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Development of dissolution tests for oral extended-release products

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Dissolution testing is well established in pharmaceutical compendia as a means of assessing finished product quality. Oral extended-release products present unique challenges in the development of dissolution test methods for their characterization. Although the current focus in the field has been on the use of dissolution testing in the later stages of product development for the purpose of establishing *in vivo/in vitro* correlations, the creative use of dissolution techniques can speed the initial stages of formulation development, particularly in the case of extended-release products.

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▼ Over the past 25 years, dissolution testing has emerged as a key development and quality control technique for the pharmaceutical industry. Measurements of *in vitro* drug release have always attempted to predict the *in vivo* performance of solid oral products[1]. The technique has evolved from simple disintegration studies to dissolution of immediate-release (IR) products for the purpose of quality control. It is now recognized as a powerful development, regulatory and quality control tool.

Evolution of dissolution testing

In the 1970s, it became apparent that dissolution was extremely useful for predicting the bioequivalence of supposedly identical IR solid oral drug products. Triggered by problems encountered with generic equivalents of digoxin tablets, a landmark series of collaborative studies was undertaken by government and industry laboratories[2–4]. It was shown that the mean dissolution time could be related to pharmacokinetic parameters such as the rate and extent of drug absorption, thus establishing a correlation between *in vivo* and *in vitro* performance. This supported the incorporation of dissolution tests and specifications into the United States Pharmacopeia (USP) General Chapters and monographs on solid oral dosage forms.

In subsequent years, dissolution test equipment was improved and standardized, and calibration tests were instituted. By the end of the decade, the USP had established a policy favoring the inclusion of dissolution tests in all monographs for solid oral dosage forms (except in cases where it was inappropriate scientifically)[5]. The addition of dissolution tests to USP monographs rendered them an excellent means of ensuring the uniformity of IR products.

Guidelines for oral extended-release products

Oral extended-release (ER) formulations (synonymous with terms such as controlled release, prolonged release and controlled delivery) provide significant advantages over IR oral dosage forms, including improved therapeutic effect, increased patient compliance by reducing dosing frequency and a decrease in the incidence and/or intensity of adverse effects. In the early 1980s it was recognized that these new, expanding technologies were unique, and that issues associated with ensuring their quality warranted special attention. Appropriately, the USP formed a subcommittee (the USP Subcommittee on Pharmaceutics – Dosage Forms and Systems) and, in 1983, published a policy that addressed dissolution of modified-release drug products for the first time[6].

This policy subsequently evolved into the USP General Chapter <724> entitled *Drug Release*. It proposed the general category of 'modified release', and further divided it into 'extended release', 'delayed release' and 'targeted release' (the latter was subsequently dropped because no products fitting the description were submitted). The original definition of 'extended release' was a dosage form that allowed at least a halving of the dosing frequency compared with the same drug presented as an IR dosage form. From that time, the USP monograph titles for all such products were compelled to include 'extended release' in the title. This definition

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has been modified recently to read 'An extended-release dosage form is defined as one that allows a reduction in dosing frequency as compared to that drug presented as a prompt-release dosage form.'[7]

Also included in the initial policy document was a set of guidelines for establishing dissolution tests and specifications for inclusion in USP monographs for ER dosage forms. Following the successes obtained with dissolution testing of IR products, the USP and the pharmaceutical industry attempted to standardize ER products in a similar manner. This made sense from the viewpoint of cost containment and harmonization. All emerging ER products were expected to fall into one of three 'cases' described in the USP policy.

First (ideal) case

USP Apparatus 1 (rotating basket) and Apparatus 2 (paddle) had been used and standardized for IR dosage forms. In the ideal case, ER products would be tested using one of these apparatus with water as the dissolution medium. The acceptance criteria were based on the dosing interval specified in product labeling. Three time points were specified, along with the ideal percent released at each point. The first time point was included to ensure that the product did not show excessive early release (dose dumping), while the final time point shows whether or not the intended dose is delivered within the dosing interval. Most dissolution tests for ER products now include four or more intervals, the middle time points defining the release profile of the product. The final requirement was that the ideal release profile should be independent of the pH of the dissolution medium.

Second case

It was realized, however, that many (if not most) ER dosage forms would be unable to conform to the ideal conditions described above. To accommodate this, the USP allowed for instances where test methods and specifications not matching those specified above would be described in detail in the individual monographs. The dissolution test method would apply to products intended to exhibit similar bioavailability, such as generic versions of innovator products. Note that testing was confined to the use of Apparatus 1 and 2.

