance of the dissolution data obtained.

Requirements for dissolution testing have been reviewed in the literature (2–6). Since *in vitro* dissolution is a physical test, defined by convention, and it is of a destructive nature, proving reliability requires special attention. It, therefore, is within the scope of these guidelines to define suitable testing equipment and experimental design as well as to suggest the background for adequate physical and analytical validation, together with verification procedures according to the state of biopharmaceutical science.

The guidelines are primarily dedicated to solid oral products. The general concepts, however, may be adapted to *in vitro* dissolution testing of drug substances/powders, semi-solid oral products, suppositories and, with distinct restrictions, to other nonoral products.

APPARATUS

Large numbers of different dissolution apparatuses are described in the literature, but only some of them withstand critical methodological examination. Two basic technical principles are applied for *in vitro* dissolution testing: the "stirred beaker method" and the "flow through procedure." The "stirred beaker method" places the test specimen and a fixed volume of fluid in a large vessel, and stirring provides mechanical (hydrodynamic) agitation. This closed system design was adopted as the first official method in USP XVIII in 1970, described as the rotating basket (apparatus 1, USP).

The rotating basket and the paddle (apparatus 2, USP) devices are simple, robust, and adequately standardized apparatuses which are used all around the world and thus are supported by the widest experience of experimental use. It is because of these advantages that the paddle and rotating basket apparatuses are recommended in various guidelines as first choice for the *in vitro* dissolution testing of immediate as well as controlled/modified-release preparations.

Because of the "single container" nature of the paddle/basket apparatus, however, experimental difficulties may arise in terms of the need for a change in pH or of any other (partial) change in the test medium during an investigation. Furthermore, a number of sparingly soluble drugs and dosage forms, particularly aerophilic multiple unit forms, tend to float initially. Proposals have been made to overcome some of these difficulties, for example, to increase solubility by addition of an appropriate amount of surfactant.

With the flow-through cell (apparatus 4, USP), the specimen is placed in a small column which is continuously flushed with a stream of fluid, simultaneously providing the medium and the mechanical agitation for dissolution of the drug substance. It can be run as an open as well as a closed system. The open system design especially provides several advantages in some of the difficult cases mentioned above and was adopted first by the Deutscher Arzneimittelcodex (German Pharmaceutical Codex, DAC) in 1981.

The flow-through apparatus is currently monographed in USP and Ph.Eur. and is also proposed for Ph.Jap. Description of the system is concordant worldwide. The paddle/basket system is described in USP, the European, the Japanese, and many other Pharmacopoeias. Some minor discrepancies are still found in details of the respective monographs. Full international harmonization is strongly recommended, as proposed in Table 1.

As a further system (apparatus 3) USP describes the reciprocating cylinder. With these four apparatuses, dissolution testing of most oral drug products should be possible on a reasonable basis. Neither too tight restrictions nor unnecessary proliferation of al-

TABLE 1
Dimensions of the Paddle/Basket Apparatuses (Millimeters)

	Ph.Eur.2	USP 23	Ph.J.12 (Suppl. 1)	Proposal (EFPIA)
Vessel				
Height	168 ± 8	160–175	160–175	160–210
Internal Diameter	102 ± 4	98–106	98–106	102 ± 4
Paddle				
Shaft Diameter	9.75 ± 0.35	9.4–10.1 (before coating)	9.75 ± 0.35	9.75 ± 0.35
Blade				
Upper chord	74.5 ± 0.5	74.0–75.0	74.5 ± 0.5	74.5 ± 0.5
Lower chord	42.0	42.0 ± 1.0	42 ± 1	42.0 ± 1.0
Height	19.0	19.0 ± 0.5	19.0 ± 0.5	19.0 ± 0.5
Radius of the disk of which the blade is cut out	41.5	41.5 ± 1.0	41.5	41.5 ± 1.0
Radius upper corners	1.2*	1.2*	1.2**	1.2
Thickness	4.0 ± 1	4.0 ± 1.0	3–5	4.0 ± 1.0
Positioning the stirring device				
Distance between inside of the bottom of the vessel and the blade	25 ± 2	25 ± 2	25 ± 2	25 ± 2
Distance between shaft axis and vertical axis of the vessel	≤2	≤2	≤2	≤2
Stirring characteristic	smoothly without significant wobble (≤ 0.5 mm)	smoothly without significant wobble		smoothly without significant wobble (≤ 0.5 mm)
Basket				
Shaft diameter	(9.75 ± 0.35) 6.4 ± 0.1	6.3–6.5 or 9.4–10.1	(9.75 ± 0.35) 6.4 ± 0.1	9.4 ± 10.1
Screen				
Wire diameter	0.254	0.254 (0.01 inch) or 0.016 inch†	No. 36 wire gauze	0.254‡
Openings	0.381	0.381 (0.015 inch) or 0.034 inch†	0.425	0.381‡
Height of screen	27.0 ± 1	27.0 ± 1.0	27.0 ± 1	27.0 ± 1.0
Total height of basket	36.8 ± 3	36.8 ± 3.0	36.8 ± 3	36.8 ± 3.0
Internal diameter of basket	20.2 ± 1	20.2 ± 1.0	20.2 ± 1	20.2 ± 1.0
External diameter of basket	22.2 ± 1	22.2 ± 1.0	22.2 ± 1	22.2 ± 1.0
External diameter of ring	25.4 ± 3	25.4 ± 3.0	25.4 ± 3	25.4 ± 3.0

