AAPS PharmSciTech **2003; 4 (1) Article 7 (http://www.pharmscitech.org).**

FIP/AAPS Guidelines to Dissolution/in Vitro Release Testing of Novel/Special Dosage Forms*

January 27, 2003; Accepted: February 14, 2003

Martin Siewert[1], Jennifer Dressman[2], Cynthia K. Brown[3], and Vinod P. Shah[4]

Contributors

Jean-Marc Aiache,[5] Nobuo Aoyagi,[6] Dennis Bashaw,[4] Cynthia Brown,[3] William Brown,[7] Diane Burgess,[8] John Crison,[9] Patrick DeLuca,[10] Ruzica Djerki,[11] Jennifer Dressman,[2] Thomas Foster,[10] Kirsti Gjellan,[12] Vivian Gray,[13] Ajaz Hussain,[4] Tom Ingallinera,[14] James Klancke,[15] Johannes Kraemer,[16] Henning Kristensen,[17] Kofi Kumi,[4] Christian Leuner,[2] Jobst Limberg,[18] Petra Loos,[19] Lenny Margulis,[20] Patrick Marroum,[4] Helga Moeller,[21] Bernd Mueller,[22] Martin Mueller-Zsigmondy,[11] Ngozi Okafo,[23] Larry Ouderkirk,[4] Shravan Parsi,[24] Saeed Qureshi,[25] Joseph Robinson,[26] Vinod Shah,[4] Martin Siewert,[1] Ramana Uppoor,[4] and Roger Williams.[7]

[1]Aventis, Frankfurt, Germany
[2]JW Goethe University, Frankfurt, Germany
[3]Eli Lilly and Company, Indianapolis, IN
[4]Office of Pharmaceutical Science, Center for Drug Evaluation and Research, US Food and Drug Administration, Rockville, MD
[5]Université d'Auvergne, Clermont-Ferrand Cedex, France
[6]National Institute of Health Sciences, Division of Drugs, Tokyo, Japan
[7]US Pharmacopeia, Rockville, MD
[8]University of Connecticut, Storrs Mansfield, CT
[9]Pfizer, Inc, La Jolla, CA
[10]University of Kentucky, Lexington, KY
[11]Novartis Pharma, Basel, Switzerland
[12]AstraZeneca, Sodertalje, Sweden
[13]V.A. Gray Consulting, Inc, Hockessin, DE
[14]AAI International, Charleston, SC
[15]CIMA Laboratories, Inc, Minneapolis, MN
[16]Laboratory and Quality Services, Eschborn, Germany
[17]University of Copenhagen, Denmark
[18]Bundesinstitut für Arzneimittel, Bonn, Germany
[19]Aventis Pharmaceuticals, Bridgewater, NJ
[20]Pfizer, Groton, CT
[21]Zentrallaboratorium Deutscher Apotheker, Eschborn, Germany
[22]Kiel University, Kiel, Germany
[23]Alza Corporation, Mountain View, CA
[24]DPT Laboratories, Ltd, San Antonio, TX
[25]Health Protection Branch, Ottawa, Canada
[26]University of Wisconsin, WI

Corresponding Author: Martin Siewert, FIP Dissolution Working Group, Aventis Pharma AG, D-65926 Frankfurt am Main, Germany. Phone: 49 69 305 17070; Fax: 49 69 305 16692; Email: martin.siewert@aventis.com.

*This article represents the scientific opinion of many experts and, in particular, is derived from a series of workshops held under the auspices of the Federation International Pharmaceutique (FIP) and cosponsored by the Royal Pharmaceutical Society (UK), the Bundesverband der Pharmazeutischen Industrie (BPI), Colloquium Pharmaceuticum (Germany), the American Association of Pharmaceutical Scientists (AAPS, US), and the US Food and Drug Administration. It is

now presented as an FIP and AAPS position paper to support activities, programs, and decisions in the scientific, technical, and regulatory community. Even though it is a "final" position paper at this stage, the authors expect further progress to be made rapidly in the relevant areas. Thus, comments and additional contributions are welcome and may be considered for a revision of the position paper in due course.