Third case

The unique nature of ER products required the consideration of a third case, one that represented a departure from previous policy. What if two ER products were listed under the same USP monograph, yet their unique ER systems had chemical or physical properties so different from each other that the use of the same dissolution test was precluded? The products might be designed to exhibit different release profiles *in vivo*, or they might even be bioequivalent. This led to the decision that a single monograph could contain multiple tests. The product label would state which test and specifications were to be used in evaluating samples of that particular ER product. Most monographs for ER products in the current USP fall into this category; it is not unusual for two bioequivalent ER products to use completely different drug release mechanisms, or for a single monograph to cover multiple products with different release profiles *in vivo*. This is perfectly illustrated by the monograph for diltiazem HCl ER capsules[8], which contains six different dissolution tests (Table 1) corresponding to at least four marketed products (Dilacor® XL, Cardizem® CD and SR, and Tiazac®) and their generic versions. In this case, a single standard dissolution test method is not appropriate for all technologies.

Table 1. Dissolution tests specified in the USP monograph for diltiazem hydrochloride extended-release capsules

	Apparatus	Medium	Time points
Test 1	Type 2 100 rpm	900 ml water	3, 9, 12 h
Test 2	Type 2 100 rpm	900 ml water	1, 4, 10, 15 h
Test 3	Type 2 100 rpm	900 ml 0.1 N HCl	6, 12, 18, 24, 30 h
Test 4	Type 2 100 rpm	900 ml water	4, 8, 12, 24 h
Test 5	Type 2 50 rpm	900 ml 0.05 M phosphate buffer pH 7.2	1, 3, 8 h
Test 6	Type 2 100 rpm	900 ml water	2, 4, 8, 12, 16 h

Current regulatory climate

Since 1980 there have been extensive dissolution-related revisions of the USP[9]. At the same time, the international community was wrestling with the same issues. In 1981 the Federation Internationale Pharmaceutique (FIP), based in The Hague, The Netherlands, published its first guidelines for dissolution of solid oral products[10].

Extended-release solid oral dosage forms have continued to gain attention as a means of providing value-added products with reasonable development costs. The pharmaceutical industry is faced with increasing pressure to maintain historic double-digit growth rates despite the escalating costs of the development and marketing of new drugs. Meanwhile, intense competition in the generic industry (due in part to insignificant barriers to entry for generic IR oral products) led to increased focus on ER dosage forms as important ER drug products were coming off patent. This provided an unique opportunity for innovative generic companies to differentiate themselves from their competition.

New demand

Although drug delivery companies had been around for years, the new demand for ER product development expertise spurred a proliferation of companies with unique patented delivery systems[11,12] (the proverbial simpler/better/cheaper mouse trap). IR solid oral products are characterized by their relative ease of formulation development, the speed with which a product can be brought to market, and a high degree of regulatory standardization. Upon entering the arena of ER products, it was recognized that many assumptions about drug product development and standardization were no longer applicable. This represented a paradigm shift for the industry and regulatory agencies alike.

Regulatory focus on in vivo/in vitro *correlation (IVIVC)*

The pharmaceutical industry's hunger for rapid drug development and approvals, and the regulatory community's need for assurances of drug product quality and performance became the driving force behind the decade-long quest for linking *in vitro* dissolution to prediction of bioavailability, particularly for ER products. In the late 1980s, attention turned to *in vitro/in vivo* correlation (IVIVC). A workshop sponsored jointly by the US Food and Drug Administration (FDA) and industry concluded that the state of science and technology at that time did not permit meaningful IVIVCs for ER products on a consistent basis, but encouraged future research in the area[13]. Two subsequent workshop reports[14,15] showed a trend towards increasing confidence in IVIVC for the estimation of *in vivo* characteristics of ER products.

In July 1988, the USP published a stimuli article[16] that addressed IVIVC. It suggested terminology defining the different IVIVC levels A–D; this article was eventually expanded into USP Chapter <1088>[17]. All of these documents supported the subsequent publication in 1997 of the FDA's *Guidance for Industry: Extended Release Oral Dosage Forms: Development, Evaluation and Application of* In Vitro/In Vivo *Correlations (IVIVC)*[18]. This guidance document formalized the levels of IVIVC correlation that should be established for ER products in order to be useful for developing dissolution test specifications and for permitting certain formulation and manufacturing changes without an *in vivo* bioequivalency study. The levels of IVIVC from this document are summarized in Table 2.

