

Review Article

Profiling *In Vitro* Drug Release from Subcutaneous Implants: A Review of Current Status and Potential Implications on Drug Product Development

Sunil S. Iyer^a, William H. Barr^b and H. Thomas Karnes^{a,*}^aDepartment of Pharmaceutics, School of Pharmacy, Virginia Commonwealth University, Richmond, VA 23298-0533, USA^bCenter for Drug Studies, School of Pharmacy, Virginia Commonwealth University, Richmond, VA 23298-0533, USA

ABSTRACT: This review presents current methods and strategies for studying the release characteristics of drugs from subcutaneous implant dosage forms. Implants are dosage forms that are subcutaneously placed with the aid of surgery or a hypodermic needle, and are designed to release drugs over a prolonged period of time. In most cases, the objective of a release test is to identify sufficiently discriminatory procedures that in turn would provide data to set meaningful specifications. Additional information obtained from successful *in vitro*–*in vivo* correlations (IVIVC) and accelerated drug release tests are extremely useful during drug product development.

Although several workers have employed different methods to monitor drug release from these dosage forms, the use of the compendial Apparatus 4 (flow-through) device has been recommended in a publication on FIP/AAPS Guidelines for drug release testing of modified release dosage forms. However, most of method development with this device has focused on oral immediate or controlled release dosage forms and little published information is available on implants. Two recent reports on workshops provide useful information on methods to evaluate drug release from controlled-release parenterals such as implants, including IVIVC and accelerated release testing. Details on such studies, however, are generally not found in the literature; possibly because of the high proprietary value of methodologies for establishing release specifications of implant dosage forms. This article reviews the current status of methodologies used in the investigation of drug release from subcutaneous implants with an emphasis on mechanistic, product development and regulatory perspectives. Copyright © 2006 John Wiley & Sons, Ltd.

Key words: implants; *in vitro* drug release; *in vitro*–*in vivo* correlation; accelerated drug release testing

Introduction

Dissolution testing has become increasingly important in quality control and formulation development [1]. Developments in these critical methodologies have come from regulatory agen-

cies, as well as industrial and academic groups seeking *in vitro* drug release methods that better correlate with *in vivo* drug release and absorption; and provide improved precision, accuracy, predictability and ease of use [2].

Folkman and Long [3] recognized the use of implants as sustained release drug delivery systems. An earlier review on the physicochemical characterization of subcutaneous pellets was given by Ballard in 1961 [4]. Further development of these dosage forms over the years has

*Correspondence to: Department of Pharmaceutics, P.O. Box 980533, Virginia Commonwealth University—School of Pharmacy, 410 North 12th Street, Richmond, VA 23298-0533, USA. E-mail: tom.karnes@vcu.edu

become necessary due to the short half-life of many pharmaceutical agents after parenteral administration [5,6]. A longer duration of action is also required for patient acceptability since it avoids the need for frequent invasive procedures. Implants are dosage forms that are subcutaneously placed with the aid of surgery or a hypodermic needle and are designed to release drugs over a prolonged period of time. A wide variety of drugs are good candidates for formulation as implants. Agents used long-term such as goserelin, leuprolide, carmustine, recombinant nerve growth factor (rhNGF) and levonorgestrel are a few examples [7]. Also, stents, which are small cylindrical tubes placed in vessels, are an important new development for delivery of drugs that must be administered continuously for a long period of time.

Prolongation of drug release from implants can be effected through the use of polymers as controlled-release matrices, or by the use of devices based on osmotic pump technology [8–10]. Biodegradable polymers offer the advantage of a single surgical procedure. Some implants employ a rate-controlling membrane that imparts zero-order characteristics to the drug release profile.

A topic of current research interest is the selection of an appropriate dissolution medium that provides 'sink conditions' based on the solubility of the drug and the dose rate [11]. Another important topic is the development and validation of a standard apparatus for the quality control of implants that release drugs. A report [12] of the workshop of the European Federation of Pharmaceutical Scientists (EUFEPS) held in February 2003 summarizes scientific support for the urgent development of a regulatory standard for controlled-release products. Of particular concern was the necessity for standards on *in vitro* release methods and for science-based guidance in the areas of *in vitro* release testing and *in vitro*–*in vivo* correlations (IVIVC). An IVIVC imparts *in vivo* validation to the *in vitro* dissolution test, which can then be used as a surrogate for bioequivalence testing [13]. In addition, more meaningful dissolution specifications can be set using the concept of an IVIVC [14]. A Guidance document [15] was issued by the Food and Drug Administration in an effort to: (a) reduce the regulatory burden by decreasing

the number of biostudies needed to get approval and maintain an extended release product on the market and (b) set dissolution specifications that are more meaningful clinically. The ultimate goal is that demonstration of valid IVIVCs would allow many of the biostudies that are generally required for major manufacturing changes to be replaced by simple *in vitro* dissolution tests. Four categories of correlations (A–D) have been described in the guidance. A Level A correlation represents a point-to-point relationship, generally linear, between *in vitro* dissolution rate and the *in vivo* input rate. It is usually considered the best type of correlation to claim biowaivers. A Level B correlation involves the principles of statistical moments. The mean *in vitro* dissolution time is compared either to the mean residence time or the mean *in vivo* dissolution time. This is not considered to be a point-to-point correlation and because a number of different *in vivo* curves will produce similar mean residence time (MRT) values, this cannot be considered discriminatory for different formulations. A Level C IVIVC represents a single point relationship between a dissolution parameter (such as percent dissolved at a particular time) and a pharmacokinetic parameter of interest, e.g. the area under curve (AUC). However, it does not reflect the complete shape of the plasma concentration curve, which is the critical factor that defines the performance of extended release products. A Level C correlation, although useful to screen and rank-order formulations in animal models during drug development, cannot be used for biowaivers or bioequivalence [16]. The fourth category, D, is a multiple Level C correlation and it represents a relationship between one or more pharmacokinetic parameters, and the amount of drug dissolved, at multiple points of time on the dissolution profile.

The FDA Guidance is applicable, directly, only to oral extended release drug products. Principles of the Guidance can be employed for non-oral dosage forms, such as implants. Additional work is needed in this area, however. Several challenges exist in method development for implants and these need to be dealt with on a case-by-case basis. This review will summarize the scientific issues related to drug release from subcutaneous implants, followed by a discussion of the current practices for these types of studies.