Concept of Dissolution/Drug Release Testing

In the pharmaceutical industry, dissolution testing is a very important tool in drug development and quality control. Although initially developed for immediate release (IR) solid oral dosage forms and then extended to controlled/modified release solid oral dosage forms, dissolution testing has recently widened to a variety of "novel" or "special" dosage forms such as suspensions, orally disintegrating tablets, chewable tablets, chewing gums, transdermal patches, semisolid topical preparations, suppositories, implants and injectable microparticulate formulations, and liposomes. For orally administered IR solid drug products, it is customary to refer to the test as a "dissolution" test, since the drug is intended to dissolve rapidly in the test medium. For non-oral dosage forms such as topical and transdermal delivery systems and suppositories, the test is referred to preferably as a "drug release" or an "in vitro release" test procedure. Because of significant differences in formulation design among these novel/special dosage forms, which in turn lead to very different physicochemical and release characteristics, it is not possible to devise a single test system that could be used to study the drug release properties of all products. Rather, different apparatus, procedures, and techniques are employed on a case-by-case basis. The method may be specific to the dosage form category, the formulation type, or the particular product.

However, the general principles of dissolution tests for solid oral dosage forms should also be applicable to in vitro dissolution/drug release tests for novel/special dosage forms. The ultimate goal of these tests is analogous to that for solid oral dosage forms—that is, to use the test for the biopharmaceutical characterization of the drug product, and for ensuring consistent product (batch) quality within a defined set of specification criteria.

Different types of dosage forms and appropriate apparatus used for drug release testing are discussed below. For several novel/special dosage forms, the methodology is well evolved and specific recommendations can be made for drug release testing—for instance, for suspensions, orally disintegrating tablets, chewable tablets, suppositories, transdermal patches, and semisolid topical dosage forms (creams, ointments, and gels). However, for conventional oral dosage forms, there may be specific formulations in the above-mentioned categories for which the evolved methods are not applicable. In several other instances—for example, chewing gums, powders, granules, solid dispersions, microparticulate formulations, and implants—more method development and refinement will be required before a final recommendation of a standardized drug release method can be made. For these dosage forms, a brief summary of the state-of-the-art is provided to guide further development. Because of the different characteristics of the novel/special dosage forms and their sites and modes of application, it is essential that apparatus selection, composition of the dissolution medium, agitation (flow rate), and temperature be given appropriate consideration during method design. In instances where a compendial (eg, US Pharmacopeia [USP], European Pharmacopoeia [PhEur], Japanese Pharmacopoeia [PhJap]) is employed for in vitro drug release testing, the experimental test conditions, qualification, and validation steps should conform to those discussed in the Federation International Pharmaceutique (FIP) and US Food and Drug Administration (FDA) guidelines on dissolution testing.[1,2]

In general, compendial apparatus and methods should be used as a first approach in drug development. To avoid unnecessary proliferation of equipment and method design, modifications of compendial equipment or development or use of alternative equipment should be considered only when it has been proven that a compendial setup does not provide meaningful data for a given (new) dosage form. Qualification and validation efforts would include those quoted above[1,2] and would be expected to demonstrate that the new method is scientifically sound and guarantees accurate, precise, and reproducible data; ensures acceptable drug product quality; and allows for some interpretation of the product's in vivo performance.

In some cases, the method used in the early phase of product/formulation development could be different from the final test procedure used for control of the product quality. Indeed, methods used for formulation screening or understanding of the release mechanism may simply be impractical for a quality control environment. It is essential that with the accumulation of experience, the early method be critically reevaluated and potentially simplified, giving preference to com-

pendial apparatus. The final method may not necessarily closely imitate the in vivo environment, but it should still test the key performance indicators of the formulation.

Dosage Forms for Which a Specific Method Can Be Recommended

Oral Suspensions (for Systemic Use)

In general, the rotating paddle method using an aqueous dissolution medium is the recommended method for dissolution testing of suspensions. To obtain representative samples, product preparation should follow a standardized procedure based on shaking or mixing. Method parameters such as sample introduction and agitation rate should be established on the basis of the viscosity and composition of the suspension matrix. The sample introduction technique must be accurate, precise, and reproducible. Even though oral suspensions of any viscosity would be exposed to similar ranges of shearing forces after administration in vivo, the in vitro agitation rate should be selected to facilitate discrimination between batches with different release properties.

For low-viscosity suspensions, an accurate dose can be delivered to the bottom of the dissolution vessel using a volumetric pipette. A slow agitation rate of 25 rpm is generally recommended for less viscous suspensions.[3] For high-viscosity samples, the dose may need to be determined by weight with a quantitative sample transfer to the dissolution vessel to ensure accuracy of the sample size introduced. High-viscosity suspensions may also require a faster agitation rate such as 50 or 75 rpm to prevent sample mounding at the bottom of the vessel.

