

New FIP Guidelines for Dissolution Testing of Solid Oral Products

Martin Siewert, Ph.D.

*Hoechst Aktiengesellschaft, Hoechst Marion Roussel
Frankfurt, Germany*

The first *GUIDELINES FOR DISSOLUTION TESTING OF SOLID ORAL PRODUCTS* were published in 1981 as a joint report of the Section for Official Laboratories and Medicines Control Services and the Section of Industrial Pharmacists of the International Pharmaceutical Federation (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 scientific as well as political interest. 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.

they are already published elsewhere, officially or semi-officially. In many international discussions, mainly over the years 1988 to 1993, consensus was reached on some essential aspects, 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, the revised guidelines will provide contributions of reasonable standardization, while acknowledging that for a number of drugs, e.g., with special physico-chemical or pharmacokinetic properties, case-by case development is required.

In general, technical terms and definitions used in the guideline have been adopted from other harmonized recommendations and mainly correspond to USP-terminology. New terms are "in vitro-in vivo comparison", "verification" and "side batches".

"In vitro-in vivo comparison" is used for 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 vitro-in vivo association can be a result of an in vitro-in vivo comparison study, but valuable information could also be obtained when a correlation in a strict sense (e.g., USP levels) is not achieved.

"Verification" defines the in vivo data set which provides evidence that the 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 the extension of "validation" also to an in vivo investigation.

"Side batches" are batches of a given drug formulation which represent the intended upper and lower specification limits. They are preferably 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, i.e., immediate-

FIP Guidelines for Dissolution Testing of Solid Oral Products (Final Draft 1995)	
Introductory remarks	
1. Concepts of dissolution testing	6. In vitro - in vivo comparison
2. Apparatus	7. Dissolution specifications
3. Experimental testing conditions	8. Interpretation, acceptance criteria
4. Qualification and validation	9. Special applications
5. Formulation characterization	10. Conclusions
References	

Figure 1: Contents of FIP Guidelines for Dissolution Testing of Solid Oral Products (Final Draft 1995)

The updated guideline (second edition; figure 1) is the result of careful discussions of the joint working group of the two FIP sections. Descriptions of test methodology are no longer necessary, because

New FIP Guidelines...continued

release (such as prompt drug releasing or conventional dosage forms) as well as controlled/modified-release products (such as controlled, delayed, extended, modified, prolonged or sustained).

Regarding apparatus for dissolution, FIP guideline refers to pharmacopoeial approaches. Other apparatus or modification of pharmacopoeial apparatus should be justified by evidence of superiority. According to the FIP guideline, any technical modification, e.g., for automation purposes, requires product by product validation.

Solubility was defined as a validation aspect. No strict definition of requirements and characteristics of sink conditions was made. Test media should be aqueous systems of pH 1-6.8. In the pH range of 6.8 - 8, justification is expected. The pH of the test media should never exceed 8. Preference is given to USP buffers in the pH range of 4-8. For the lower pH range, HCl solutions are preferred. Deaeration should be prescribed in an individual test procedure if the product is sensitive, thus being part of the individual validation effort. The agitation rate should be 50 - 100 rpm in paddle or basket, not exceeding 150. Agitation speeds of 100 - 150 rpm would require justification. In regard to sinkers, flexibility in the position of regulatory authorities is kindly recommended. The use of a particular sinker should be justified on a case-by-case basis.

Regarding apparatus qualification, FIP guideline allows in-house standards in addition to or even as a substitute to USP calibrators. Calibration should be performed routinely twice per year, as well as related to any significant change, repairs, etc. of equipment.

The validation chapter of the guideline refers to automation validation and to analytical validation as laid down in ICH guideline.

The purpose of establishing dissolution specifications is to ensure batch to batch consistency within

a range which guarantees acceptable biopharmaceutical performance in vivo. Therefore, specification limits 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. A further classification is described in the FIP guideline. Setting of dissolution specifications should take into consideration the capability of the manufacturing process and the commonly accepted range of 95% to 105% of stated amount for average content of drug substance.

For in vitro-in vivo comparison studies at least 12 volunteers are recommended. The number of batches to be tested depends on the nature of the dosage form as well as the achieved correlation level.

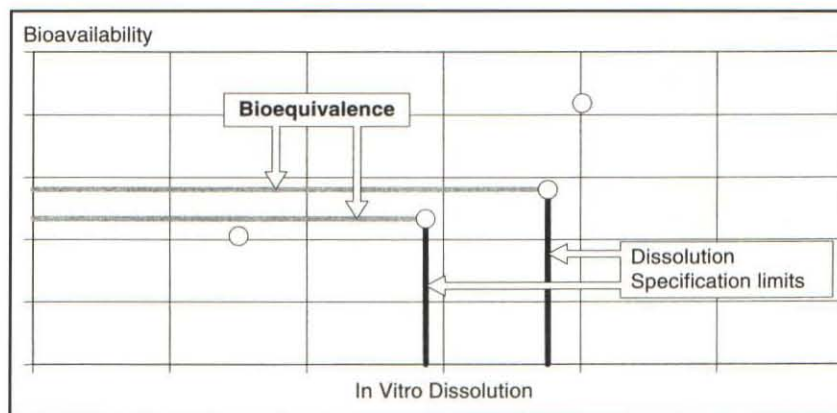


Figure 2: Application of a rank order correlation for verification of in-vitro dissolution specifications

For controlled/modified release dosage forms, FIP guideline allows two alternatives for verification if levels A-C according to USP cannot be reached: rank order correlation and side batch approach.