Apparatus Selection

A dissolution process involves two sets of variables relating to the apparatus and the medium. The apparatus variables include the type of apparatus and its hydrodynamics, including agitation and flow-rate. The medium variables include volume, composition, and concentration of the drug as function of time. When the drug concentration continues to increase in the dissolution medium to about one-third of the saturation value at a particular temperature, it is commonly referred to as a 'non-sink condition'. On the contrary, a 'sink condition' refers to the excess solubilizing capacity of the dissolution medium, a condition at which the concentration of the drug is maintained at a constant low level, well below saturation [17]. According to the flow characteristics and sink conditions, dissolution devices have been classified [18] into: (a) natural-convection non-sink methods (e.g. Levy static disk method [19]), (b) forced-convection non-sink methods (e.g. USP 1 and 2 apparatuses [20]), (c) forced-convection sink methods (e.g. the dialysis method of Barzilay and Hersey [21]), and (d) continuous-flow/flow-through methods (e.g. Langenbucher method [22]). The application of a universal dissolution or release rate test, in a compendial sense, is desirable but largely impractical [23]. Each drug and the dosage form prepared from it have to be studied individually and usually retrospectively, after *in vivo* data are available. This is because, achievement of the ideal correlation requires selection of the *in vitro* parameter that has the greatest relevance to the drug absorption characteristics. A dissolution rate apparatus suitable for both research and quality control purposes should meet certain criteria (Table 1). The apparatus should have simplicity of design, convenience of operation and provision for an easy introduction of the dosage form under investigation. The inherent variability in the apparatus must be less than the inherent variability in the products being tested. This requires that the essential components be specifically definable and reproducible. It must be capable of reproducing a given intensity of agitation or flow, with fixed geometry for successive runs under a constant setting. It must

Table 1. Criteria for apparatus selection

-
- (a) Simple design
 - (b) Convenience in handling, operation and cleaning
 - (c) Well-defined components for reproducible results
 - (d) Provision for an easy introduction of the test product and sample withdrawal for analysis
 - (e) 'Biorelevant' to the extent feasible, i.e. should mimic physiological condition at the site of implantation
 - (f) Allow effective and controlled agitation
 - (g) Potential for use in accelerated drug release tests
 - (h) Economical
-

be flexible in the effective degree of agitation; by altering the stirring rate or flow rate or some similar parameter. The apparatus should be economically practical. Ideally, apparatus variables should allow testing of formulations in such a way that facilitates elucidation of the mechanism(s) and critical variables for drug release, e.g. disintegration, deaggregation, erosion, permeation, etc.

Current reports on testing drug release from implants involve subjecting the implants to unstirred conditions in vials containing media. In their study with buserelin implants, Schliecker *et al.* [24] withdrew samples at different time intervals for the estimation of drug released, and the volume withdrawn at each time point had been replenished with fresh media. The cumulative release profile has been depicted in Figure 1. Other workers report complete media replacement at each time point [6,25]. Neither of these approaches, however, employs physiologically relevant media and flow rates; and thus there is a need to devise new strategies for the investigation of drug release from implants.

Shah *et al.* [26] describe *in vitro* release testing and dissolution of many special dosage forms. They state that the methodologies are well evolved for several special dosage forms and provide specific recommendations for drug release testing of suppositories, transdermal patches and semi-solid topicals (creams, ointments and gels). However, for several other dosage forms, e.g. implants, chewing gums, powders, granules, solid dispersions and micro-particles, more method development and refinement is needed before a final recommendation on standardized drug release methods can be made. The cell of the compendial flow-through

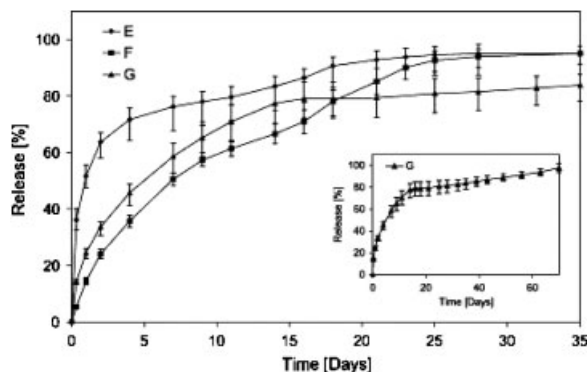


Figure 1. *In vitro* cumulative release profiles obtained by placement of three batches of implants in unstirred vials. The insert shows the release of batch G implants for 70 days (reproduced with permission from Elsevier; Reference [24])

apparatus (Apparatus 4), for which specifications are provided in the United States Pharmacopeia (USP) Chapter on Drug Release [27], has been suitably modified to accommodate implants (Figure 2). The inner diameter of these cells has been considerably reduced, compared to the tablet cell. This results in a low volume of the acceptor compartment. The implant is placed in a vertically mounted cell on a screen that permits fresh dissolution medium to enter from the bottom. The cell is closed by a second screen at a height h (defined by the length of the implant) that filters the liquid and prevents the removal of any undissolved particles. The dissolution medium is pumped through the cell from a reservoir after having passed the heat exchanger for temperature control. The medium leaving the cell is analyzed for drug content, either continuously or at fixed intervals. An important advantage is that the continuous flow-through type of arrangement, when used as an open system, ensures the existence of sink conditions since fresh medium flows past the implant throughout the period of study. Furthermore, the effects of pH on drug release can be easily investigated using this system, although alteration in pH would not be appropriate for biorelevance. There remains, however, a need to establish suitable calibrators and standardization of this apparatus. Although the USP recommends that media flow be pulsed to avoid clogging of filters, other options such as an HPLC pump or intermittent flow should also be considered [28]. The stan-

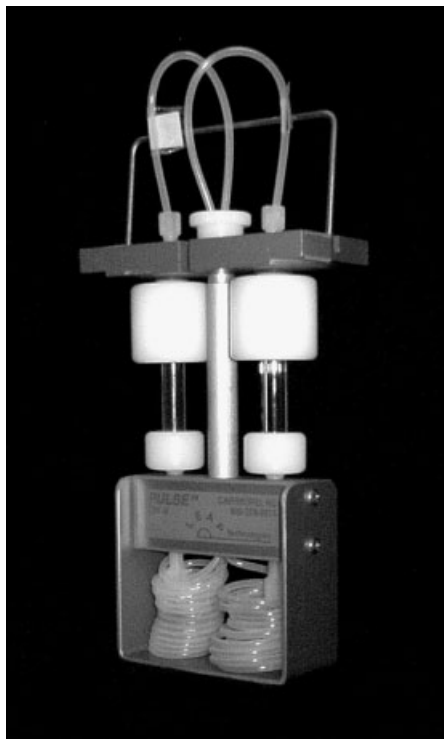


Figure 2. A flow-through cell apparatus

dardization process may also include temperature measurements in the cell, wherever feasible, to verify that readings of the instrument match the temperature inside the cell. Also, flow rate should be checked, and adjusted before the start of a run, and verified at the end of a run.