Ideally, sample weight/volume should reflect a typical dose of the product. However, testing a partial dose—for instance, ≥10% to 20% of the usual product dose—is recommended rather than using a surfactant to obtain sink conditions.

Orally Disintegrating Tablets

Orally disintegrating tablets (ODTs) create an in situ suspension by rapidly disintegrating, typically within 1 minute or less. Administration of ODTs may not inherently result in a faster therapeutic onset but can circumvent problems such as difficulty in swallowing traditional solid oral dosage forms like tablets and capsules. Taste masking (drug coating) is very often an essential feature of ODTs and thus can also be the rate-determining mechanism for dissolution/release.

In vitro dissolution testing should therefore follow the principles of solid oral dosage forms (tablets) or suspensions (see previous section). The rotating paddle would be the method of first choice, with an agitation rate of, for example, 50 rpm. Higher agitation rates may be necessary in the case of sample mounding. The method can be applied to the ODTs (finished product) as well as to the bulk intermediate (in the case of coated drug powder/granulate). A potential difficulty for in vitro dissolution testing may arise from floating particles.

A single point specification is considered appropriate for ODTs with fast dissolution properties. For ODTs that dissolve very quickly, a disintegration test may be used in lieu of a dissolution test if it is shown to be a good discriminating method.

If taste masking (using a polymer coating) is a key aspect of the dosage form, a multipoint profile in a neutral pH medium with early points of analysis (eg, ≤5 minutes) may be recommended. It has to be noted that this early time point in the profile is intended to address the taste-masking properties of the formulation and may not affect the product's biopharmaceutical properties. Such a dissolution criterion (typical example: ≤10% dissolved in 5 minutes) would largely depend on the taste intensity of the drug and may enable the in vitro evaluation of the taste-masking properties while avoiding organoleptic measurements.

Chewable Tablets

In principle, the test procedure employed for chewable tablets should be the same as that used for regular tablets. This concept is based on the possibility that a patient might swallow the dosage form without proper chewing, in which case the drug would still need to be released to ensure the desired pharmacological action.[4] Where applicable, test conditions would preferably be the same as used for conventional tablets of the same active pharmaceutical ingredient, but because of the nondisintegrating nature of the dosage form, it may be necessary to alter test conditions (eg, increase the agitation rate) and specifications (eg, increase the test duration). The reciprocating cylinder (USP apparatus 3) with the addition of glass beads may also provide more "intensive" agitation for in vitro dissolution testing of chewable tablets. As another option, mechanical breaking of chewable tablets prior to exposing the specimen to dissolution testing could be considered. While this option

would more closely reflect the administration of the product and the corresponding formulation and manufacturing features, no approach for validating such a method has been reported in the literature or presented during the workshops.

Transdermal Patches

Although several apparatus and procedures have been used to study in vitro release characteristics of transdermal patches, it is desirable to avoid unnecessary proliferation of dissolution test equipment. Current compendial apparatus include the paddle over disk/disk assembly method (USP apparatus 5/PhEur 2.9.4.1), the rotating cylinder (USP apparatus 6/PhEur 2.9.4.3), the reciprocating disk (USP apparatus 7), and a paddle over extraction cell method (PhEur 2.9.4.2).

The paddle over disk procedure with a watch glass-patch-screen sandwich assembly is considered to be the method of choice, as it has been shown experimentally that this procedure results in almost the same release profile as other, more complicated apparatus for all US-marketed transdermal patches.[5] The configuration of this assembly ensures that the patch is prevented from floating during the testing period. Special attention needs to be given to the proper positioning of the patch so that the drug-loaded surface is exposed to the medium.

The pH of the medium ideally should be adjusted to pH 5 to 6, reflecting physiological skin conditions. For the same reason, the test temperature is typically set at 32°C (even though the temperature may be higher when skin is covered). PhEur considers 100 rpm a typical agitation rate and also allows for testing an aliquot patch section. The latter may be an appropriate means of attaining sink conditions, provided that cutting a piece of the patch is validated to have no impact on the release mechanism.

Semisolid Topical Dosage Forms

Semisolid topical dosage forms include creams, ointments, and gels. In vitro drug release from semisolid topical dosage forms has been extensively investigated using the Franz cell diffusion system[6] with a synthetic membrane and to some extent using the enhancer cell.[7] Comparative studies indicate that the 2 types of apparatus generate similar data.