Uses of IVIVC

The advantages of having an IVIVC include a scientific justification for biowaivers, where applicable, and for setting meaningful dissolution specifications. In 1993 the FDA issued its *Guidance for Industry: Oral Extended (Controlled) Release Dosage Forms:* In Vivo *Bioequivalence and* In Vitro *Dissolution Testing*[19], which was applicable to abbreviated new drug applications (ANDAs). It was followed in November 1996 by the FIP's current version of its *Guidelines for Dissolution Testing of Solid Oral Products*[20], which recognized that there was insufficient information to set guidelines for all solid dosage forms. It confirmed the need for case-by-case development for special cases, including modified release products. In September 1997, the FDA issued a guidance document aimed specifically at modified-release solid oral dosage forms, defining the requirements for scale-up and post-approval changes (SUPAC-MR)[21]. It organized post-approval changes into categories and defined which supporting studies (if any) a drug company must perform in order to implement the desired change.

The issuance of the FDA's SUPAC-MR document and the *Application of IVIVC* guidance in September 1997 gave the industry regulatory direction. However, most companies have been slow to initiate extensive implementation. This may be due in part to the feeling within the industry that it is probably not possible to develop a strong IVIVC for every product, and that the decision to develop such correlations should rest with drug companies and not regulatory agencies unless specific waivers are being sought. This is a natural response considering the complexity of developing an IVIVC for a formulation whose drug release may be affected by a number of formulation components such as coatings, solubilizing agents and the ER system itself. At present, it can be

Table 2. Extended release oral dosage forms: *in vitro/in vivo* correlations

Correlation level	Estimation procedure	Usefulness	Correlation characteristics
A	Two stage (1) Deconvolution (2) Compare fraction drug absorbed to fraction drug dissolved	Highest correlation Most common type seen in NDAs submitted to the FDA	(1) Generally linear (2) Point-to-point between *in vitro* dissolution and *in vivo* input rate (3) Non-linear may also be appropriate
B	Uses the principle of statistical moment analysis. Mean *in vitro* dissolution time compared to mean residence time or mean *in vivo* dissolution time	Least useful for regulatory purposes. Rarely seen in NDAs	(1) Uses all *in vitro* and *in vivo* data (2) Not a point-to-point correlation
C	A single point relationship between dissolution parameter (e.g. $t_{50\%}$) and a PK parameter (e.g. AUC, C_{max})	Limited usefulness for formulation development	Does not reflect the complete shape of plasma concentration-time curve
Multiple level C	Relates one or several PK parameters to amount of drug dissolved at several time points	Limited. Seen infrequently in NDAs	

Correlation levels. *Guidance for Industry – Extended Release Oral Dosage Forms: Development, Evaluation and Application of* In Vitro/In Vivo *Correlations*, CDER, FDA, September 1997.

argued that much of the real value of the dissolution test for ER products lies in the early stages of formulation development, where it can improve efficiency and reduce costs[22,23].

Dissolution tests for oral ER products

Dissolution test methods evolve in parallel with a new formulation. Devane and Butler[24] have described the relationship between *in vitro* behavior and *in vivo* performance as dynamic and inseparable from all stages of product development. In the early stages of drug product development, *in vitro* dissolutions are performed to support the choices made between different formulation candidates. Further cycles of formulation optimization and performance testing, both *in vivo* and *in vitro*, characterize the development process up to the determination of the final formulation. After product approval, dissolution testing is used to assess product quality and, as outlined in the *SUPAC-MR* guidelines[21], to evaluate formulation and manufacturing changes.

The term 'assumed *in vivo*/*in vitro* relationship' has been coined to describe the initial model in which dissolution data is used to develop prototype formulations[24]. In the first stage of formulation evaluation, dissolution testing can provide valuable information about possible risks such as dose dumping, food effects and the interaction of drug substances with other formulation components. Generic products present special formulation challenges. When developing a bioequivalent product, it may be useful to compare dissolution test profiles of the innovator product under various conditions to those of test fomulations, always keeping in mind the differences between ER systems. Even in cases where a single test method cannot provide good IVIVC for two different ER systems, several different methods may correlate to individual *in vivo* parameters such as C_{max} and T_{lag}. A rank order can often be established that may prove useful in guiding the direction of formulation development. Prototypes selected are tested using an array of test conditions to check formulation robustness and other properties. Often, one of the many dissolution test methods explored initially is found to provide the best IVIVC as the formulation development progresses.

