

OVERVIEW OF WORKSHOP: IN VITRO DISSOLUTION OF IMMEDIATE RELEASE DOSAGE FORMS: DEVELOPMENT OF IN VIVO RELEVANCE AND QUALITY CONTROL ISSUES

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Scientists from industry, academia, and the regulatory agencies met to discuss the role of dissolution tests with immediate release dosage forms. Dissolution is clearly important in formulation development and can provide evidence for later use in quality control. Regulatory agencies also need such information in assessing "change" in manufacture to decide when in vivo information would be required. The workshop examined the limitations of dissolution as a surrogate for in vivo testing. As well as calibration and specification issues, a major challenge is to provide tests for highly water insoluble drugs in which formulation is used to enhance bioavailability. General specifications are difficult and case-by-case consideration is often required.

Key Words: Dissolution; Formulation development; Critical manufacturing variables; Capsules; Solubility; Permeability; *In vivo*:*in vitro* correlation

THE DIA DISSOLUTION WORKSHOP on *in vitro* dissolution of immediate release dosage forms was held June 6-7, 1995 in Toronto, Ontario, Canada. The workshop was planned to discuss issues and difficulties with dissolution tests and standard setting for conventional or immediate release (IR) solid oral dosage form drug products (tablets, chewable tablets, and hard and soft gelatin tablets). The objectives of the two-day workshop were:

1. Identify problems with dissolution in pharmaceutical formulation development and optimization,

2. Identify sources of variation in dissolution testing equipment and calibration,
3. Assess the use of dissolution in detection of manufacturing process variables,
4. Discuss/decide if dissolution can be a surrogate (*in vivo* relevance) for bioavailability in "change" situations,
5. Discuss development of quality control tests that are discriminatory in terms of bioavailability and/or manufacturing variables, and
6. Evaluate methods of analyzing dissolution profiles.

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The workshop was divided into four sessions. The first session, entitled "Dissolution in Drug Development," discussed the rationale for dissolution in drug product development, its use in early formulation develop-

ment, setting dissolution specifications, *in vivo* confirmation, and selection of conditions based on drug and dosage forms. The second session, entitled "Methodology," included apparatus and conditions, and calibration and similarities or differences among jurisdictions, internationally. On the second day, the third session, entitled "Dissolution: A bioequivalence interface," dealt with physicochemical properties, their influence on dissolution and when they are important in bioavailability, as well as manufacturing variables and their *in vivo* relevance. The final session, entitled, "Measurement of Change," addressed scale-up and postapproval changes (SUPAC), rationale for tolerances and the methods of statistical comparison and their use in developing dissolution standards. Some papers are available in full text; this overview attempts to summarize the remainder.

SESSION I

Dr. J. Robinson alluded to the profusion of new products, both conventional and modified release, that are coming to market as innovator patents expire. He has concerns because drug product development is a highly complex craft based on a substantial amount of empirical or semiempirical information in technical areas. The dosage form often assists bioavailability with formulation components, but these may also hinder.

The drug substance properties influence the *in vitro* dissolution and bioavailability behavior and investigators attempt to predict those that are well behaved, based on factors such as water solubility, stability in the solid state, chemical reactivity, and tissue permeability. The biological properties, however, are less influenced by dissolution. These include poor absorbability (bioavailability), dose in-proportionality, profound food effect, gastric motility, slow onset of action, and inter- and intra-subject variability (from various biological processes such as metabolism).

If the criterion for a dissolution test is

"one in which differences in bioequivalence are reflected by differences in dissolution," then extensive data are required to validate the dissolution test. Clearly, however, the expense of *in vivo* studies results in "data rich" dissolution test information bases compared with sparse databases on bioequivalence. There are many examples in the literature of poor dissolution properties resulting in poor bioavailability. There are also many examples of large differences in dissolution profiles showing no effect on bioavailability. There are relatively few examples when similar dissolution properties of formulations resulted in differences in bioavailability. The dissolution standards in the United States Pharmacopeia, however, have rarely been validated with *in vivo* testing.

The recent drug classification system (1) based on solubility and permeability, by defining the rate limiting steps in *in vivo* absorption, is intended to simplify dissolution requirements and regulatory scrutiny. It should be scientifically sound to factor dissolution requirements to formulation release characteristics, for example, dosage forms which release more than 80% of active ingredients in a physiologically relevant medium in 30 minutes or less would not require rigorous dissolution specifications. The drug classification system allows use of dissolution as a surrogate for slight changes in process or formulation. Whether this can be extended to new formulations of such a drug without testing bioavailability remains contentious.