Depending on the solubility of the drug substance, the receptor medium may need to contain alcohol and/or surfactant. Deaeration is critical to avoid bubble formation at the interface with the membrane. A synthetic membrane often serves as an inert support membrane. Depending on the characteristics of the drug product, it may also be possible to conduct the in vitro test without a synthetic support membrane.[8] For some ointments, the Franz cell has been used with and without membranes, resulting in no differences in release rate results. The drug release characteristics usually follow the Higuchi model.[9] As with transdermal products, the test temperature is typically set at 32°C to reflect the usual skin temperature. Deviations might be justified when products are for specific sites of action; for example, vaginal creams may be tested at 37°C.

Ideally, sample weight/volume should reflect a typical dose of the product. However, it is preferable to use a partial dose rather than adding a surfactant or alcohol to the receptor medium in order to obtain sink conditions.

No compendial apparatus, procedures, or requirements for in vitro release testing of semisolid topical dosage forms have been described in relevant pharmacopeias to date. However, the FDA's Guidance for Industry on Scale Up and Post Approval Changes for Semisolid (SUPAC-SS) dosage forms describes the release rate studies using the vertical diffusion cell (Franz cell) procedure and requires in vitro release rate comparison between prechange and postchange products for approval of SUPAC-related changes.[10]

Because of the value and importance of release rate, it is highly desirable to determine the release data of semisolid dosage forms.[11] There is also a need to develop compendial test method(s). It is expected that given the variety of formulations, sites of applications, and release rates for semisolid topical dosage forms, no single test procedure would be suitable for the development, biopharmaceutical characterization, and quality control of all semisolid topical dosage forms. Based on the foregoing statement, the inclusion of a single apparatus in pharmacopeias may not be the desired solution. However, the Franz cell (7) is considered the most promising apparatus for investigation of postapproval changes.

Suppositories

In principle, for hydrophilic suppositories that release the drug by dissolving in the rectal fluids, the basket, paddle, or flow-through cell can all be used.

Lipophilic suppositories release the drug after melting in the rectal cavity and are significantly affected by

the rectal temperature, reported as typically 36 to 37.5°C.[12] In vitro release testing also requires knowledge of the melting point/range of the product being tested. The test temperature should take into consideration physiological conditions but may also be at or slightly above the melting point, for example, at 37 to 38.5°C (which can be justified, eg, for suppositories used for patients with fever).

After melting, the drug will have to partition between the lipophilic base and the receptor fluid. This may lead to a distribution equilibrium between the 2 phases rather than complete dissolution. For this reason, sink conditions during the test are essential in order to simulate the in vivo situation, where absorption across the rectal membrane is continuously reducing the concentration of the drug in the rectal fluids.

The use of membranes in the test is in principle attractive since it is the most elegant way to obtain a filtered clear solution for immediate assay. However, it introduces an artificial process of transport and is thus in general not recommended.

For lipophilic suppositories, a modified basket method, a paddle method with a wired screen and a sinker,[13] and a modified flow-through cell with a specific dual chamber suppository cell (PhEur 2.9.3-6.) have all been recommended. To achieve the specified temperature in the test cell, the temperature in the water bath may have to be set up to 5°C higher.

Experience with the compendial flow-through cell has shown that it may generate highly variable data because of the behavior of the suppository in the cell,[14] in particular for formulations containing spreading agents. In such cases, and then deviating from the general recommendation, membrane-based physicochemical test methods[15] may be considered.

No single test method will be suitable for all suppository formulations. However, from the set of available methods described above, it should be possible to select an adequate in vitro release test in most cases. Recommendation of a method of first choice is inappropriate, based on the variety of formulation characteristics of suppositories. However, when starting development of an in vitro dissolution/release test, it might be advantageous to begin with the basket or paddle in the case of hydrophilic and with the modified flow-through cell in the case of lipophilic suppositories.

Vaginal dosage forms are often designed for local therapeutic effects. Nevertheless, if an in vitro release test is to be designed, the recommendations for suppositories may be followed.

Liquid-Filled Capsules

Liquid-filled capsules can consist of either hydrophilic or lipophilic formulations. In the case of lipophilic formulations, they may or may not include a surfactant for self-emulsifying purposes. The USP recommends a dissolution test procedure using the rotating paddle method (apparatus 2) with a minimum amount of surfactant, if needed (eg, dissolution of valproic acid or methoxsalen capsules). If the liquid-filled capsule contains a water-soluble base, then addition of surfactant is generally not needed; however, this is a function of the solubility of the active pharmaceutical ingredient as well as the formulation itself. The rotating paddle can have disadvantages for some liquid-filled capsule formulations, as it might be difficult to keep the formulation immersed. Also, emulsified formulations might separate at the liquid-vessel-air interface, and/or formulations could adhere to paddle or beaker walls.