TABLE 1
Continued

	Ph.Eur.2	USP 23	Ph.J.12 (Suppl. 1)	Proposal (EFPIA)
Vent hole diameter	2	2.0	2	2.0 ± 0.5
Height of coupling disk	5.1 ± 0.5	5.1 ± 0.5	5.1 ± 0.5	5.1 ± 0.5
Positioning of the stirring device:				
Distance between inside of the bottom of the vessel and the basket	25 ± 2	25 ± 2	25 ± 2	25 ± 2
Distance between the shaft axis and the vertical axis of the vessel	≤ 2	≤ 2	≤ 2	≤ 2
Stirring characteristic	smoothly without significant wobble	smoothly without significant wobble		smoothly without significant wobble

* proposals to come (Re: USP 23 Suppl. 2 and PA/PH/SG(94)83, May 94)
** proposed in JP Forum Vol. 3 No. 3 (July, 1994), see Figure 1
† basket to be used is indicated in the individual monographs
‡ should correspond with the requirements for standards, eg, International Standard ISO 2194–1972

ternative dissolution apparatuses should be encouraged. If an individual drug product cannot be accommodated by one of the apparatuses, described above, alternative models or appropriate modifications have to be developed. In such a case, however, superiority of the alternative or the modification has to be proven in comparison to the well established and standardized apparatuses. In the past, many papers intended to justify an alternative model by proving that *in vitro* dissolution results were equivalent or similar to those obtained with, for example, the paddle method. According to the understanding of these guidelines, the latter provides clear evidence that the paddle method should be used!

Modification of the apparatus as described in the Pharmacopoeias or the harmonization proposal in Table 1 can be intended for automation, for example, of the sampling procedure. In such cases, whether it is, for example, sampling via the hollow shaft of paddle or basket or permanent sampling probes in the beaker, which could potentially influence agitation characteristics (7), or any other measure, that results are equivalent with and without the modification should be validated on a product-by-product basis.

EXPERIMENTAL TESTING CONDITIONS

For all applications, *in vitro* dissolution data should at least allow some interpretation with regard to *in vivo* biopharmaceutical performance. In order to increase their predictive value, attempts have been made to adjust *in vitro* test conditions (8–11) as close as possible to physiologic conditions. Nevertheless, several examples demonstrate that such conditions can also lead to misinterpretations and are not able to guarantee *in vitro* results routinely relevant to the *in vivo* situation (12).

In general, an aqueous medium should be used. Attempting to strictly mimic the physi-

ologic gastrointestinal environment (eg, composition of gastric or intestinal fluid) is not recommended: the testing conditions should be chosen as far as is reasonable based on the physico-chemical characteristics of drug substance, within the range which a drug or dosage form could experience after oral administration. These following ranges were established based on several conferences and recommendations (eg, 13,14,15).

For basket/paddle methods the volume should be 500–1,000 ml. Nine hundred ml had been introduced historically; 1,000 ml should be easier to handle in a metric system, this volume being practical with all equipment commercially available today. Therefore, 1,000 ml should be considered for new drug products or in case of a revision of existing test procedures. This recommendation does not mean that 1,000 ml should be adopted to all existing test procedures and specifications. Although larger vessels, such as up to 4,000 ml, could be advantageous for poorly soluble drugs, they are not described in compendia, and thus are not as well standardized and, therefore, should be regarded as modification of a compendial method (see the next section).

The pH of the test medium should be set within pH 1 and 6.8. A higher pH needs to be justified on a case-by-case basis and in general should not exceed pH 8. For low pH in the acidic range 0.1N HCl should be used. If, in a certain case, artificial gastric juice without enzymes (pH 1.2) is advantageous, this should be demonstrated. In the pH-range of 4.5–8.0 USP buffer solutions are recommended, because their buffer concentration (ionic strength) is not as high as that of, for example, buffers of Ph.Eur., which have not been designed for dissolution testing.

The use of water as a dissolution medium bears the disadvantage that test condition details, such as pH and surface tension, can vary depending on the source of the water and may be changed during the dissolution test itself, due to the influence of the drug products and to the (re)absorption of carbon dioxide from air. Further additives, for example, enzymes, salts, or surfactants, could be considered in specific cases. Their use should be justified as regards nature and concentration of additive (16). Addition of organic solvents should be avoided.