The flow-through apparatus has also been recommended in the Fédération Internationale Pharmaceutique/American Association of Pharmaceutical Scientists (FIP/AAPS) Guidelines on Dissolution/*In Vitro* Release Testing of Novel/Special Dosage Forms [28]. The article presents the consensus of experts in a series of sponsored workshops. The authors advise against the 'unnecessary' proliferation of modified apparatuses for special products when the standard compendial equipment can produce equivalent results. In such cases, the compendial apparatus should be used. They also state, however, that for special non-oral dosage forms, it is difficult to find an appropriate balance between the general recommendation to avoid 'unnecessary' proliferation of dissolution apparatus and to acknowledge the formulation specific characteristics and

requirements of a new product under development.

The flow-through cell represents conditions similar to those encountered *in vivo* because the entire content of the receptor compartment is replaced on a continuous basis [22]. However, a major limitation of the apparatus is that the implant is directly placed in the flow of the medium and this may not be a true representation of the *in vivo* environment. When placed subcutaneously, the implant is expected to release drug into its immediate vicinity (comprised of tissue fluid and cells), followed by passive diffusion or possibly facilitated transport into the cells and the vascular system before finally reaching the systemic circulation (Figure 3). Nicolaidis *et al.* [29] reported discrepancies in the dissolution behavior even with tablets that could be attributable to inherent design problems in the *in vitro* system and to inadequate simulation of *in vivo* hydrodynamics (including slow flow rates, vertical positioning of the cell and possible sedimentation of the solids). The authors also speculated that the piston pump did not

allow for simulation of bi-directional movement of chyme or segmental mixing, and had been operated at flow rates (between 2.5 and 12 ml/min) that represented the average net flow in the aboral direction. The need for an alternative flow pattern has also been suggested as a means to mimic actual hydrodynamics *in vivo*. Fyfe *et al.* [30] used NMR imaging to better understand the physical changes that solid oral dosage forms undergo within a flow-through cell under dynamic media flow conditions. Understanding the flow-through cell therefore, presents an opportunity for future research. The quote by Salvador Dalí (1904–1989), the famous Spanish artist, ‘Have no fear of perfection—you’ll never reach it’, would best describe this endeavor.

Physiological Factors at the Subcutaneous Implantation Site Influencing Drug Absorption

The structural characteristics of interstitial space are similar in all tissues, consisting of a fibrous

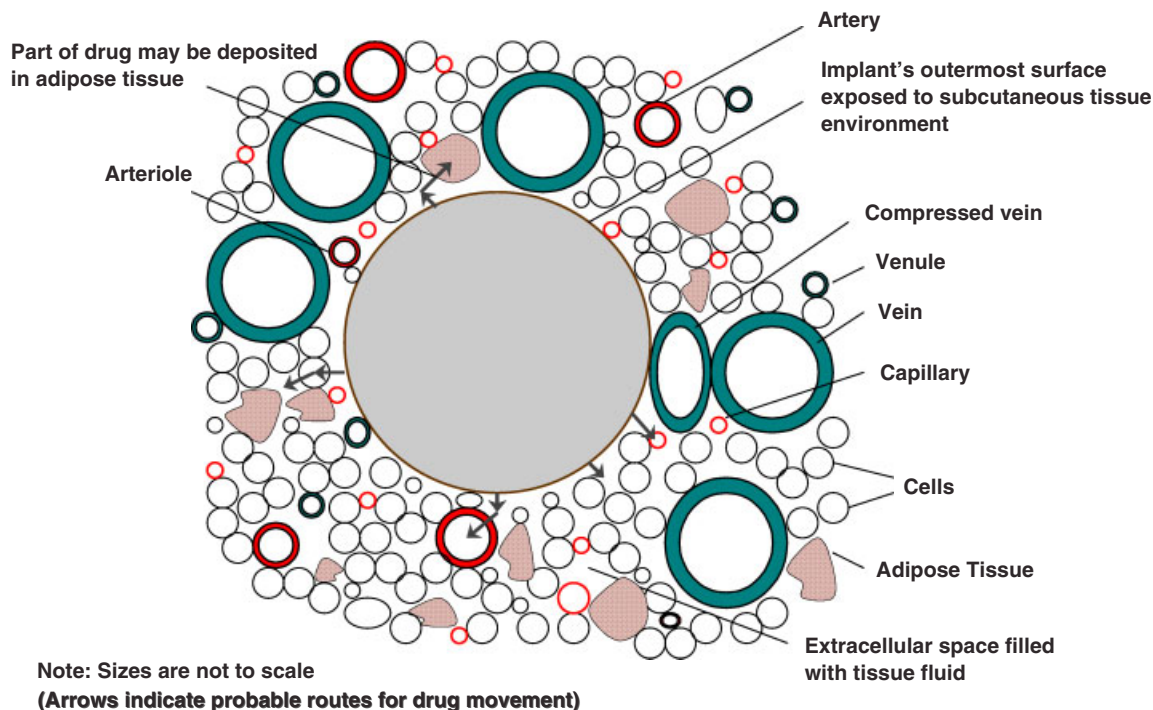


Figure 3. Visualization of subcutaneous tissue environment around an implant

collagen framework supporting a gel phase made up of glycosaminoglycans, salts and plasma-derived proteins [31,32]. The glycosaminoglycans are polyanionic polysaccharides that are charged at physiological pH (7.4) and are bound covalently to a protein backbone to form immobilized proteoglycans. Hyaluronan is an exception that may be removed from the interstitium via lymph vessels. The proteins present in the interstitial space are qualitatively the same as those present in plasma, although quantitatively, they are present in lower concentrations. This results in the interstitial colloid osmotic pressure (COP₁) being less than that in plasma [33]. The interstitium however, displays a high degree of structural heterogeneity. It is believed that a network of endogenous macromolecules effectively reduces the distribution volume such that the interstitial space acts in a size exclusion manner, excluding very large molecules, and thereby affecting their interstitial occupancy [34,35].