Dissolution can be applied as a guide in formulation development, to monitor process reproducibility, in setting manufacturing specifications, to assess the influence of stability conditions, and as a surrogate for bioavailability in carefully defined conditions (eg, scale-up and postapproval change).

There is an assumption that the use of *in vitro* dissolution is a quality control tool, linking the characteristics of a pivotal bioequivalence batch to future production. In the absence of *in vivo:in vitro* correlation there is a lack of confidence. Establishment of a correlation, however, depends on whether

dissolution or a physiological process is rate limiting. The biopharmaceutical classification system assists in this.

Dr. Dahl discussed dissolution in the development of tablet products and suggested a decision process for selecting a dissolution methodology, presenting some examples. Drug development involves three stages: formulation screening, formulation qualification, and production.

In screening formulations, the effect of physicochemical properties of drug substance and the influence of excipients is examined in small scale studies to identify qualitative components and possible critical parameters. In qualification, information on scale-up, effects of quantitative composition, and range of critical parameters are studied. For production, scale-up and batch-to-batch are studied. Factors involved for raw materials include: polymorphs, crystal habit, particle size, bulk density and solubility; for excipients, binding, and so forth. Critical processing factors include granulation type, compression force, milling, and so forth.

One example cited involved a slightly soluble organic acid that was sensitive to the amount of water used in granulation and this affected the bioavailability. A second was a good example of the effect of particle size of a poorly water soluble (0.1%) substance on bioavailability, that is, micronized drug was more readily dissolved and bioavailable. An example with ascorbic acid, however, described a fast dissolving product which gave lower bioavailability. This was explained by the fact that ascorbic acid is absorbed by active transport and saturation of this transport occurs with faster dissolution. Thus, it is important to have knowledge of drug substance and excipients and to study impact of formulation and process variables to validate the dissolution tests applied.

Selection of tablet formulation is most simplified when a correlation exists between *in vitro* and *in vivo* measures, otherwise consistent and reproducible *in vitro* dissolution tests are required to ensure satisfactory product performance.

Dr. Ewart Cole addressed formulation and manufacturing problems with hard gelatin capsules. Manufacture involves knowledge of properties of drug substance, filler or diluent, disintegrant, and lubricant or glidant. Examples of formulation affecting dissolution from hard gelatin capsules included amount of starch or other disintegrant, amount of magnesium stearate and binders as well as process variables, such as mixing shear or blending time. These manufacturing variables, as well as changes during storage, appear to be well tracked by dissolution. For hard gel capsules, however, discrepancies between dissolution and bioavailability occur due to pellicle formation from cross-linking. It is shown that dissolution in media without enzymes does not dissolve the pellicle whereas pellicle formation does not influence bioavailability. The Swiss pharmacopoeia has adopted a two-stage test for capsule *disintegration*. If six capsules fail to disintegrate in time, a second set is tested in simulated gastric fluid with pepsin and, if disintegration then occurs in the standard time, capsules are considered acceptable. Such a two-stage dissolution test is also supported by *in vivo* bioavailability findings.

In summary, for hard gelatin capsules dissolution is effective in detection of formulation and process variables as well as stability changes during storage. It is less effective in prediction of *in vivo* behavior.

Dr. Frank Morton explained the advantages of presenting poorly water soluble drugs formulated in soft gel capsules to improve their dissolution and bioavailability properties. Formulations in soft gel capsules contain drug in:

1. Solutions in hydrophilic, lipophilic, or amphiphilic solvents,
2. Suspensions in hydrophilic or lipophilic bases, and
3. The drug as an oil, either neat or diluted.

The choice of dissolution conditions and apparatus differ according to the nature of the drug and its presentation. The rupture of the

shell is the critical point in dissolution of medicament in soft gel capsules. The USP described about seven drugs in soft gel dosage forms and Apparatus 1 or 2 is applied with different conditions. The European pharmacopoeia recommends the flow-through apparatus but it does *not* work for these dosage forms!