Agitation typically should be obtained in the basket/paddle apparatus by stirring at 50–100 rpm and in general should not exceed 150 rpm. Although maximum discriminatory power should be obtained with the lowest stirring rate, in many cases, experience with 75 rpm was felt to represent a reliable agitation for paddle equipment (17). For the flow through cell, flow rates should be set between eight and 50 ml/min.

Regarding temperature, $37 \pm 0.5°$ C should generally be used for oral dosage forms. Slightly increased test temperatures (eg, $38 \pm 0.5°$ C) are under consideration for special applications, for example, for rectal dosage forms, lower temperatures (eg, $32 \pm 0.5°$ C) for transdermal systems.

Relevant parameters to be considered for the definition of test conditions are solubility and deaeration. In former guidelines (1), "sink" conditions were requested. "Sink" was defined in different ways, for example, as 10–20% (1) or approximately 30% (18) of solubility concentration to assure that dissolution is not significantly influenced by solubility characteristics. Since "sink" conditions per se do not guarantee *in vivo-in vitro* associations and since reliable and predictive *in vitro* profiles in certain cases can be obtained by violating "sink" conditions, solubility and drug substance concentrations during the test should be a matter of validation studies to demonstrate that a chosen *in vitro* test method yields biopharmaceutically relevant results.

Case-by-case validation is also required regarding deaeration since some formulations will be sensitive whereas others are robust in this concern, thus making deaeration unnecessary. The dearation method has to be clearly characterized, since different methods can also have impact on dissolution profiles (19).

Ph.Jap.XII is currently the only Pharmacopoeia that requires a specific (very solid) sinker device for all capsule formulations.

USP recommends a few turns of wire helix when specimen tend to float. The EFPIA harmonization proposal suggests a similar one. Sinkers can significantly influence the *in vitro* dissolution profile of a drug (20). Since they are used especially with formulations causing problems during test performance, for example, flotation, they will alter the dissolution profile, so that other recommendations (18) are not applicable.

The use of sinkers, therefore, has to be part of case-by-case dissolution validation as well as of *in vitro-in vivo* comparison studies. Any strict requirement on use of sinkers or specific sinker types lacks scientific justification.

QUALIFICATION AND VALIDATION

Due to the nature of the test method, quality by design is an important qualification aspect for *in vitro* dissolution test equipment. Besides the geometrical and dimensional accuracy and precision as described and commented in the chapter on apparatus (including Table 1), any irregularities such as vibration or undesired agitation by mechanical imperfection are to be avoided. Besides the specification of the apparatus, qualification of dissolution equipment has to consider critical parameters, for example, temperature of test medium, rotation speed/flow rate, volume, and sampling probes and procedures, to be monitored periodically during the periods of use.

An apparatus suitability test with calibrators is a further important aspect of qualification and validation. The use of USP calibrator tablets (disintegrating as well as nondisintegrating) is recommended. Since some individual drug products might reveal similar or even higher sensitivity against technical variance in comparison to USP calibrator tablets, "in-house" standards are judged acceptable as additional, or, if validated, equivalent for calibrator tablets.

The suitability test has to cover each individual apparatus and to consist of the full USP program, meaning both calibrator types. Paddle and basket equipment, as well as 12 mm and 22.6 mm flow-through cell have to be qualified, unless only paddle or basket, respectively only small or large cell is used in one specific piece of equipment. The system suitability test of USP Apparatus 3 has to be performed with both a multiparticulate and a monoparticulate standard formulation. A system suitability test for flow-through cell has just been established and will soon be published for USP.

Apparatus suitability tests are recommended to be performed not less than twice per year per equipment and after any occasion of equipment change, significant repair, or movement. A change from paddle to basket or vice versa, however, may not require recalibration.

Additional validation aspects are precise product-related operation instructions (eg, deaeration procedure). Dissolution results may be influenced by the physical behavior of the specimen such as floating, adherence to the walls, and so forth. Thus, critical inspection and observation of test performance during the test procedure is required. This approach is especially important to explain any "out-lying" results and it clearly limits the extent of automation for a number of drug formulations.

Validation of automated systems, either concerning the sampling and analytical part or also including media preparation and test performance, has to consider accuracy and precision and avoid contamination by any dilutions, transfers, cleaning, or sample or solvent preparation procedures. There should be proof that there is no interference. This shall be evidence of no significant differences between data obtained with the manual dissolution equipment (see 2) and the automated system, including manipulations such as permanent sampling probes, additional valves, hollow shafts, and so forth. Since sensitivity to such modification may be formulation related, validation of automated dissolution equipment has to be established on a case-by-case basis.