The blood capillaries supplying the subcutaneous space are generally continuous in structure and are characterized by tight endothelial junctions and an uninterrupted basement membrane. The subcutaneous vessels are substantially larger than those in the dermal tissue (1500 μm for the veins and 600 μm for the arteries) [36]. These are relatively permeable to the exchange of small, lipophilic molecules. In addition, aqueous 'pores' or channels are present which provide diffusivity to some hydrophilic molecules [31]. A series of classic papers by Renkin and Pappanheimer attempt to offer a functional understanding of the 'pore theory' of capillary permeability and its relation to restricted diffusion of solutes [37–39]. The measurement of permeability revealed that the fractional area available for exchange decreased as the size of the diffusing molecule increased. Furthermore, using a simple model of permeability pathways as uniform cylindrical pores penetrating an otherwise impermeable membrane, the authors have calculated that the pores occupy only 0.02–0.2% of the area of capillary walls. They speculated that permeability of hydrophilic solutes is restricted to intercellular regions. In the case of large molecules, lower levels of permeability were observed with increasing a_e (effective hydrodynamic radius

calculated using the Stokes–Einstein equation). However, the steep fall in values of P (permeability coefficient) was limited by an extension of smaller slope, which indicated the presence of a separate transport mechanism, quantitatively insignificant for small molecules but important for large. Renkin suggested that part or all of the extension of permeability beyond the small pore might be attributed to transport by micropinocytotic vesicles; a phenomenon known as 'cytopempsis' [40].

Even the site of administration affects the absorption of drugs. The absorption of insulin and human growth hormone (hGH), for example, increased with subcutaneous injection in the abdomen in comparison to the thigh or upper arm [41]. Simonsen *et al.* [42] observed significant regional differences in the washout rates of xenon (^{133}Xe) from subcutaneous, abdominal adipose tissue. Among the various layers of subcutaneous tissue (*viz.* pre-peritoneal, superficial subcutaneous and deep subcutaneous), normal blood flows were found to range from 1.5 to 2.5 ml 100 (g min)⁻¹ [43]. Sindrup *et al.* [44] reported nocturnal variations (mean increase of 84%; upto 200% in some cases) along with postural changes (30–40% in the beginning of night period) in the subcutaneous blood flow rate in the lower leg of normal human subjects. Zuidema *et al.* [45] reported that the subcutaneous adipose layer has important retarding effects on the absorption of drugs administered as an oily suspension or liposomes. These studies emphasize that several factors need to be considered in the mechanistic interpretation of drug release data from implants.

Method Development and Optimization

Traditionally, the flow-through apparatus has been operated at a flow rate of 16 ml/min, although flow rates ranging from 12.5 to 50 ml/min have been investigated [46–48]. The rate of flow of 16 ml/min, however, was chosen to be consistent with the compendial paddle or basket-type apparatus for oral dosage forms, such that about 1 l of the dissolution medium flows past the implant in 1 h. In our view, this may not

represent an appropriate range of flow-rate when the apparatus is employed for controlled-release parenterals such as implants or depots, and may not be suitable for 'biorelevant' flow conditions. In an *in vivo* situation, the implant will be exposed to slow-moving fluid in the subcutaneous tissue with convection and/or diffusion processes predominating until the released drug reaches a vascular or cellular barrier (Figure 3).

Another important aspect in dissolution method development is the choice of a suitable medium (Table 2). As mentioned in the previous paragraph, much of the research activity has been focused, quite understandably, on oral dosage forms. The most common dissolution medium used for the study of non-oral dosage forms has been phosphate buffer saline (PBS) at pH 7.4. The report on the EUFEPS Workshop provides a general opinion that in order for *in vitro* data to achieve biorelevance, physiological variables at the site of implantation should be considered [12]. This includes, but is not restricted to, body temperature, blood flow, drug metabolism due to enzymes, muscle pH, buffer capacity, and osmolality. It was also recognized that there is a need for examining the mechanisms of the *in vivo* release process while developing *in vitro* release methods. From this standpoint, various physiological buffers such as Hank's balanced salts solution, Kreb's bicarbonate buffer, Earle's balanced salts solution, etc. with suitable modifications have potential for application to such studies [49,50]. Consideration of pH and osmolality changes of the media as a function of time, however, will be necessary [51].

Table 2. Factors influencing the selection of a 'biorelevant' medium for *in vitro* drug release studies

-
- (a) Solubility of drug and dose rate and influence of 'sink' conditions
 - (b) Stability of the drug in media during the complete period of study
 - (c) Well characterized media components capable of maintaining its pH and osmolality over the entire study period
 - (d) Stability of media components: temperature effects depending on the type of study (real-time/accelerated study)
 - (e) Economy for use during the entire period of study
-

Method development for such dosage forms is an active area of research [52].

A very important aspect of method development is consideration of the degradation of drugs and the dosage form matrix in the dissolution media. Degradation of drugs might be observed due to maintenance of the release media for a prolonged period of time under temperatures above room temperature. This can be overcome by a frequent change of the media or by measurement of the concentration of the drug remaining within the product, rather than that in the release medium [12]. The latter approach, however, may be neither feasible, nor economical, during studies involving implants. The implant cannot be expected to retain its original shape when removed from the apparatus after a few months of study, and would be lost permanently for further release profiling if data indicate the presence of high drug content. Variability in dissolution data could arise from the degradation of protein formulations or from acidic byproducts generated from polymers (such as poly(lactic-co-glycolic) PLGA matrices) into the media [12]. Biodegradation of polymers has been described as being a bulk process consistent with 'autocatalysis', whereby the liberated carboxylic end groups catalyze further ester group cleavage [53,54]. This description supports the hypothesis that physicochemical changes in the implant matrix, as a function of time, influence drug release characteristics. Besides chemical degradation, polymers also undergo enzyme-catalyzed degradation *in vivo*. Even relatively inert polymers (including nylon, poly(ether urethane), poly(terephthalate), poly(hydroxybutyrate), poly(ϵ -caprolactone) or poly(glycolic acid), are degraded by enzymes such as esterase, proteinase, papain and elastase [55].