An example of a very soluble drug in soft gel is ethosuximide and it is formulated in a hydrophilic solution and readily meets the standard of 75% (Q) in 45 minutes in water. Nifedipine is a sparingly soluble drug in hydrophilic solution which again dissolves (simulated gastric fluid without pepsin). For etoposide, however, which has very low aqueous solubility, a mixed solvent of 500 ml water, 200 ml ethanol and 20 ml acetic acid is required for solution (75% Q in 45 minutes). Clofibrate is an oil and to effect dissolution 5% sodium dodecyl sulphate is required.

Stirring rate is important for many soft gel applications. For a high dose, soluble drug, such as acetaminophen or ibuprofen, inadequate stirring can result in precipitation. For low solubility, again, appropriate stirring rates may be required, along with surfactant. In some cases, drugs may precipitate from dispersion and a cosolvent such as ethanol is required for dissolution.

There can be problems in dissolution with drugs which use *in vivo* lipolysis to improve bioavailability, such as cinnarizine. Cosolvents are necessary. As with hard gelatin, soft gel capsules suffer from pellicle formation and with nifedipine, for example, problems of dissolution with storage have been observed. Again use of a medium with pepsin overcomes the problem of crosslinkage, but it will have to be supported with bioavailability evidence.

Dr. Storey's paper is published separately. In it the permeability model is challenged for some drugs; the need for dissolution tests of highly soluble drugs is questioned, and the problem of an effective dissolution test for very poorly soluble drugs, formulated with surfactant, is discussed.

Dr. McClintock presented a paper on problems of setting dissolution specifications, with examples. The regulatory agencies expect the USP apparatus to be applied, and for IR dosage forms, a Q value of 70–80% dissolved within an hour. A problem is selection of a dissolution medium that is physiological; water, buffers, and added surfactant are accepted, whereas cosolvents are questioned. Formulations in development are tested with several conditions and some are validated with an *in vivo* model. To develop a quality control test, the operating conditions are selected, a typical batch is tested with an animal model, operating parameters are adjusted to achieve a profile, and a Q value and changes in manufacturing process are related to the dissolution profile.

Problems which arise at this stage are that the dissolution test is too sensitive, showing major differences for minor changes in processing, or a major processing change is not detected by dissolution. In both cases the value of dissolution is questioned.

Examples included a product that was 100% dissolved in 10 minutes in water (apparatus 2, 50 r.p.m) and although highly water soluble, gave low bioavailability but good clinical efficacy. The value of the dissolution test was questioned.

Another extremely insoluble compound exhibited "good" bioavailability. A medium with propanol was applied and it detected some stability differences. Extensive process changes, however, were *not* detected with dissolution and the dissolution process was solubility rate limited. There did not appear to be a means of obtaining a meaningful standard for this product!

In a final example, questioning the value of dissolution, a highly water soluble sodium salt precipitated out of solution as free acid at low concentrations. A dissolution test at pH 9 with 20% propanol failed to detect major changes in bioavailability between formulations and no suitable predictable dissolution conditions were found.

In conclusion, the questions from this challenging presentation were that the physi-

cochemical properties of some compounds preclude the development of appropriate dissolution test conditions. If evidence of this is acceptable to regulators, what is the quality control alternative for such compounds?

Dr. Mark Eller spoke on the *in vivo* confirmation of dissolution specifications of IR products. He emphasized that it is never too early in the development program to start thinking about final product dissolution specifications. The theoretical framework of high or low solubility and permeability is useful to consider in predicting problems.

A development scheme for a dosage form could be in four phases: first, a clinical trial formulation, then a pilot formulation, then testing in change of site and/or process, and finally after process optimization, scale-up to production runs will occur.

For permeation the octanol/water system is commonly used to classify drugs. Correlations are more readily obtained with poorly water soluble drugs. *In vitro/in vivo* correlations, however, are rare for IR products. In fact, with high solubility and high permeability the *in vivo* profile of a tablet is often superimposable with solution.

There are cases in which manufacturing variables influence tablet performance. These may be at the granulation, drying, or tableting stages of processing and each of these stages may be optimized by tracking dissolution response. Such variables as amount of water, time of addition of water, and knead time are altered and compared with dissolution results. Several confirmation batches may be made and one "typical" batch and one batch outside the operational performance may be tested in a bioavailability study to see if there is a difference. The frequently used strategy is to challenge the dissolution properties with an *in vivo* bioavailability study.