The modified dual chamber flow-through cell as recommended for lipophilic suppositories (PhEur 2.9.3-6.) is considered an appropriate test apparatus for liquid-filled capsules. It can be run as an open or a closed (this may be important for self-emulsifying formulations) system. One potential disadvantage is that screens might be blocked during the test.

Other apparatus have also been successfully used, such as the rotating basket (which keeps the formulation immersed but might result in blocked meshes) and the reciprocating cylinder (which offers good mechanical agitation but a limited media volume).

Especially during the development phase, a range of test media should be used to characterize and understand the formulation characteristics. In the case of lipid-filled capsules, enzymes in addition to surfactants may be necessary to simulate digestion if this is a rate-limiting step for dissolution and absorption in vivo. The advantage of using lipases is that it more closely reflects physiological conditions. The disadvantages are that it can be expensive and labor-intensive when used as a routine test and it typically leads to higher variability.

No single test method will be suitable for all liquid-filled capsules. However, the set of available methods described above should enable the selection of an appropriate test in most cases.

Dosage Forms Requiring More Work Before a Method Can Be Recommended

Chewing Gums

In the case of chewing gums, the intensity and frequency of shearing forces/activities (ie, "chewing" action) can have a large influence on drug release rate. The European Pharmacopoeia provides a description of a stainless steel 3-piston-apparatus that is required for testing of "medicated chewing gums" (PhEur 2.9.25).[16] The test is typically operated at 37°C and at 60 cycles/minute. Test media with a pH of 6 are commonly used, since this pH corresponds to reported[17] saliva pH values of 6.4 (adults) or 7.3 (children). In particular during development, it is recommended to keep the "chewing residue" for later analysis/assay. However, to date there has been insufficient international experience with this apparatus to draw a firm conclusion about its suitability.

Powders, Granules, Solid Solutions, and Solid Dispersions

The flow-through apparatus offers specific sample cells for studying drug release from powder and granular dosage forms. However, it is important to note that the dissolution behavior of these dosage forms may be greatly influenced by their wettability, surface area, and particle size distribution. Thus, the in vitro release test results constitute one of a group of physicochemical parameters needed to characterize the product. For powders, especially when exhibiting poor wettability, it may be necessary to add a surfactant to the dissolution medium to obtain reproducible dissolution results. Care should be taken to use a level of surfactant that does not increase the solubility of the drug to the extent where the test is no longer discriminatory. In certain cases, a physical mixture of the powder with glass beads and/or other substances that encourage wetting may be used.

Solid solutions and dispersions may be presented in oral dosage forms such as capsules and tablets. If this is the case, their in vitro release characteristics can be determined using the same methods typically used to characterize the release from solid oral dosage forms. Solid solutions and dispersions often lead to a supersaturation of the medium. Therefore, for these types of formulations, dissolution tests under nonsink conditions can be a predictive tool during formulation development as well as for batch-to-batch quality control. Especially during product development, running the in vitro release test somewhat longer (eg, for up to 4 hours) should be considered to assess the potential for precipitation.

Parenterals: Implants and Microparticulate Formulations

The compendial and the modified flow-through cell have been used successfully for implants and microparticulate formulations. The compendial flow-through apparatus is modified with regard to the inner diameter to suit the special properties for testing parenterals—that is, a low volume of fluid is used in the acceptor compartment. The flow rate of the medium has to be set very slow. Use of High Pressure Liquid Chromatography (HPLC) pumps may be considered to provide the necessary accuracy and precision at very low flow rates. In this case, the flow-through system may need to be redesigned with small internal diameter tubing. Intermittent flow might also be an option. Static or rotating bottles have also been used for in vitro release testing.

As tests are often run over a long time period (eg, several weeks to months), measures have to be taken to compensate against evaporation. Suitable preservatives may be added to prevent microbial contamination. Standard preservatives, including cetylammonium bromide, benzalkonium chloride, parabens, phenol derivatives, and mercury salts, along with appropriate concentrations to be used, are listed in many pharmaceutical textbooks. The selection has to be based on criteria such as compatibility with the active pharmaceutical as well as other formulation ingredients and the pH of the test medium. Issues with these compounds include their ionization properties, physicochemical interactions, and analytical interferences. 0.1% sodium azide has also been used as preservative, but because of safety concerns, it cannot be generally recommended.