Factors influencing initial dissolution test development

The selection of test conditions for a new formulation project is determined by the desired *in vivo* behavior of the proposed formulation, the known properties of the drug substance and the characteristics of the ER system. The more information that is available, the easier it is to design an initial set of dissolution test conditions[25–28]. When the properties of the drug (e.g. pharmacokinetics) and the ER system are well known, it is usually possible to establish a valid target profile for the proposed new formulation based on previous experience with the technology.

Target formulation characteristics

When designing an ER oral formulation, several questions must be answered. What is the desired *in vivo* profile for the proposed formulation? What is currently known about the *in vivo* absorption characteristics of the drug of interest, and its dissolution characteristics? Clearly, IVIVC is most easily established when dissolution and not absorption is the rate-limiting step in the dissolution–absorption system for the drug. If an IR form of the drug is marketed, what pharmacokinetic data are available? With this type of information, a theoretical *in vivo* profile can be generated and dosage strength(s) decided upon[29]. If a generic formulation is desired, what are the characteristics of the innovator product? Deconvolution[30–32] of *in vivo* results can be used to generate target dissolution profiles from plasma concentration-time data of selected products.

In some instances, it may be advantageous to develop different ER formulations for the same drug that yield different *in vivo* profiles for different therapeutic applications. An example of this was recently reported in the development of dissolution tests for two different ER formulations of the same insoluble drug using variations of a hydrophilic matrix technology[33]. Not only were different dissolution apparatus and media used for the product release tests, but also the need for completely different test systems at a very early stage of product development were determined.

Drug substance properties

Amidon's biopharmaceutic classification of drugs (on the basis of their solubility and gastric permeability) for predicting the probability of achieving IVIVC[34] is widely referenced for IR formulations. Information about drug solubility at different pH values is crucial, and is related to its ionic state. Knowledge of the pK_a of the drug is therefore relevant. The particle size of the drug substance may also play a role in determining the release characteristics of a formulation, particularly if the drug is poorly soluble in aqueous solutions[35].

The solubility of the drug is important in establishing sink conditions during a dissolution experiment[36]. The term 'sink condition' denotes a state in which the concentration of the drug in a solubilizing medium is very low compared with that of a saturated solution of the drug in the same medium (see Ref. 39 for a theoretical discussion). For practical purposes, the USP considers that 'sink conditions' have been met in a dissolution test if the saturated solubility of the drug in the dissolution medium is at least three times the concentration of a completely dissolved tablet in the volume of media used in the test. However, it is not always necessary to achieve sink conditions for a dissolution test to provide relevant information. One laboratory has reported that IVIVC is more likely to be obtained when the saturated solubility of the drug is approached[26].

Drug stability during the dissolution test must also be considered. A typical dissolution test at 37°C for ER dosage forms runs for 12–24 h or more, and analysis of the samples can take up to an additional 24 h. The stability of the drug in solution must be ascertained; it is prudent to assume minimal product stability at the outset. Both solubility and stability may vary as a function of pH, constraining the range of dissolution test conditions used.

Extended-release system properties

The properties of the ER system, whether it be a matrix system, microspheres, an osmotic pump or a layered tablet, will often dictate certain dissolution test parameters. For a hydrophilic matrix system that swells during dissolution, USP Apparatus 1, with its rotating basket design, is not appropriate. The matrix literally clogs the holes in the basket, disrupting the hydrodynamics of the test.

The behavior of some ER systems can be modified by the physical and chemical properties of the drug substance. For example, release of drug from a swellable monolithic matrix is controlled by the dissolved drug gel layer thickness, which depends mostly on the matrix properties, but under certain circumstances can be influenced by the degree of drug loading and drug solubility[38,39]. The release characteristics of many ER systems show some dependence on pH and may be affected by other excipients within the formulation to varying degrees depending upon the dissolution-test conditions.

The ER technology may also affect how the test samples are analyzed: it may be preferable to use HPLC to separate matrix components from the active ingredient if they generate significant interference during UV analysis of dissolution test samples[40]. Microspheres present their own unique challenges – a pH-change protocol in USP Apparatus 2 is difficult and may require specially adapted equipment for products based on a bead technology.