Validation of the analytical procedures applied in dissolution testing, either automated or conventional, has to comply with "Valida-

tion of Analytical Procedures" (ICH 2) and "Validation of Compendial Methods" (<1225>, USP). Validation aspects thus are accuracy, precision (repeatability, reproducibility), specificity, linearity, and range. Special care has to be taken regarding stability of the drug in test medium and sample solutions, since the test procedure often includes exposure to hydrolytic media at 37° C over significant time spans.

FORMULATION CHARACTERIZATION

During development of the drug formulation, as a basis for any *in vitro-in vivo* comparison study as well as for the final choice of test conditions for quality control purposes, the respective dosage form has to be thoroughly characterized *in vitro* with respect to its biopharmaceutical performance. Special attention has to be paid to controlled/modified-release preparations, since sufficient information has to be gained about how much the dosage form itself, rather than variations in test conditions, "control" the rate of drug release.

Therefore, extensive dissolution tests are necessary to understand the delivery system and to have a rationale for the design of, for example, an *in vitro-in vivo* comparison study. The *in vitro* test profile will preferably consist of numerous individual dissolution tests under many different test conditions, involving the pH of test media and agitation within the ranges given in the section on experimental testing conditions. Variation of ionic strength, surfactants, enzymes, or apparatus should be evaluated, if an influence on dissolution is expected for the individual formulation.

For formulation characterization, dissolution tests should be performed under the different test conditions until actual dissolution (eg, mean of six specimen) exceeds 80% of labeled amount. When, even with test prolongation, results remain significantly below 80% and solubility is not the limiting parameter, recovery control should be performed to prevent misinterpretation of dissolution data.

Since most *in vitro* characteristics can be related to physiological parameters (Table 2) the information from formulation characterization *in vitro* can be used later as a tool to demonstrate the reliability of an *in vitro-in vivo* comparison, based on a distinct *in vitro* model, as well as for interpretation of all those examples where no or only a poor correlation of *in vitro* and *in vivo* data can be achieved. It is obvious, however, that a meaningful *in vitro-in vivo* comparison (see the next section) is the more probable, the less affected *in vitro* dissolution of a given drug formulation is by changes in the environmental test conditions.

IN VITRO-IN VIVO COMPARISON

An *in vitro* test system for a given drug formulation serves as the tool at which it is designated only if it can distinguish between "good" and "bad" batches. "Good" here means "of acceptable and reproducible biopharmaceutical performance *in vivo*." Thus, *in vivo* relevance of an *in vitro* test system is sought. The purpose of *in vitro-in vivo* comparison studies in this sense is the scientific verification of the *in vitro* test system and the respective specification limits for a given drug formulation.

Regarding extended-release dosage forms the USP (18) has categorized correlative methods, harmonized in a wide international consensus, as correlation level A (1 : 1 relationship between *in vitro* and *in vivo* dissolution, calculated by numerical deconvolution [22,23], according to the Wagner-Nelson method [24] or to the Loo-Riegelmann method [25]), correlation level B (statistical moment analysis [26,27]), and correlation level C (single-point correlation of a dissolution time versus a pharmacokinetic parameter). Depending on the correlation level finally obtained, *in vitro* dissolution properties will be decisive for the necessity of how many batches should be included for a correlation study, for example, for establishment of *in vitro* dissolution specification limits.

TABLE 2
Physiological Variables Contributing to Biopharmaceutical Performance Especially for Controlled/Modified Release Formulations and Aspects of *In Vitro* Modeling

Physiological Variable	*In Vitro* Modeling Possible by
Intragastric pH	pH-profile
Gastrointestinal motility, peristaltics, shearing forces	Agitation-profile
Fat, lipophilic, and other compounds	Addition of lipids (fat and/or fatty acids) or other compounds (eg, fiber materials)
Enzymes	Addition of enzymes
Bile	Addition of surfactants
Gastrointestinal transit-times	???

According to recent recommendations, one single batch may be sufficient for a scientifically and formally acceptable correlation (15,18), only in case of a correlation level A and a product with a drug release completely independent from environmental conditions, which then is represented by only one dissolution curve. Scientific and pragmatic approaches for level A correlations have been proposed (28). In case of a level A correlation, manufacturing site changes, minor formulation modifications, scale-up considerations, and setting of specifications can be based and justified without further *in vivo* studies.

In all other cases at least two or three different batches have to be used, offering differences in their biopharmaceutical properties, sufficient for correlation purposes. Nevertheless, these differences have to be "effected" by only small modifications of manufacturing variables within the ranges of the given process. In cases where differences cannot be achieved by these variations of the production process, different formulations of a drug substance are to be obtained for *in vitro-in vivo* comparison. Any correlation received for different formulations, however, bears the risk of being somewhat arbitrary. A final evaluation of type and influence of the changes in the manufacturing processes requires thorough *in vitro* dissolution tests ('biopharmaceutical profile'; see the previous section) prior to an administration to human volunteers in a clinical study.