The composition of the medium should take into consideration the osmolarity, pH, and buffer capacity of the fluids at the site of administration, which are usually assumed to resemble those of plasma (or muscle) but with lower buffer capacity. However, the main challenges with this type of dosage form are to determine the appropriate duration of the test and the times at which samples are to be drawn in order to characterize the release profile adequately. The possibility of running the test under accelerated conditions is attractive and has been successfully applied through elevated test temperatures (even above glass transition temperatures of the polymers involved) and at pH values offering faster drug release.[18]

To evaluate whether accelerated test data are predictive, the Weibull shape factor should be considered.[19] Verification of the validity of using accelerated test conditions could also include an Arrhenius plot after obtaining release rate constants from linearized release profiles.[20]

For real-time (long duration) and accelerated tests employing potentially adverse temperatures or pH values, the stability of the active ingredient has to be taken into account, either analytically or through appropriate algorithms, when calculating release data.

An in vitro release test for assessing the quality and for process control of liposome drug products is important, but the challenge remains to develop and identify a reliable method that can characterize drug release from the product.[21]

Formulation Characterization

To characterize the release from the dosage form adequately, one must generate a drug release profile in which release (dissolution) values are determined as a function of time. This multipoint characterization has been in place for modified release oral dosage forms for some time and is also recommended for slower dissolving immediate release products. Because many of the dosage forms discussed here are complex in composition and release mechanism, a multipoint drug release test will be required to characterize release from the drug product in general and to test for possible alterations in the release profile during storage. Multipoint tests may also be needed for batch release testing in order to confirm acceptable batch-to-batch consistency. Typical cases where multipoint tests are likely to be needed include transdermal patches, semisolid preparations, chewing gums, implants, microparticulate formulations, solid solutions, solid dispersions, and liposomes. However, in other cases such as powders, granules, suspensions, ODTs (unless multipoint testing is used for evaluation of taste masking), chewable tablets, and rapidly releasing suppositories, a single point specification may be sufficient for batch-to-batch quality control. In these cases, the timepoint must be properly derived from profiles generated during the development phase of the product.

Experimental Test Conditions

The experimental test conditions should be discriminating enough ("mild" conditions) to detect manufacturing variables that may affect biopharmaceutical product performance. Test conditions that may not be able to discriminate adequately among products/batches with different in vivo release profiles include those with very high agitation/flow rates, the use of strongly alkaline solutions to dissolve poorly soluble acids, and the use of very high surfactant concentrations to create sink conditions, to name but a few.

As for solid oral dosage forms, development of in vitro dissolution/release tests and specifications for novel/special dosage forms should take into account relevant bioavailability or clinical data. However, expectations with respect to the quality and/or level of in vitro/in vivo correlation should not be set as high as for solid oral dosage forms, because of the higher level of complexity and data variability for novel/special dosage forms.

Ideally, physiological conditions at the site of administration should be taken into account when selecting the in vitro dissolution/release test conditions. The complexity of the release mechanism of some novel/special dosage forms and the lack of knowledge about the conditions under which release occurs in vivo make it difficult to design physiologically based tests in all cases, but it should be possible to conceive a test that can detect the influence of critical manufacturing variables, differentiate between degrees of product performance, and to some extent characterize the biopharmaceutical quality of the dosage form.

As the release mechanism and site of application vary dramatically among the novel/special dosage forms, the experimental test conditions have to be tailored according to the conditions at the site of administration (eg, temperature of the test) and the release mechanism (eg, chewing gums will require different agitation rates than suspensions). Within a given category, it may be necessary to have product type-specific dissolution tests (eg, separate tests for lipophilic and hydrophilic suppositories), and in some cases for products containing the same drug and administered in the same type of novel/special dosage form but with a different release mechanism (analogous to the range of tests available in the USP for theophylline extended release dosage forms).

Test procedures for dissolution testing of solid oral dosage forms—that is, immediate release and modified release dosage forms—have been significantly refined and standardized over the past quarter century. The methods are well on their way to harmonization across pharmacopeias and regulatory requirements. It is anticipated that through further refinement and standardization of in vitro release testing for nonoral

and special dosage forms, harmonization of tests for these dosage forms will take considerably less time.