Other considerations

Coatings are often used to give the prototype formulation useful characteristics, such as an initial lag period before drug release. The physical and chemical properties of the coating material may come into play when developing the optimal method. Enteric coatings are designed to maintain their integrity under acidic conditions, releasing drug as the pH of the environment becomes neutral. The pH of the dissolution medium thus plays a major role in the analysis of products using such coatings.

We have encountered a case during development of a generic formulation where the decision was made to change from a pH-independent coating to a pH-dependent coating material; this necessitated changing not only the dissolution medium but also the apparatus type. The brand product monograph called for testing in USP Apparatus 2 using 0.1 N hydrochloric acid as the medium. The pH-dependent coating maintained its integrity in this medium with the result that no drug was released. Use of a medium with a higher pH resulted in coating disintegration but, because of the chemical properties of the drug substance, the dissolution profile was also affected, slowing to the point where the *in vitro* test was no longer representative of *in vivo* performance. Increasing the paddle speed was not sufficient to correct the problem, and we eventually had to substitute Apparatus 3 (which has more favorable hydrodynamics, see below) for Apparatus 2 to achieve a meaningful profile.

The buffer species has been reported to significantly influence the release of drug from ER dosage forms coated with certain cationic polymers[41]. Chloride ion concentration has been shown to influence the tablet-to-tablet variability in a dissolution test with some types of methacrylic acid copolymer coatings[42].

Apparatus selection

Although many ER systems have been described in the literature[11,12,43,44], fewer than 25 out of the hundreds of product monographs currently listed as of the 8th supplement to USP XXIII describe oral ER products. Of those 25, only two (lithium carbonate and verapamil hydrochloride) contain tests that do not specify either Apparatus 1 or Apparatus 2. This reflects the time interval between innovation and compendial acceptance of an oral ER product.

Seven types of dissolution apparatus are described in the current USP XXIII. Apparatus 1 and Apparatus 2 (Figure 1) are the most widely used for solid oral dosage forms. We will not discuss the use of these apparatus here. The reader is referred to Hanson's excellent handbook[36] for detailed descriptions of the use and standardization of these workhorses of dissolution. Apparatus 3–7 were devised in response to the recent explosion of new drug delivery technologies. Apparatus 3 and 4 were added to the USP in 1990 for the convenience of European companies that were using them to characterize ER products, while 5, 6 and 7 are used mainly for transdermals (Apparatus 7 has also been used

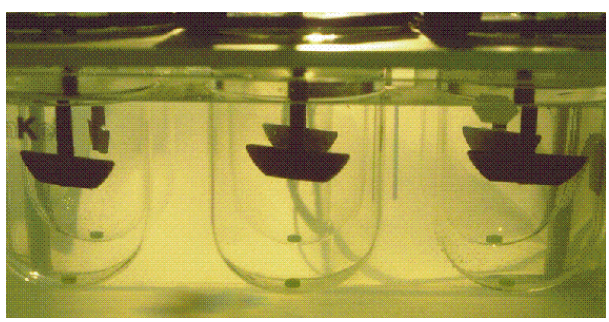

Figure 1. USP Apparatus 2.

for oral ER products using osmotic-pump technology[45,46]). In order to discourage proliferation of dissolution apparatus, the USP requests that monograph applicants prove the necessity of the alternative method over the well-established and standardized Apparatus 1 and 2.

Most ER systems are sensitive to agitation; the greater the agitation the faster the release profile of the drug product. Ideally, an ER product should not be overly sensitive to agitation in order to allow for varying gastric conditions. The rotation of the basket or paddle in Apparatus 1 and 2, the agitation rate of the reciprocating cylinders of Apparatus 3, and the flow rate in Apparatus 4 are typically adjusted to yield at least 80% dissolved by the end of the specified dosing interval as suggested in the current FIP guidelines[10]. Makers of new ER products gain a strategic advantage if they can specify several intermediate time points and make the specifications relatively narrow. This makes it difficult for generics to use the same release test for their equivalent products, forcing them to petition the USP to include additional test procedures and slowing their entry into pharmacopeia.