During normal subcutaneous wound healing with implants, the implant may be smoothed-surfaced, and chemically inert. If this is the case, a densely fibrous and relatively avascular tissue capsule will form around the implant within a few weeks that effectively walls off the implant from its environment [56,57]. This process, called 'fibrous encapsulation', must also be considered. The fibrous capsule potentially imposes both diffusion and perfusion transport limitations that may render the implanted device less effective.

An additional potential barrier to diffusion results from the infiltration of proteinaceous material into the pores of compressed implants. This has been termed 'ghost' formation by Folley [58] and occurs due to infiltration, followed by deposition, of tissue protein inside the pores of the surface of the matrix. Folley observed that when a fragment of a 'ghost' was burnt, it swelled first and then charred giving off the smell of burning wood. This suggested that it consisted primarily of scleroprotein formed as a result of the reaction of animal tissues to the presence of a foreign body. Although there are conflicting opinions whether plugging of the pores of the implant matrix would significantly affect drug release, due consideration may be necessary when viewing *in vitro* dissolution data mechanistically [5,59,60]. Factors such as fluid volume, viscosity, tissue barriers, phagocytosis, tissue inflammation, etc. can also affect *in vivo* release and absorption. A look into the mass balance for such *in vitro* release tests has been suggested [12], although problems may arise while withdrawing the implant from the apparatus after a prolonged period of testing.

An important factor affecting drug release is the physicochemical properties of the drug itself. For example, a slower release is observed for the same polymer system with increasing drug hydrophobicity. Furthermore, basic drugs may behave as catalysts, which could potentially enhance the degradation rate and hence the release rate. This is in contrast to the neutralization of the polymer terminal carboxyl residues by basic drugs, thereby reducing autocatalysis due to acidic end groups [25]. The various considerations for developing 'biorelevant' *in vitro* drug release tests for implants are listed in Table 3.

A verification of standards that specify the apparatus/agitation rate, medium, study design, assay, and acceptance criteria is mandatory to satisfy the performance tests of the USP. Overall, the procedure must yield data to allow an accept/reject decision relative to the set acceptance criteria. However, there is a need to develop a general guideline/recommendation on how to develop and validate a dissolution procedure. To achieve this objective, the USP is in the process of incorporating a new general chapter. Aspects of method development and

Table 3. Considerations for method development of 'biorelevant' *in vitro* drug release tests for implants

- | |
|---|
| (a) Suitable apparatus |
| (b) Appropriate flow-rate/agitation |
| (c) Medium of physiological relevance (pH, buffer capacity, osmolality) |
| (d) Degradation of drug and dosage form |
| (e) 'Ghost' formation |
| (f) Drug metabolism |
| (g) Tissue response such as fibrous encapsulation, inflammation, etc |
| (h) Determination of sampling interval |
| (i) Methods for accelerated release testing |

validation for dissolution studies that had been addressed somewhat superficially in other general information chapters [61,62] will be examined in greater detail in the new general chapter. The chapter is currently available for public comment [11]. It will serve as a guide during assay method development for the investigation of drug release, but the chapter lacks the specifics that can be applied directly to special dosage forms such as implants. The discussion on dissolution media, for example, is entirely focused on method development for oral dosage forms.

Development of IVIVC for Implants

An IVIVC adds *in vivo* relevance to *in vitro* data. For solid oral dosage forms with immediate release characteristics, drugs that are classified as Class II (low solubility and high permeability class) according to the FDA's BCS Guidance document [63], are likely to be good candidates for an IVIVC [64]. This is because, in most cases, *in vitro* dissolution will be the rate-limiting step for absorption of a drug in this class, and subsequently its appearance in *in vivo* circulation. IVIVCs also tend to decrease the regulatory burden by reducing the number of biostudies required in support of a drug product. This would enable a faster and more efficient processing of regulatory filings. As an additional benefit to the developers, these correlations can support more liberal *in vitro* dissolution specifications, wherever justified (Table 4). IVIVC for controlled-release dosage forms would be beneficial if utilized in one or more of the following

Table 4. An example set of specifications for implant dosage forms

(a) *Critical parameters during development*

- Extensive physicochemical characterization including the type of polymer matrix used
- Impact of formulation variants
- Intended duration of action
- Stability
- In vitro* (refer Table 3)
- In vivo*
 - Identification of animal model during early development
 - Drug pharmacokinetics
 - Degradation/Metabolic pathways of drug and dosage form matrix
 - Safety and efficacy

(b) *Specifications based on experience*

- Standard/compendial procedures for intravenous systems
 - Residual solvent
 - Sterility testing
 - Pyrogen testing
 - Drug content/assay
 - Drug related substances
- Dosage form specific
 - Appearance and size
 - Weight
 - pH dependent drug release (especially for osmotic pump-based systems)
 - Site for implantation

ways: (a) as a surrogate to bioequivalency studies which might be required for scale-up and post-approval changes (SUPAC), especially where minor post-approval changes may include site of manufacture, formulation or strength; (b) to support and/or to validate the use of dissolution testing and specifications as a quality control tool for process control since dissolution specifications may be shown to be relevant to *in vivo* data; (c) predict *in vivo* performance of a formulation based on *in vitro* dissolution data, which may be used in the justification of dissolution specifications and may aid in the design of formulation release-time profiles resulting in optimal plasma concentration-time profiles; (d) identify appropriate dissolution conditions for a formulation which result in data relevant to *in vivo* performance [65]. At this point, it is imperative to point out that although few reports for successful IVIVCs with implants are available [24, 66], none of the *in vitro* tests can be considered to be physiologically relevant.

An animal model is considered appropriate for the exploration of a possible IVIVC during drug

development, although it is not to be used for demonstration of bioavailability or bioequivalence in the regulatory setting [12]. According to FIP Guidelines, a rank order correlation is a sufficient verification of a specification under the assumption that no quantitative interpolation is necessary [67,68].