If it can be established that dissolution is sensitive to changes in critical manufacturing variables and further, that lots even at the lower end of the specifications are bioequivalent, then it is advantageous for postmarket changes. Whether this is always neces-

sary is controversial. Probably such *in vivo* challenge would not be needed for IR highly soluble drugs in IR dosage forms.

SESSION II

The second session on methodology was led off by Gerry Shiu (Food and Drug Administration). His full paper appears later. In summary, he described the various types of apparatus. Regulators prefer the use of official apparatus (USP 1 and 2) when possible. The "bio-diss" and flow-through apparatuses are not usually of importance for IR products.

Application of different types of media were discussed; clearly physiological aqueous media are preferred to systems with alcohol. Enzymes are sometimes required, as with capsules, but enzymes are also subject to interbatch variability. In general, the specifications for an IR would involve a single point, whereas multiple points may be required in detecting change (formulation, site, etc.).

Dr. Qureshi has published his findings elsewhere (2), critiquing the current calibration of dissolution systems. This has also been explored in a recent conference (3). In brief, there are problems with the calibrations which appear to be too variable even if found to be within the given acceptance range. He argued that the prednisone, disintegrating calibrator is more suitable for Apparatus 2 (paddle) and the nondisintegrating salicylic acid more suitable for Apparatus 1 (basket). In addition, the use of vacuum in deaeration was found to be inferior to heat or heat with filtration under vacuum. More work is obviously required.

Dr. Lee Grady defended the USP "Third Generation" dissolution test philosophy and this paper is included (4). The pooling of samples in the case of fast dissolving products was considered with some scepticism. Some industry representatives argued that periodic skip testing, such as every fifth batch, might be preferable.

Dr. Malcolm Summers spoke on the British Pharmacopoeia (BP) perspective and

noted the differences between the BP and USP and most regulatory agencies. The BP, while moving toward the USP for harmonization of apparatus, test conditions, and some specifications will not adopt a policy of *universal* application for solid oral dosage forms. Dissolution standards would be appropriate only for less soluble actives and thus will not be required for highly soluble drugs in IR capsules or tablets. The BP is concerned about low solubility drugs and has work in progress to examine the flow-through apparatus for this type of drug. There will, however, be consultations with manufacturers. In general, dissolution specifications for IR products would have a single point acceptance criterion.

Dr. Martin Siewert presented a summary of the International Pharmaceutical Federation (FIP) revised dissolution guideline published in this issue. This is a very comprehensive document which includes advances in the specialty over the past decade, as considered in a FIP joint working group of industry and regulatory scientists. Differences among regulators in different jurisdictions and in different compendia were noted, along with proposals for harmonization. The chapters in the guidelines are: Concepts of dissolution testing, apparatus, experimental testing conditions, qualification and validation, formulation characterization, *in vitro*—*in vivo* comparison, dissolution specifications, interpretation/acceptance criteria, special applications, and conclusions.

Dr. Helga Möller presented a brief overview of a “biopharmaceutical concept” for oral IR products, particularly how to set dissolution specifications. Thus, in specific standard development, the physical and chemical characteristics of the drug substance, the dosage form, the pharmacokinetic characteristics of the drug and dosage form (linearity, etc.), the composition and manufacturing difficulty, and relationship among these factors have to be considered.

It was proposed that a general case might be made for IR dosage form standards of $\geq 75\%$ (Q) in 30 minutes, under physiological or justified conditions, “Case 1.” There can

be, however, special drugs for which $\geq 75\%$ (Q) in 15 minutes would be preferred based on *in vivo* findings, “Case 2.” For other IR dosage forms of particular drugs, prolongation of *in vitro* dissolution > 30 minutes may be necessary. For “Case 3,” factors involved in the prolongation would have to be investigated and justified.

SESSION III

The second day of the workshop began Session III: “Dissolution: A bioequivalence interface,” with a presentation by Dr. Roger Williams, Deputy Center Director, FDA, Center for Drug Evaluation and Research, with the United States FDA perspective. He summarized the current United States requirements for new drug application (NDA) products and for generic abbreviated new drug application (ANDA) products. Following the bioequivalence studies just prior to marketing approval, supplementary requirements for both NDAs and ANDAs followed parallel paths (preapproval inspection, approval, scale-up with three production batches, and changes thereafter, with supplements).