Applications

A specific value of in vitro dissolution/drug release testing is recognized in its application as a batch-to-batch quality control test and its value in evaluation and approval of SUPAC. SUPAC-SS defines the levels of changes with respect to component and composition, site of manufacturing, scale of manufacturing, and process and equipment changes.[10] In vitro drug release is used to ensure product sameness for semisolid dosage forms under SUPAC-related changes. The same principles can easily be extended to other dosage forms where the product sameness can be ensured by profile comparison between prechange and postchange products using an appropriate in vitro test and profile comparison (eg, for transdermal patches).[22] In addition to this, the dissolution/drug release test can also be used for providing biowaivers for lower strengths of a product from a given manufacturer, once the higher strength is approved based on the appropriate bioavailability/bioequivalence test procedure.

Even though less experience is available with novel/special dosage forms than is available with conventional dosage forms, in vitro/in vivo correlations have been established. In such cases it is legitimate to use in vitro dissolution as a surrogate for the in vivo performance of a drug product, as long as the rate-limiting step is the release of the drug from the formulation; regulations should also support this. Because of the typically higher variability of in vivo and in vitro data in the case of many novel/special dosage forms, expectations about the quality and level of in vitro/in vivo correlations might have to be adjusted in comparison to those for conventional dosage forms.

It is worth noting that in general, an in vitro dissolution/release test is expected for each novel/special dosage form regardless of whether the intended effect is systemic or nonsystemic (eg, topical semisolid dosage forms), for formulation development, for investigations to support postapproval changes, and for batch-to-batch quality control. It has to be noted, however, that because of the specific formulation design, because of potential (physicochemical) interactions between the dosage form and the physiological environment at the site of administration, and because of the necessary design of in vitro dissolution equipment for novel/special dosage forms, dissolution/release data in vitro might be more strongly influenced by test or equipment parameters or less predictable for in vivo release than is usually experienced for conventional dosage forms. Therefore, a scientifically sound assessment of the relevance and validity of an in vitro dissolution test should affect the final decision about the application of the test and the specifications set for batch-to-batch quality control.

Setting Specifications: Acceptance Criteria/Limits

The in vitro dissolution/drug release specifications should be primarily based on manufacturing experience, formulation screening experience, and pivotal clinical trial batches or other biobatches. Compared with solid oral dosage forms in basket and paddle dissolution equipment, the novel/special dosage forms have not been as thoroughly tested with respect to variability of data and, where the newer types of apparatus are used, qualification of the equipment. In general, criteria and specification limits (ranges) may be similar to those for solid oral dosage forms. However, further experience needs to be gained to better understand the desired level of standardization, and it can be expected that in some instances the appropriate ranges and criteria for acceptance of release data of novel/special dosage forms will be very different from those for solid oral dosage forms.

In general, in vitro dissolution/release specifications apply throughout the shelf life of a drug product ("end-of-shelf-life specification"). Nevertheless, acknowledging the nature and design of some novel/special dosage forms, changes of dissolution/release properties within specifications within the shelf life have to be taken into consideration. Thus, pharmaceutical manufacturers may be well advised to apply internally "time of batch release" specifications, if appropriate, which are stricter than formal end-of-shelf-life specifications.

Conclusions

An appropriate drug release test is required to characterize the drug product and ensure batch-to-batch reproducibility and consistent pharmacological/biological activity.

For novel/special dosage forms more than for solid oral dosage forms, it is difficult to find the appropriate balance between the general recommendation to avoid "unnecessary" proliferation of dissolution apparatus and acknowledging the formulation-specific characteristics and requirements of a new product under de-

Table 1. Apparatus Used for Novel/Special Dosage Forms

Type of Dosage Form	Release Method
Method can be recommended	
Solid oral dosage forms (conventional)	Basket, paddle, reciprocating cylinder, or flow-through cell
Oral suspensions	Paddle
Orally disintegrating tablets	Paddle
Chewable tablets	Basket, paddle, or reciprocating cylinder with glass beads
Transdermals—patches	Paddle over disk
Topicals—semisolids	Franz cell diffusion system
Suppositories	Paddle, modified basket, or dual chamber flow-through cell
More work needed before method can be recommended	
Chewing gum	Special apparatus (PhEur)
Powders and granules	Flow-through cell (powder/granule sample cell)
Microparticulate formulations	Modified flow-through cell
Implants	Modified flow-through cell

velopment. We consider an apparatus unnecessary when for a newly developed dissolution test a comparison of the modified equipment with standard compendial equipment indicates that the results are equivalent. In such situations, clearly the compendial apparatus should be used.

Table 1 contains the current status of scientific development in the relevant area and recommends, where possible, the method of first choice. Specifically, this means that in developing a new product in the given formulation category, the recommended method should be tried first. Only if this method does not result in meaningful dissolution/release data should an alternative method be applied or developed. In such cases, other compendial or modified compendial methods should be assessed first, as described in the relevant section of this paper.