New methods for the establishment of dissolution specifications for controlled release formulations have now been proposed in the FDA guidances [15,69]. For a comparison of dissolution profiles, Moore and Flanner [70] proposed the 'model-independent' approach using the f1 (a function of the average absolute difference between two dissolution curves, referred to as a 'difference' factor) and f2 (a function of the reciprocal mean square-root transform of the sum of square distances at all points, referred to as 'similarity' factor) factors. The f2 factor has been recommended as a simple measure for the comparison of profiles [15,69,71]. The other method involves a 'model-dependent' approach using Probit, Logistic or Weibull fitting to dissolution data. Sathe *et al.* [72] have found the model dependent approach to be useful for a comparison of inter-lot *in vitro* dissolution profiles. IVIVC modeling may also involve a time scaling approach in which the scale of the ordinate axis is shifted to account for the lag-time prior to drug release, provided the time scaling factor remains the same across all formulations tested [15,73]. In the example shown in Figure 4, linear regression of absorption versus dissolution indicated a fairly large negative *y* intercept, although a strong linear relationship is evident [74]. Based on the concepts presented by Hwang *et al.* [75], a shift in absorption data by -1.35 h resulted in an intercept value close to zero (Figure 4b).

A report of the 2004 Annual Meeting of the Controlled Release Society suggests that a multivariate model-dependent comparison of data can be useful for the flow-through apparatus [76]. For oral controlled-release dosage forms, a multi-dimensional approach involving pH as the primary factor has been reported to be a better predictor of *in vivo* performance [77,78]. During the bioequivalence characterization of implants however, it may not bear relevance unless a significant change in the microenvironment at

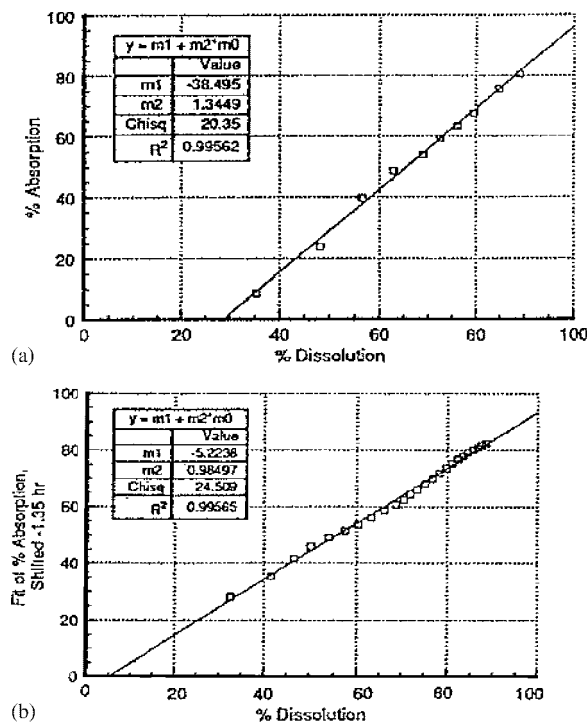


Figure 4. Illustration of the application of time-shift to absorption time profile prior to assessment of a relationship to dissolution. (a) Linear regression of absorption vs dissolution, with a large negative y intercept. (b) Linear regression after adjusting the time scale to correct for lag in estimated absorption (reproduced with kind permission of Springer Science and Business Media; Reference [74])

the implantation site occurs. Young *et al.* [79] presented an approach that involved modeling sections of the pharmacokinetic profile of a drug having multiple peaks in its *in vivo* profile after administration as a microsphere parenteral formulation. At this point of time however, no single method exists for handling data that would be applicable to most implantable dosage forms and a case-by-case analysis is often reported in most literature. Besides plasma drug levels, approaches involving tissue concentrations or surrogate markers may also be useful for IVIVC development for implants.

Accelerated *In Vitro* Release Testing

Dissolution analysis of extended release formulations is time-consuming since real-time data collection would require the study to be con-

ducted over a period of weeks or months. This is disadvantageous in early research and unacceptable for effective process control [80]. While real-time *in vitro* release studies under physiological conditions is essential to evaluate these systems, an accelerated (short-term) *in vitro* release method would be helpful for a rapid assessment of formulation and processing variables [81]. The benefit of utilizing an accelerated method is twofold: (1) to differentiate formulations prepared from a similar polymer varying in molecular weight, drug loading, particle size, and morphology, and (2) to correlate short-term release with real-time release in order to predict real-time release. Accelerated tests should also be biorelevant if possible and the mechanism of drug release should not be altered. In these tests, only the rate of drug release should increase [82].

Although accelerated dissolution rate analysis (ACDRA) has been used for tablets especially during at-line tests (conducted by the use of process dedicated testing equipment on the production line) [83,84], an in-depth investigation of this technique for controlled release parenterals including implants has not been reported. Of the various parameters (temperature, solvent, ionic strength, pH, enzymes, surfactants and agitation rate) that can be altered, the easiest way to achieve accelerated release has been reported to be an increase in temperature [84]. During these studies, a variety of factors affect the dissolution stability of the drug however. These include processing factors, formulation variables, drug and excipient solubility/hygroscopicity/thermal behavior, and the product packaging itself in terms of its moisture barrier properties. Further insight can be gained by an investigation of the drug's stability under elevated temperatures. Verification of the validity of using these conditions could include an Arrhenius plot after obtaining release rate profiles from linearized release profiles [85]. The question remains, however, what constitutes a significant change in the dissolution profile, since defined limits for the consideration of percent drug remaining in the medium after a designated test time are not available thus far in any guidance [86].

The specifications for accelerated release should include a determination of an early time,

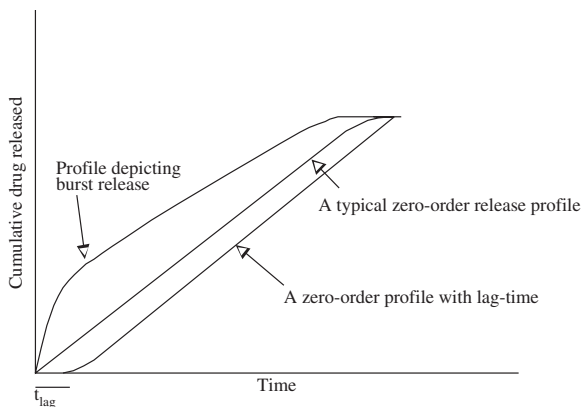


Figure 5. Schematic to show different release profiles from drug delivery devices

mid-point time and >80% of the cumulative amount released. For a prediction between accelerated and real time release, it has been suggested that the time to reach a cumulative release of approximately 100% be used to determine whether a relationship can be established for products with different real time release rates [12]. In our opinion however, since most implants are designed for drug release over a period of a few months, waiting for this time period for complete drug release is not practical during product development. When a controlled release parenteral delivery system produces an initial burst release (shown in Figure 5), the recommendation is to augment accelerated release tests by an initial real time study that allows adequate assessment of this burst. It has been suggested to use mathematical modeling to predict long-term release from accelerated release profiles [82].