At the preapproval stage the emphasis on designing dissolution was continuity with the biobatch. After approval, with no change, dissolution is the quality control and is usually the compendial standard. For changes postapproval, the level of change determines the requirement. These can be considered in three classes: “minimal,” in which the *in vitro* test is accepted, “maximal,” requiring a full bioequivalence characterization with application of metrics and statistical criteria, and “moderate,” with dissolution *profiles* with or without bioavailability, depending on the drug and product characteristics. (For metrics and statistics, criteria are to be developed.) The factors and levels of change were considered in the scale-up and postapproval change initiative which considers the solubility/permeability factors and the therapeutic index of the substance, the formulation (IR, SR, semi solid/suspension, solutions), and critical formulation and manufacturing variables,

as well as the time on the market. The goals for FDA are to finalize the SUPAC documents and extend SUPAC principles to other parts of the drug life cycle (IND period). Finally, the international harmonization aspect was discussed including the International Conference on Harmonization, the World Health Organization "interchangeable multiple source drug products" document (5), and the idea of worldwide reference drug product standards.

Dr. Henning Blume of the Central Laboratories of German Pharmacists (ZL) did not agree on general test conditions for particular drugs. *In vivo* verification would be a prerequisite for use of dissolution in quality control. Then it could be used in stability testing and scale-up.

The validation of the test is essential with systematic variation of test conditions to characterize biopharmaceutical properties and evaluation of *in vivo/in vitro* conditions for *formulation-specific* quality control specifications. With such evidence dissolution can be used as a surrogate for *in vivo* testing for specific formulations.

Examples of clinically significant differences with a one-point (80% in 45 minutes) specification described include: glibenclamide, aspirin, doxycycline, penicillin V, and sotalol. This general standard is *not* appropriate to characterize all IR products. Perhaps 80% in 15 minutes could be used. In his opinion, however, it should be evaluated case by case.

Peter Jeffs presented the Canadian regulatory (Health Protection Branch) perspective. The uses of dissolution included: quality control as a performance indicator, stability studies, development, dose-dumping check in modified release, assessing change (source, site, manufacturing, and formulation variables), and new strengths when proportional.

Dissolution standards are expected for *all* solid oral dosage forms and suspensions. They are expected to be reliable and meaningful, with sufficient knowledge of the *in vivo* relationship. If it does not have discriminatory power, the value of the dissolution test is questionable. The Canadian viewpoint is somewhat similar to SUPAC in terms of

reliance on dissolution for batch-release, site change, source change of drug substance, new strength, and batch size. For major changes in formulation process, or equipment, justification would be required for not doing a bioequivalence study.

A series of questions concluded this talk. When to use dissolution alone for change? When should profiles be required? How are comparative profiles interpreted? How is discriminatory power verified? When can dissolution be a surrogate for bioequivalence in minor and major (generic/formulation) changes?

The next two talks considered manufacturing variables and *in vivo* relevance, starting with Dr. Vinod Shah (FDA) and the "concept of mapping." This paper follows and explains the process of relating critical manufacturing variables to dissolution profiles and to *in vivo* bioavailability. The goal is to develop product specifications that will assure bioequivalence of future batches, prepared within the limits of acceptable dissolution specifications.

Dr. George Lukas spoke on the topic of "manufacturing variables influencing dissolution" and his paper also follows. It is a review of recent literature to demonstrate that manufacture of a tablet or capsule product in a reproducible manner requires thorough knowledge of the processing conditions as well as the formulation. Although these variables are closely linked, the presentation focused on manufacture such as granulation and compression.

SESSION IV

The final session of the workshop, Session IV, was devoted to assessment of change. It was lead off by Dr. Larry Lesko (FDA), who provided details of the SUPAC initiative of FDA, with an overview of two research projects to support the recently published *Federal Register* guidance for change (6). These are the biopharmaceutical drug classification system projects at the Universities of Michigan and Uppsala (1) and the manufacturing research contract at the University of Maryland to identify critical manufacturing vari-

ables. In biopharmaceutical classification, suffice it to say that drug substances are characterized into four classes according to their solubility and permeability, with dissolution conditions and standards being set accordingly.