The in vitro drug release test for some novel/special dosage forms such as semisolid dosage forms and transdermal drug delivery systems has proven to be as valuable as the dissolution test for solid oral dosage forms. The in vitro drug release test also shows promise for other dosage forms, such as chewable tablets, suspensions, and suppositories. For yet other dosage forms, such as chewing gums, powders, and parenterals, further method development and refinement will be needed to make the drug release test a generally applicable, robust, and valuable tool.

REFERENCES

1. FIP guidelines for dissolution testing of solid oral products [Duplicate publication of FIP guidelines for dissolution testing of solid oral products. Pharm Ind. 1997;59:760-766]. Dissolut Technol. 1997;4:5-14.

2. FDA guidance for Industry: dissolution testing of immediate release solid oral dosage forms, August 1997; extended release solid oral dosage forms: development, evaluation and application of in vitro/in vivo correlations, September 1997.

3. USP 24/NF 19, <1088> 2000:2051.

4. FDA Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations. October 2000.

5. Shah VP, Tymes NW, Skelly JP. In vitro release profile of clonidine transdermal therapeutic systems and scopolamine patches. Pharm Res. 1989;6:346-351.

6. Shah VP, Elkins JS, Williams RL. Evaluation of the test system used for in vitro release of drugs from topical dermatological drug products. Pharm Develop Technol. 1999;4:377-385.

7. Fares HM, Zatz JL. Measurement of drug release from topical gels using two types of apparatus. Pharm Tech. 1995;19(1):52-58.

8. Shah VP, Elkins JS. In vitro release from corticosteroid ointments. J Pharm Sci. 1995;84:1139-1140.

9. Higuchi WI. Analysis of data on medicament release from ointments. J Pharm Sci. 1962;51:802-804.

10. FDA Guidance for Industry: SUPAC-SS Nonsterile Semisolid Dosage Forms. Scale-Up and Post Approval Changes: Chemistry, Manufacturing, and Controls; in Vitro Release Testing and in Vivo Bioequivalence Documentation. May 1997.

11. Flynn GL, Shah VP, Tenjarla SN, et al. Assessment of value and applications of in vitro testing of topical dermatological drug products. Pharm Res. 1999;16:1325-1330.

12. Honma K, Honma M, Kohsaka M, Fukuda N. Seasonal variation in the human circadian rhythm: dissociation between sleep and temperature rhythm. Am J Physiol. 1992; 262:885-991.

13. Gjellan K, Graffner C. Comparative dissolution studies of rectal formulations using the basket, the paddle and the flow-through methods, I: paracetamol in suppositories and soft gelatin capsules of both hydrophilic and lipophilic types. Acta Pharm Nord. 1989; 1, 343-354.

14. Gjellan K, Graffner C. Comparative dissolution studies of rectal formulations using the basket, the paddle and the flow-through methods, II: ibuprofen in suppositories of both hydrophilic and lipophilic types. Int J Pharm. 1994;112:233-240.

15. Setnikar I, Fantelli S. Liquefaction time of rectal suppositories. J Pharm Sci. 1962;51:566-571.

16. Chewing gum, medicated, drug release from. In: European Pharmacopoeia. 4th ed. Strasbourg, France: Directorate for the Quality of Medicines of the Council of Europe; 2002:227-228, general chapter 2.9.25.

17. Diem K, Leutner C, eds. Documenta Geigy, Scientific Tables. 7th ed. Summit, NJ: Geigy Pharmaceuticals; 1975:643.

18. Shameem M, Lee H, DeLuca PP. A short term (accelerated release) approach to evaluate peptide release from PLGA depot formulations. AAPS PharmSci. 1999;1(3):article 7.

19. Sathe P, Tsong Y, Shah VP. In vitro dissolution profile comparison: statistics and analysis, model dependent approach. Pharm Res. 1996;13:1799-1803.

20. Makino K, Arakaw M, Kondo T. Preparation and in vitro degradation properties of polylactide microcapsules. Chem Pharm Bull. 1985;33(3):1195-1201.

21. Burgess DJ, Hussain AS, Ingallinera TS, Chen M. Assuring quality and performance of sustained and controlled release parenterals: workshop report. AAPS PharmSci. 2002;4(2):article 7.

22. Van Buskirk G, Gonzalez MA, Shah VP, et al. Scale-up of adhesive transdermal drug delivery systems. Pharm Res. 1997;14:848-852.