Conclusion

Pharmaceutical development and manufacturing is evolving from an art to one that is science and engineering based. Using available knowledge effectively in regulatory decisions that establish specifications and evaluate manufacturing processes can substantially improve the efficiency of both manufacturing and regulatory processes [87]. Characterization of the release profile of

any drug from an implant constitutes an important step towards using the resulting data for *in vitro-in vivo* correlation and accelerated release testing. A universal test is normally sought for most areas of regulated science, and dissolution testing is no exception [88]. As Edward Teller, the Hungarian-born American nuclear physicist has well stated, 'The science of today is the technology of tomorrow'. Dissolution/release testing, when applied and evaluated correctly, remains the single most important *in vitro* test to ensure functional quality and batch-to-batch uniformity. As has been discussed previously, the constraints offered by the maintenance of biorelevant conditions (apparatus and medium) may provide less flexibility during method development. Issues such as tissue inflammation, fibrous encapsulation and 'ghost' formation may alter the release profile of a drug *in vivo*. In addition, stability issues of the drug and dosage form have to be considered during the establishment of specifications. Further complications arise due to protein degradation or autocatalysis of the polymer matrix in the media, especially during the use of accelerated tests. These have to be dealt with on a case-by-case basis. Accelerated studies remain an attractive research endeavor since these will considerably reduce testing time, aiding in the rapid assessment of formulation and processing variables. Thus, for the near future, the approach that is adopted for drug release testing of an implant should be expected to vary considerably from that followed for an oral dosage form.

References

1. Gray V. *Dissolution Testing: An Overview and a Summary of Recent Trends and Regulatory Activities*. V. A. Gray Consulting Inc.: DE, Website: http://www.tabletscapsules.com/free/tc_20031001_20.pdf [15 April 2004].
2. Sirisuth N, Eddington ND. *In vitro-in vivo* correlation definitions and regulatory guidance. *Int J Generic Drugs*. Website: <http://www.locumusa.com/pdf/members/ivive-01.pdf> [21 January 2004].
3. Folkman J, Long DM. The use of silicone rubber as a carrier for prolonged drug therapy. *J Surg Res* 1964; 4: 139-142.
4. Ballard BE. The physicochemical properties of drugs that control their absorption rate after implantation. *Ph.D. Thesis*, University of California, San Francisco, 1961.

5. Davis BK. Diffusion in polymer gel implants. *Proc Natl Acad Sci* 1974; **71**: 3120–3123.
6. Mohl S, Reithmeier H, Winter G. Poster presentation: sustained release of BSA from implant systems by using physiological lipids. *Colorado Protein Stability Conference*, Breckenridge, CO, July 2002, Website: http://www.chemie.uni-muenchen.de/pb/aks/winter/Mohl_poster_denver_072002.pdf [17 October 2003].
7. Okumu FW, Cleland JL. Implants and injectables. In *Modified-Release Drug Delivery Technology*, Rathbone MJ, Hadgraft J, Roberts MS (eds). Marcel Dekker Inc.: New York, 2003; 633–638.
8. Langer R, Peppas NA. Advances in biomaterials, drug delivery, and bionanotechnology. *AIChE J* 2003; **49**: 2990–3006.
9. Stevenson CL, Theeuwes F, Wright JC. Osmotic implantable delivery systems. In *Handbook of Pharmaceutical Controlled Release Delivery*, Wise DL (ed.). Marcel Dekker Inc.: New York, 2000; 225–254.
10. Eckenhoff B, Theeuwes F, Urquhart F. Osmotically actuated dosage forms for rate-controlled drug delivery. *Pharm Technol* 1987; **11**: 96–105.
11. Pharmacopeial Previews. <1092> The dissolution procedure: development and validation. *Pharm Forum* 2004; **30**: 351–363.
12. Burgess DJ, Crommelin DJA, Hussain AS, Chen ML. Assuring quality and performance of sustained and controlled release parenterals: EUFAPS workshop report. *AAPS Pharm Sci* 2004; **6**: article 11.
13. Sunkara G, Chilukuri DM. IVIVC: an important tool in the development of drug delivery systems. *Drug Delivery Technol*. Website: <http://www.drugdeliverytech.com/cgi-bin/articles.cgi?idArticle=144> [7 February 2004].
14. Uppoor VRS. Regulatory perspectives on *in vitro* (dissolution)/*in vivo* (bioavailability) correlations. *J Control Rel* 2001; **72**: 127–132.
15. FDA. Guidance for Industry: Extended Release Oral Dosage Forms: Development, Evaluation and Application of *In Vitro/In Vivo* Correlations, 1997.
16. Shah J. Presentation: *in vitro-in vivo* correlation (IVIVC) for parenteral sustained release formulations. *AAPS Annual Meeting and Exposition: Sunrise School Session 'IVIVC: A Useful Tool in the Development of Drug Delivery Systems'*, Baltimore, MD, November 2004.
17. Rohrs BR. Dissolution method development for poorly soluble compounds. *Diss Tech* 2001; **8**: 1–5.
18. Banakar UV. Dissolution testing devices. In *Pharmaceutical Dissolution Testing*, Swarbrick J (ed.). Marcel Dekker Inc.: New York, 1992; 53–105.
19. Levy G. Effect of certain tablet formulation factors on dissolution rate of the active ingredient I: importance of using appropriate agitation intensities for *in vitro* dissolution rate measurements to reflect *in vivo* conditions. *J Pharm Sci* 1963; **52**: 1039–1046.
20. <711> Dissolution. *USP24/NF19*. The United States Pharmacopeial Convention. Rockville, MD, 2000; 1941–1943.
21. Barzilay RB, Hersey JA. Dissolution rate measurement by an automated dialysis method. *J Pharm Pharmacol* 1968; **20**(Suppl): 232S–238S.
22. Langenbucher F. *In vitro* assessment of dissolution kinetics: description and evaluation of a column-type method. *J Pharm Sci* 1969; **58**: 1265–1272.
23. Wagner JG. *Biopharmaceutics and Relevant Pharmacokinetics*. Drug Intelligence Publications: IL, 1971; 110–114.
24. Schliecker G, Schmidt C, Fuchs S, Ehinger A, Sandow J, Kissel T. *In vitro* and *in vivo* correlation of buserelin release from biodegradable implants using statistical moment analysis. *J Control Rel* 2004; **94**: 25–37.
25. Malmsten M. Degradation of surfactants and polymers in drug delivery. In *Surfactants and Polymers in Drug Delivery*, Swarbrick J (ed.). Marcel Dekker Inc.: New York, 2002; 293–317.
26. Shah VP, Siewert M, Dressman J, Moeller H, Brown CJ. Dissolution/*in vitro* release testing of special dosage forms. *Diss Tech* 2002; **9**: 1–5.
27. <724> Drug Release/Physical Tests. *USP24/NF19*. The United States Pharmacopeial Convention. Rockville, MD, 2000; 1945–1946.
28. Siewert M, Dressman J, Brown C, Shah VP. FIP/AAPS Guidelines for dissolution/*in vitro* release testing of novel/special dosage forms. *Diss Tech* 2003; **10**: 6–15.
29. Nicolaidis E, Hempenstall JM, Reppas C. Biorelevant dissolution tests with the flow-through apparatus? *Diss Tech* 2000; **7**: 8–15.
30. Fyfe CA, Grondey H, Blazek-Welsh AI, Chopra SK, Fahie BJ. NMR imaging investigations of drug delivery devices using a flow-through USP dissolution apparatus. *J Control Rel* 2000; **68**: 73–83.
31. Porter CJH, Charman SA. Lymphatic transport of proteins after subcutaneous administration. *J Pharm Sci* 2000; **89**: 297–310.
32. Langevin HM, Cornbrooks CJ, Taatjes DJ. Fibroblasts form a body-wide cellular network. *Histochem Cell Biol* 2004; **122**: 7–15.
33. Aukland K, Reed RK. Interstitial lymphatic mechanisms in the control of extracellular fluid volume. *Physiol Rev* 1993; **73**: 1–78.
34. Watson PD, Grodrins FS. An analysis of the effects of interstitial matrix on plasma-lymph transport. *Microvasc Res* 1978; **16**: 19–41.
35. Bert JL, Mathieson JM, Pearce RH. The exclusion of human serum albumin by human dermal collagenous fibres and within human dermis. *Biochemical J* 1982; **201**: 395–403.
36. Whang JM, Quinn JA, Graves DJ, Neufeld GR. Permeation of inert gases through human skin: modeling the effect of skin blood flow. *J Appl Physiol* 1989; **67**: 1670–1686.
37. Pappanheimer JR, Renkin EM, Borrero LM. Filtration, diffusion and molecular sieving through peripheral capillary membranes: a contribution to the Pore theory of capillary permeability. *Am J Physiol* 1951; **167**: 13–46.
38. Renkin EM. Filtration, diffusion and molecular sieving through porous cellulose membranes. *J Gen Physiol* 1954; **38**: 225–243.
39. Renkin EM. Multiple pathways of capillary permeability. *Circ Res* 1977; **41**: 735–743.
40. Renkin EM. Transport of large molecules across capillary walls. *Physiol* 1964; **7**: 13–28.