Concerning controlled/modified-release products there is international consensus that levels A to C, with a quality ranking A > B > C, are acceptable for correlation, for example, for setting specifications. A number of different reasons (see Table 3) could be responsible for "poor" or no correlation.

Even with highly sophisticated techniques it is often difficult to obtain meaningful *in vitro-in vivo* comparisons, especially when regarding biopharmaceutically very similar (bioequivalent?) products, such as batches of one drug formulation, representing the upper and the lower specification limit.

Recently, proposals have been made (29) in which *in vitro-in vivo* comparison results scientifically and formally could suffice as verification of dissolution specification of controlled/modified-release products. In case of a significant quantitative correlation, specifications can be derived by interpolation, when batches outside the specified biopharmaceutical range are tested for *in vitro-in vivo* comparison. Then, at least three batches should be tested *in vitro* and *in vivo*. A qualitative, that is, rank-order correlation, verifies specification ranges, when at least three batches are tested *in vivo* and *in vitro* and the dissolution data of two of the experimentally investigated batches are concluded bioequivalent and their dissolution characteristics are defined as upper and lower specification limits.

Where no correlation is obtained from an *in vitro-in vivo* comparison study, an alterna-

TABLE 3
Possible Reasons for Poor *In Vivo-In Vitro* Correlations

Fundamentals
• *In Vivo* dissolution is not the rate limiting step for drug absorption
• No *In Vitro* test is able to model *in vivo* dissolution
Study design
• Inappropriate *In Vitro* test conditions
• Inappropriate *In Vivo* test conditions
Dosage form
• Drug release not controlled by the dosage form
• Drug release strongly affected by intestinal transport kinetics
Drug substance
• Nonlinear pharmacokinetics (eg, saturable first pass effect), absorption window, chemical degradation in the gastrointestinal tract
• Absorption of undissolved particles
• Large intraindividual variability

tive approach could consist of demonstrating bioequivalence of the proposed formulation to formulations with dissolution profiles at the upper and lower limits of the specification (13). The number of volunteers to be included in such comparative bioavailability studies or in an *in vitro-in vivo* comparison study is to be defined on a case-by-case basis but in general should not be less than 12.

The batch size of a formulation for *in vitro-in vivo* comparison studies need not be of full production scale. Parameters for manufacture of these batches, especially of formulations representing the intended specification limits, should be defined from process validation studies according to the expected maximum variability of process parameters ("side batches"). Concerning immediate-release dosage forms a suitable design for an *in vitro-in vivo* comparison study could consist of a two-way crossover between an oral solution and a formulation representing the (lower) specified dissolution limit.

DISSOLUTION SPECIFICATIONS

The purpose of establishing dissolution specifications is to ensure batch-to-batch consistency within a range which guarantees acceptable biopharmaceutical performance *in vivo*. Specification limits, therefore, have to be defined based on experience gained during the drug development stage, especially regarding clinical development and/or bioequivalence studies. In most cases, deduction of specification limits requires thorough *in vitro-in vivo* comparison studies as described in the previous section.

For immediate-release formulations typically one limit is specified to ensure that most of the active ingredient is released within the preset time period. Regarding the deduction of specification limits, different procedures are recommended, depending on the individual dissolution characteristics. It is clearly stated, however, that the following categorization only concerns the specification verification process. It does not qualify or disqualify drug formulations with dissolution properties, characterized by a specification time of less than 15 minutes.

In case of very fast drug release, single point dissolution data during the development period and a single point specification, consisting of a parameter quantitating the extent and a parameter to define the time, are judged sufficient. A formulation is in this concern understood as very fast releasing, when at least 80% of the drug substance, corresponding to "Q" = 75% is dissolved in 15 minutes under reasonable and justified test conditions. In this case dissolution specifications can be defined based on *in vitro* data obtained during drug development without an *in vitro-in vivo* comparison study.

Immediate-release formulations with a specified dissolution time of more than 15 minutes will require an *in vitro-in vivo* comparison study and dissolution profiles with several (eg, three) points, obtained during

development, to define specification limits. Formulations with a specified dissolution time of less than 45 minutes may require two specified dissolution times for quality control purposes.

Delayed-release formulations should be treated like immediate-release products for the purpose of setting specifications for the second dissolution test period, following the initial acidic test phase. For controlled/modified-release formulations (except delayed-release) dissolution specifications should consist of at least three points. The first specification is intended to prevent "dose dumping" and, therefore, should be set after a testing interval of one to two hours or corresponding to a dissolved amount of 20 – 30% of labeled drug substance. The second specification point should define the dissolution pattern and thus be set around 50% release of labeled drug substance. The final specification point should ensure (almost) quantitative drug release, which is generally understood as less than or equal to 80%. The dissolution run in quality control therefore should be extended for the time interval until at least 80% of drug substance is dissolved. Shorter test intervals can be acceptable in special cases but require justification on the basis of an *in vitro-in vivo* comparison study and should at least cover 24 hours.