Applications of Apparatus 3

Apparatus 3 (reciprocating cylinder) is well-suited for ER formulations. It replaced the cumbersome rotating bottle method and maintained the free movement of the dosage form through the media[47]. Because the cylinders can move from one media-containing vessel to the next, the dosage form is able to dissolve into a larger volume of media than the 1000 ml limit of Apparatus 1 or 2. It is suitable for bead technologies because the dosage form is contained within a cylindrical chamber with screens at the top and bottom. Proponents of Apparatus 3 cite superior hydrodynamics with this design, and it is particularly useful for the analysis of products containing poorly soluble drugs[48,49]. In addition, the dissolution rates with this type of apparatus appear to be relatively unaffected by the presence of dissolved gases in the media, unlike Apparatus 1 and 2[50]. Its major drawback is that, in a typical ER product dissolution test, each of its 36 vessels must be individually hand-sampled. Automatic sampling devices for Apparatus 3 have been marketed, but (in our experience) they are not yet technically reliable for a 24 h dissolution, rendering them impractical for day-to-day quality control applications. Calibrator tablets and beads for Apparatus 3 have become available within the past few years from the USP, further standardizing this useful dissolution apparatus for ER products.

Applications of Apparatus 4

Apparatus 4 (flow-through cell) is a versatile technology that can be set up to provide either laminar or turbulent flow[51,52]. It consists of a reservoir and a pump for the dissolution medium, a flow-through cell and a water bath that maintains the temperature of the medium. Five types of cells are currently available[53], accommodating everything from powders to tablets, gelatin capsules to transdermals. Apparatus 4 can be used as an off-line system, in which the dissolution medium is not recirculated. Continuously flowing fresh medium across the sample makes the technology compatible with poorly-soluble drugs[53] and allows for pH changes. The drawback is that this requires a large volume of dissolution medium, approximately 60 l for a typical test. Apparatus 4 can also be run in the on-line mode, in which the dissolution medium is recirculated. In practice, Apparatus 4 is not as technically robust or reliable as Apparatus 1, 2 and 3. Apparatus suitability protocols and calibrator tablets for Apparatus 4 are not yet available from the USP.

Media selection

Historically, attempts were made to adjust *in vitro* test conditions to make them as close as possible to physiological conditions in order to increase their predictive value[27,54]. Dissolutions are normally performed at 37°C ± 0.5°C. The dissolution characteristics of an ER product should be determined over the entire range of physiological pH, which is generally described as being from approximately pH 1 to 7.5. But how long does a dosed tablet remain at each pH in the body? This is influenced by various factors, including the food that the patient has consumed. Bioavailability will be affected by the time a tablet spends in each part of the gastrointestinal tract, the presence or absence of food (which in turn affects pH[56]), the size and extent of the meal and the nature of the food (fatty or fibrous). Our ability to mimic this environment, even with the present state of our knowledge of the gastrointestinal tract[57], remains limited. The variables are numerous, particularly in the case of an ER formulation, in which the ER system itself may also be affected by variables such as pH, agitation or ionic strength. It is no coincidence that the best IVIVCs shown to date have been with specific categories of ER systems that are essentially unaffected by such factors[21].

Range of pH and ionic strength

Candidate formulations are tested routinely over the physiological pH range to gain information regarding the robustness of the formulation. Regulatory guidelines suggest monitoring the integrity of an enteric coating by using gastric pH (1.2) for the first 2 h, followed by intestinal pH (6.8 or 7.5) for the remainder of the test[20]. Using USP Apparatus 3, it is possible to take the tablet through six or more successive pH changes in a single dissolution run. This method can identify formulations that dose dump without going through a series of experiments using media of different pH values. As formulation development progresses, *in vivo* results from pilot biostudies may suggest the inclusion of intermediate pH values such as 3.5 and 5.5 in the test. As discussed above, the properties of the drug substance may dictate the pH range used. Additionally, the release characteristics of many ER

systems show some pH dependence. This should be taken into consideration during optimization of the test method.

Varying the ionic strength and the type of buffers used can reveal sensitivities caused by the drug itself, the ER system or the coating material. The use of water is discouraged because its pH and other properties depend on the water source and may also vary during the dissolution run as the dosage form dissolves[20].