Conditions for Class I are a single point dissolution specification 85% (Q) in 15 minutes in 900 ml of pH 1.0 hydrochloric acid, with no problems with *in vivo* dissolution, absorption, and bioavailability (eg, metoprolol and propranolol). In Class II, a multiple pH dissolution specification such as in pH 1.0 hydrochloric acid and pH 4.5, 6.5, and 7.5 buffers are used and 90% dissolved over a longer time. Whereas bioavailability may not be a problem, formulations would be sensitive to change and *in vivo/in vitro* correlation may be expected (eg, naproxen and piroxicam). For Class III, highly soluble, but poorly permeable, a single pH, multipoint dissolution profile would be expected, for example, with ranitidine. For Class IV, poor solubility and poor permeability, interaction among formulation factors, and gastrointestinal variables cannot be predicted from *in vitro* dissolution and, for formulation or manufacturing changes, studies of bioequivalence would be required, as, for example, with furosemide.

In the University of Maryland contract, a factorial design was used to vary manufacturing processes and batch size with metoprolol, propranolol, naproxen, naproxen sodium, piroxicam, and ranitidine. Among these products, major differences in dissolution characteristics (for changes with each drug) were obtained. Also, predicted and "actual" dissolution data were in close agreement. Predicted differences in dissolution for SUPAC, Level 1 changes for composition, were slight. Broad differences in dissolution profiles achieved from SUPAC, Level 2, components and compositional changes, however, did not result in significant differences in bioequivalence. There were, nonetheless, some rank order changes between dissolution and bioavailability. From this evidence, dissolution tests and specifications suggested by the Biopharmaceutical Drug Classification System

appear to be conservative and support the SUPAC IR guidance.

Dr. Andreas Ohm presented some examples of critical manufacturing variables (as defined by the 2nd American Association of Pharmaceutical Scientists workshop on controlled/modified release) and *in vitro* dissolution tests. Some of these principles also apply to immediate release. Examples of mixing order of superdisintegrant, different granulation procedures, amount of water in granulation, and high shear mixing were shown to have dramatic effects on dissolution profiles of drugs such as nifedipine and nisoldipine. Certain of these changes in processing impacted on bioavailability. No general rule can be established, however, to indicate which of these manufacturing parameters are critical and these must be studied on a case-by-case basis with the drug during development. This also refers to the specifications for dissolution.

Dr. Coffin-Beach, representing a generic manufacturer's viewpoint, reiterated some of the problems of drug formulation and manufacture in other presentations. Typically, it appears that when generic manufacturers match dissolution profiles with originators' formulations, about 25% of the "matches" do not conform to bioequivalence requirements. Having achieved "matching" bioequivalence, however, the variations from source of active ingredient formulation, manufacturing process, and stability must be tested. There must be an attempt to determine how much dissolution variability is reasonable. Overall, the advice is not to set "optimistic" specifications in respect to dissolution profiles.

The final two presentations were concerned with the statistics of comparing dissolution profiles, a subject not yet fully consensual. The papers from Drs. Yi Tsong and James Polli follow to further the debate on shape (profile) comparison. Model independent approaches are suggested for further study.

CONCLUSION

This workshop brought together experts from Europe and North America representing in-

dustry, academia, and the regulatory agencies to consider *in vitro* dissolution of IR dosage forms. Clearly, for such dosage forms, dissolution is important in development and information at this stage sometimes allows definition of specifications for later quality control use, such as manufacturing versus dissolution profile changes. Regulatory agencies need such information in assessing SUPAC to decide when *in vivo* information should be required. Ideally, there would be an association between dissolution and *in vivo* behavior, but there are many exceptions for IR. The simple case is the highly soluble, highly permeable drug in which the risk of poor formulation is low and for which rapid dissolution provides a good estimate of performance. Other drugs with limitations on permeability and dissolution, as well as with physiological characteristics which influence absorption and bioavailability, set more challenges for design of meaningful dissolution specifications. The SUPAC initiative of FDA has moved somewhat toward resolution of problems for such drugs. Nonetheless, industrial participants challenged regulators and compendia concerning the utility of dissolution specifications that do not appear to be physiologically relevant. These occur with highly water soluble drugs, when absorption is not dissolution-rate controlled and with

water-insoluble compounds, formulated with agents to enhance absorption. On the other hand, regulators demand tests to provide confidence in lot-to-lot performance.

Calibration aspects of the apparatus and methods of comparing profiles (assessment of change) were also fruitfully discussed. Although several issues remain, for many IR products there is consensus on how to develop meaningful dissolution specifications, based on drug and formulation characteristics. In general, such specifications should be formulation-specific even when a pharmacopoeial monograph test is used.

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