The acceptance range for the dissolution pattern at the time intervals specified should be defined case-by-case on the basis of the *in vitro-in vivo* comparison study and taking into consideration the capability of the manufacturing process and the commonly accepted range of 95–105% of stated amount for the average content of drug substance. Where both upper and lower limits are specified at any time point, the difference between them should usually not exceed 20% of the labeled content of drug substance in the formulation unless limits have been shown to provide reproducible and acceptable *in vivo* performance (13).

INTERPRETATION OF ACCEPTANCE CRITERIA

Dissolution test specifications should include the definition of limits, the number of units to be examined, and respective acceptance criteria. The procedure of data interpretation should be harmonized internationally and the existing compendial requirements should be uniform.

At the time being some pharmacopoeias do not give any advice for the acceptance criteria, for example, Ph.Eur. and some of them, for example, BP 1993 and Ph.Jap. XII, deviate very much from the USP 23. For example, BP 1993 requires for immediate-release products five units for each step of testing. Ph.Jap. XII recommends for each step to use six units to be tested. This is similar to USP 23 but both Pharmacopoeias (BP and Ph.Jap.) do not specify the extent of the failure of individual units. Therefore, it is recommended to follow the acceptance criteria in accordance with USP 23 for immediate-release products, controlled/modified-release (extended-release) products, and delayed-release products (Table 4).

SPECIAL APPLICATIONS

A specific value of dissolution testing is recognized in its applications in scale-up and manufacturing changes for immediate-release and controlled/modified-release oral products. The American Association of Pharmaceutical Scientists/Food and Drug Administration/United States Pharmacopoeia (AAPS/FDA/USP) Scale-up workshops (30, 31) recommend certain types and ranges of changes for which the sameness of *in vivo* product performance is assumed, based on *in vitro* dissolution data. In addition, the SUPAC-IR document of FDA (32) defines the level of changes with respect to components and composition, site of manufacturing, the scale of manufacturing, and process and equipment changes in manufacturing for an immediate-release oral formulation. Depending on the level of change, different levels of dissolution testing are recommended to assure continuing product quality and performance characteristics. Respectively, the documentation needed to assure the product performance varies, depending on therapeutic range, solubility, and permeability factors of the drug. For changes greater than the

TABLE 4
Acceptance Tables According to USP 23 <724>

Stage	Number Tested	Acceptance Criteria
		4a: Immediate-Release Dosage Forms
S_1	6	Each unit is not less than Q + 5%
S_2	6	Average of 12 units $S_1 + S_2$ is equal to or greater than Q, and no unit is less than Q – 15%
S_3	12	Average of 24 units $S_1 + S_2 + S_3$ is equal to or greater than Q, not more than 2 units are less than Q – 15%, and no unit is less than Q – 25%
		4b: Extended-Release Dosage Forms
L_1	6	No individual value lies outside each of the stated ranges and no individual value is less than the stated amount at the final test time
L_2	6	The average value of the 12 units ($L_1 + L_2$) lies within each of the stated ranges and is not less than the stated amount at the final test time; none is more than 10% of labeled content outside each of the stated ranges; and none is more than 10% of labeled content below the stated amount at the final test time
L_3	12	The average value of the 24 units ($L_1 + L_2 + L_3$) lies within each of the stated ranges, and is not less than the stated amount at the final test time; not more than 2 of the 24 units are more than 10% of labeled content outside each of the stated ranges; not more than 2 of the 24 units are more than 10% of labeled content below the stated amount at the final test time; and none of the units is more than 20% of labeled content outside each of the stated ranges or more than 20% of labeled content below the stated amount the final test time
		4c: Delayed-Release Dosage Forms
		Acidic stage
A_1	6	No individual value exceeds 10% dissolved
A_2	6	Average of 12 units ($A_1 + A_2$) is not more than 10% dissolved, and no individual unit is greater than 25% dissolved
A_3	12	Average of the 24 units ($A_1 + A_2 + A_3$) is not more than 10% dissolved, and no individual unit is greater than 25% dissolved
		Buffer stage
B_1	6	Each unit is not less than Q + 5%
B_2	6	Average of 12 units ($B_1 + B_2$) is equal to or greater than Q, and no unit is less than Q – 15%
B_3	12	Average of the units ($B_1 + B_2 + B_3$) is equal to or greater than Q, not more than 2 units are less than Q – 15%, and no unit is less than Q – 25%

acceptable values in the scale-up workshop report, additional dissolution profile determinations in several media are recommended for immediate-release products.