A rank order correlation is judged sufficient if bioequivalence can be proven for two batches and dissolution characteristics of these batches are used as dissolution specification limits. (figure 2)

In accordance with the European Note for Guidance, bioequivalence of side batches towards target profile will also be accepted in lack of correlation. (figure 3)

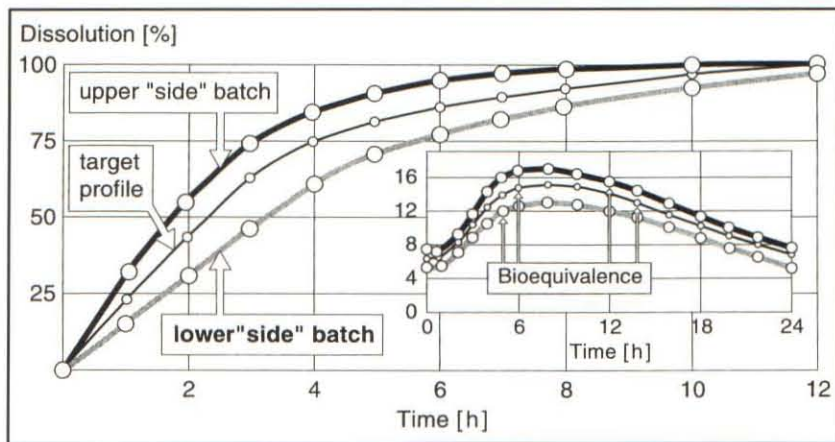


Figure 3: In-vivo verification of in-vitro test systems and specification based on the side-batch approach (example)

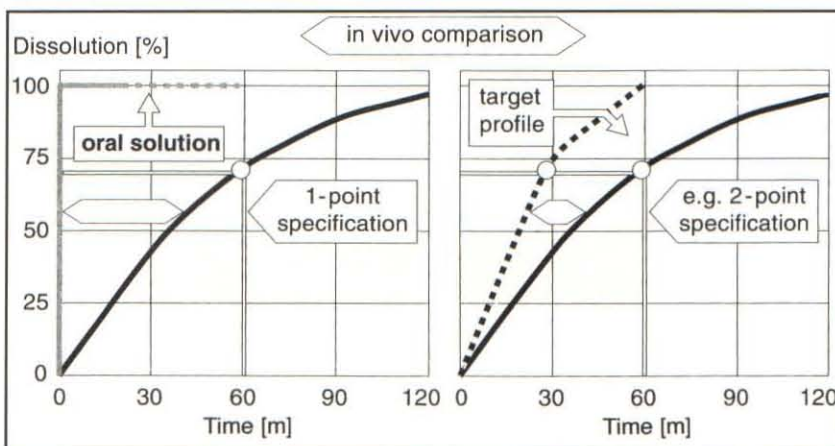


Figure 4: Specification type and verification study design concepts for immediate release products with Q specified for greater than 15 minutes

For very fast releasing formulations, FIP recommends not to require an in vitro-in vivo comparison study and to specify drug dissolution with a one time-point limit of at least 80% dissolution ($Q=75\%$) in 15 minutes or less. For immediate release products with Q specified at a time interval greater than 15 minutes but less than 45 minutes, an in vitro-in vivo comparison study is judged necessary and one specification limit will typically be sufficient.

When the specified time interval for Q exceeds 45 minutes, an in vitro-in vivo comparison study is required and a two or more point specification might be appropriate.

However, they are not intended to represent any official requirements in this field.

The final draft of the new FIP guideline was published in 1995 in *DIE PHARMAZEUTISCHE INDUSTRIE*(1), and in *PHARMACOPOEIA FORUM*(2).

Comments to the author are highly appreciated. Please address remarks to:

Dr. Martin Siewert
c/o Hoechst AG, Hoechst Marion Roussel
D-65926
Frankfurt, Germany.

A typical in vitro-in vivo comparison study for immediate release products could consist of the comparison of a limit type profile vs. an oral solution. In case of a more "moderate" release product, study design could be similar to controlled release formulations. (figure 4)

The guidelines should be helpful and applicable for all involved in in vitro dissolution testing. However, there was special emphasis 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.

New FIP Guidelines...continued

Acknowledgements / Remarks:

The draft of the FIP Guidelines (1995) was prepared by the FIP Dissolution Working Group with contribution 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. McGiveray, Ottawa; F. Langenbacher, Basel; L. Leeson, Montville; L. Lesko, Rockville; H. Möller, Frankfurt; S. Qureshi, Ottawa; V. P. Shah, Rockville; M. Siewert, Frankfurt; R. Süverkrüp, Bonn; J. O. Waltersson, Uppsala; and E. Wirbitzki, Frankfurt.

The full text of the FIP Guidelines for Dissolution Testing of Solid Oral Products Final Draft 1995 was published in the following international journals:

1. Die Pharmazeutische Industrie, 57, (5), 362-369, 1995
2. Pharmacopoeial Form, 21, (5), 1371-1382, 1995

In November 1996 a workshop will be held to finalize the Guideline text. Announcements/invitations will be distributed separately.