Media choices for poorly-soluble drugs

It is generally agreed that the use of nonaqueous media, such as organic solvents, should be avoided. If the drug is not freely water-soluble, the use of surfactants should be considered[35,58–60] (solubility values in these solutions should be obtained initially); the addition of small amounts of antifoaming agents may be necessary, particularly when employing Apparatus 3 (Figure 2). We have achieved good IVIVC with surfactant-containing media. However, Figure 3 illustrates just how system specific such IVIVCs can be. It shows the marked difference in dissolution profiles in 30% polyethylene glycol of two bioequivalent dosage forms using matrix and osmotic pump technologies. This emphasizes the point that caution must be exercised in using an innovator-product's dissolution profile to guide generic formulation development, particularly for ER products.

Measuring the release of a poorly-soluble drug into aqueous media (with subsequent solubilization during sample preparation) has, in our experience, sometimes provided useful information during formulation development. We have successfully used the release of an insoluble drug in water to assess the effect of solubilizing agents within the dosage form itself.

Media choices for simulating food effects

The presence of food often changes the *in vivo* behavior of drug products. There have been many ingenious attempts to mimic food effects *in vitro* – for example, products have been soaked in oil prior to testing and milk has been used as dissolution medium[61–63]. We find Apparatus 3 uniquely suited to study these effects. A medium containing 30% peanut oil yielded good IVIVC for fed studies of products using our hydrophilic matrix technology[64,65].

Future directions

Current applications of dissolution testing include formulation selection, assessment of product quality and evaluation of product and process changes. As described above, there is plenty of room for innovation. Dissolution testing will continue to be extremely important in the early stages of formulation design and optimization. Methods that are too complicated or which fail to meet compendial requirements may still provide advantages in product development. As our pool of experience grows, it will be possible to make more meaningful decisions based on dissolution test data. The perception of what constitutes an acceptable method has been colored by the quest for IVIVC. At the 37th *Annual Land O'Lakes Conference on Pharmaceutical Analysis*, held in August 1997, the experience of the attendees was that regulatory agencies were willing to consider almost any dissolution test protocol as long as a solid IVIVC could be established for the method.

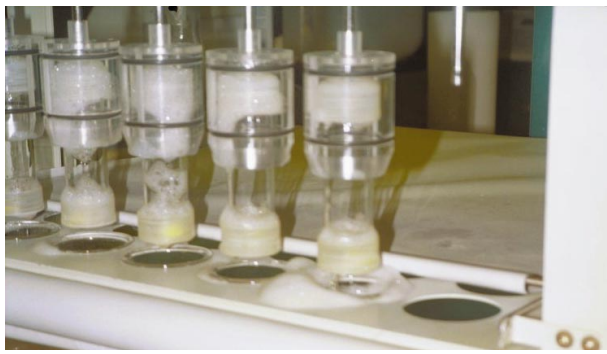

Figure 2. Foaming of surfactant-containing media in USP Apparatus 3.

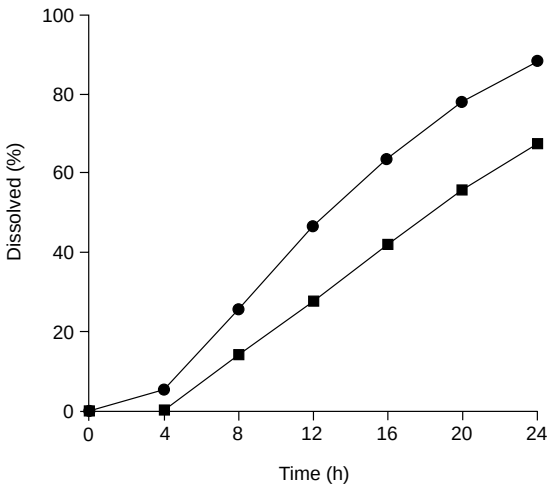

Figure 3. Comparison of dissolution profiles of two bioequivalent extended-release (ER) drug products based on hydrophilic matrix (black circle) or osmotic pump (black square) technology.

Issues relating to IVIVC will continue to be discussed[23,24,28,66]. It is uncertain at the present time whether the drive to establish IVIVCs will attempt ultimately to encompass all dissolution tests listed in official monographs intended for product release, or whether companies will be able to decide for themselves how far to pursue it. Past work has reflected this struggle, as tests have been discarded after proving to be insensitive to changes in parameters critical to *in vivo* performance or hypersensitive to variables not affecting it[67,68]. Regardless of the outcome, dissolution testing has established itself as a regular quality control procedure in good

manufacturing practice and will, at the very least, remain a simple and cost-effective indicator of a product's physical consistency.

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