For major changes that are likely to have a significant impact on formulation quality and performance, an *in vivo* bioequivalence study is recommended in addition to extensive dissolution profile testing. For manufacturing site change, scale-up, equipment changes, and minor process changes dissolution testing is deemed sufficient to assure product quality and performance.

In vitro dissolution tests have also been

used to try to simulate food effects on bioavailability. So far, these different attempts (33–39) have had extremely limited success in prediction (40). Assuming that gastrointestinal transit times are significantly contributing to potential food effects on bioavailability, the value of an *in vitro* model for food effects will be limited to an evaluation of whether direct drug-food-interaction could be of relevance for the observed changes in bioavailability in the *in vivo* study.

CONCLUSIONS

In many international discussions, mainly over the years 1988–1993, consensus was reached on some essential aspects of dissolution testing of solid oral products, to which these guidelines refer. On the other hand, many aspects have either not yet been sufficiently explored or have not been harmonized. In these cases, for example, more precise specifications of dissolution media and proposals for *in vitro-in vivo* comparison approaches and verification of specifications for immediate-release, delayed-release, and controlled/modified-release preparations, the revised guidelines will provide contributions for reasonable standardization, while acknowledging that for a number of drugs, for example, with special physico-chemical or pharmacokinetic properties, case-by-case development is required.

These guidelines should be helpful and applicable for all involved in *in vitro* dissolution testing. There was special emphasis, however, on providing reliable guidance for industrial research and development, process validation, and quality control, making the guidelines especially applicable for industry, drug authorities, and control laboratories but also for universities, hospitals, pharmacies, or others, when involved in (bio)pharmaceutical quality evaluation.

In general, these guidelines should be understood as recommendations based on scientific knowledge and experience. They should be helpful in the dialogue with drug regulatory authorities. They are not intended, however, to represent any official requirements in this field.

REFERENCES

1. FIP Guidelines for Dissolution Testing of Solid Oral Products. *Pharm Ind*. 1981;43:334–343.
2. Pernarowski M. Dissolution Methodology. In Leeson LJ, Carstensen JT (Eds.). *Dissolution Technology*. Washington, DC; APhA: 1974.
3. Krowczynski L. Kritischer Vergleich von Geräten und Methoden zur Bestimmung der Auflösungsgeschwindigkeit von Tabletten. *Pharmazie*. 1978;33:241–247.
4. Dakkuri A, Shak AC. Dissolution Methology: an Overview. *Pharm Technol*. 1982;2:41–53.
5. Lathia CD, Banakar WV. Advances in Dissolution Technology: Design, pros and cons. *Drug Dev Ind Pharm*. 1986;12:71–105.
6. Siewert M. Associations and Specifications. In Blume H, Grundert-Remy U, Möller H (Eds.) Controlled/Modified Release Products. Stuttgart: Wissenschaftliche Verlagsgesellschaft; 1991.
7. Wells CE. Effect of Sampling Probe Size on Dissolution of Tableted Drug Samples. *J Pharm Sci*. 1981; 70:232–233.
8. Stricker H. Optimierung und Justierung der Versuchsbedingungen von in vitro-Tests: Feste perorale Arzneizubereitungen. *Acta Pharm Technol*. 1984;30:113–125.
9. Stricker H. In-vitro-Studien zum Auflöse- und Resorptionsverhalten oral verabreichter Arzneistoffe und die Korrelation mit der biologischen Verfügbarkeit. *Pharm Ind*. 1976;38:232–234.
10. Dibbern HW. Verfügbarkeitsprüfung in vitro: Forderungen, Möglichkeiten, Grenzen. *Pharm Ind*. 1984; 46:381–385.
11. Das SK, Gupta BK. Simulation of physiological pH-time profile in in vitro dissolution study: Relationship between dissolution rate and bioavailability of controlled release dosage form. *Drug Dev Ind Pharm*. 1988;14:537–544.
12. Blume H, Ali SL, Siewert M. Zur pharmazeutischen Qualität von glibenclamidhaltigen Fertigarzneimitteln. *Pharm Ztg*. 1984;129:983–989.
13. EEC Note for Guidance. Quality of Prolonged Release Oral Solid Dosage Forms. 1991.
14. Guidelines for Design and Evaluation of Oral Sustained Release Dosage Form. Ministry of Health and Welfare of Japan. Yakuskin-1-5; 1988.
15. Workshop Report In Vitro and In Vivo Testing and Correlation for Oral Controlled/Modified-Release Dosage Forms. *Pharm Res*. 1990;7:975–982.
16. Shah VP, Konecny JJ, Everett RL, McCullough B, Noorizadeh AC, Skelly JP. In Vitro Dissolution Profile of Water-Insoluble Drug Dosage Forms in the Presence of Surfactants. *Pharm Res*. 1989;6(7):612–618.
17. Shah VP, Gurbarg M, Noory A, Dighe S, Skelly JP. Influence of Higher Rates of Agitation on Release Patterns of Immediate-Release Drug Products. *J Pharm Sci*. 1991;81(6):500–503.
18. <1088> In-vitro and in-vivo evaluation of dosage forms USP 23;1995.

19. Qureshi SA, McGilveray IJ. Impact of Different Deaeration Methods on the USP Dissolution Apparatus Suitability Test Criteria. *Pharm Forum.* 1994;20(6): 8565–8566.
20. Soltero RA, Hoover JM, Jones FT, Standish M. Effects of Sinker Shapes on Dissolution Profiles. *J Pharm Sci*. 1898;78:35–39.
21. U.S. Pharmacopeia 23, Supplement 1: Drug Release <724> 2535;1995.
22. Langenbucher F. Numerical convolution/deconvolution as a tool for correlating in vitro with in vivo drug availability. *Pharm Ind*. 1982;44:1166–1172.
23. Langenbucher F. Improved algorithms correlating body response with drug input. *Pharm Ind*. 1982; 44:1275–1278.
24. Wagner JW, Nelson F. Percent absorbed time plots derived from blood level or urinary excretion data. *J Pharm Sci*. 1963;57:918–928.
25. Loo JCK, Riegelmann S. New method for calculating the intrinsic absorption rate of drug. *J Pharm Sci*. 1968;57:918–928.
26. Brockmeier D, Voegele D, von Hattingberg HM. In vitro-in vivo correlation, a time scaling problem? *Arzneimittelforschung*. 1983;3 33:598–601.
27. von Hattingberg HM. Momenten-Analyse und in vitro/in vivo Korrelation. *Acta Pharm Technol*. 1984;30:93–101.
28. Cardot JM, Beyssac E. In vitro/in vivo Correlations: Scientific Implications and Standardisation. *Eur J Drug Metab Pharmacokinet.* 1993;18(1):113–120.
29. Siewert M. Presentation given at BIO-International '94 pre-conference satellite. 1994.
30. Workshop Report: Scale-Up of Immediate Release Oral Solid Dosage Forms. *Pharm Res.* 1993;10:313–316 and *Eur J Pharm Biopharm*. 1993;39 (1):40–43.
31. Workshop II Report: Scale-Up of Oral Extended Release Dosage Forms. *Pharm Res*. 1993;10:1800–1805 and *Eur J Pharm Biopharm*. 1993;39 (4):162–167.
32. FDA Immediate Release Scale-up and Post Approval Change (SUPAC) Expert Working Group of the Chemistry Manufacturing Controls Coordinating Committee of the Center for Drug Evaluation and Research (1994) Interim Guidance Immediate Release Solid Oral Dosage Forms—Pre- and Post-Approval Changes. 1994.
33. Maturu PK, Prasad VK, Worsley W, Shiu GK, Skelly JP. Influence of a high fat breakfast on the bioavailability of theophylline controlled-release formulations: an in vitro demonstration of an in vivo observation. *J Pharm Sci*. 1986;75:1205–1206.
34. Wearly L, Karim A, Pagone F, Streicher J, Wickman A. Food-Induced Theophylline Release/Absorption Changes from Controlled-Release Formulations: A Proposed in Vitro Model. *Drug Devl Ind Pharm*. 1988;14:13–28.
35. Karim A. Importance of Assessing Food Effects in Evaluating Controlled-Release Formulations. (1988) In: Yacobi A und Halperin-Walega E. *Oral Sustained Release Formulations: Design and Evaluation*. New York: Pergamon Press; 1988;157–181.
36. El-Arini K, Shiu GK, Skelly JP. Theophylline-Controlled Release Preparations and Fatty Food: An in vitro Study Using the Rotating Dialysis Cell. *Pharm Res*. 1990;7:1134–1140.
37. Macheras P, Koupparis M, Tsaprounis C. Drug dissolution studies in milk using the automated flow injection serial dynamic dialysis technique. *Int J Pharm*. 1986;33:125–136.
38. Junginger HE, Verhoeven J, Peschier LJC. Eine neues in vitro-Modell zur Erkennung von Wechselwirkungen zwischen Retardarzneimitteln zur oralen Applikation und Nahrungsmitteln. *Pharm Ztg Wiss*. 1990;2:53–58.
39. Krämer J, Lindauer RF, Siewert M, Stricker H, Blume H. Extended-Release Theophylline Alternative In Vitro Dissolution Methods. *Eur J Drug Metab Pharmacokin*. 1993;18:37.
40. Siewert M. In vitro-Dissolution Testing of Oral Controlled Release Products. In: Gundert- Remy U und Möller H. *Oral Controlled Release Products Therapeutic and Biopharmaceutic Assessment*. Stuttgart, Germany: Wissenschaftliche Verlagsgesellschaft: 139–154.