41. Berger M, Cuppers HJ, Hegner H, Jorgens V, Berchtold P. Absorption kinetics and biologic effects of subcutaneously injected insulin preparations. *Diabetes Care* 1982; **5**: 77–91.
42. Simonsen L, Enevoldsen LH, Bülow J. Determination of adipose tissue blood flow with local ¹³³Xe clearance. Evaluation of a new labeling technique. *Clin Physiol Funct Imaging* 2003; **23**: 320–323.
43. Enevoldsen LH, Simonsen L, Stallknecht B, Galbo H, Bülow J. *In vivo* human lipolytic activity in preperitoneal and subdivisions of subcutaneous abdominal adipose tissue. *Am J Physiol Endocrinol Metab* 2001; **281**: E1110–E1114.
44. Sindrup JH, Kastrup J, Jorgensen B, Bülow J, Lassen NA. Nocturnal variations in subcutaneous blood flow rate in lower leg of normal human subjects. *Am J Physiol Heart Circ Physiol* 1991; **260**: H480–H485.
45. Zuidema J, Pieters FAJM, Duchateau GSMJE. Release and absorption rate aspects of intramuscularly injected pharmaceuticals. *Int J Pharm* 1988; **47**: 1–12.
46. Qureshi SA, Caillé G, Brien R, McGilveray IJ. Drug release characterization of extended-release nifedipine products using a flow-through dissolution apparatus. *Proc Int Symp Control Rel Bioact Mater* 1994; **21**: 668.
47. Qureshi SA, Caillé G, Brien R, Piccirilli G, Yu V, McGilveray IJ. Application of flow-through dissolution method for the evaluation of oral formulations of nifedipine. *Drug Dev Ind Pharm* 1994; **20**: 1869–1882.
48. Cammarn S, Sakr A. Predicting dissolution via hydrodynamics: salicylic acid tablets in flow through cell dissolution. *Int J Pharm* 2000; **201**: 199–209.
49. Waymouth C. The nutrition of animal cells. *Int Rev Cytol* 1954; **3**: 1–68.
50. Waymouth C. Osmolality of mammalian blood and of media for culture of mammalian cells. *In Vitro* 1970; **6**: 109–127.
51. Lelong IH, Rebel G. pH drift of 'physiological buffers' and culture media used for cell incubation during *in vitro* studies. *J Pharm Toxicol Methods* 1998; **39**: 203–210.
52. Chidambaram N, Burgess DJ. A novel *in vitro* release method for submicron sized dispersed systems. *AAPS Pharm Sci* 1999; **1**: article 11.
53. Pitt CG. Biodegradable drug delivery systems based on aliphatic polyesters: application to contraceptives and narcotic antagonists. In *Controlled Release of Bioactive Materials*, Baker R (ed.). Academic Press Inc.: New York, 1980; 19–43.
54. Pitt CG. Poly- ϵ -caprolactone and its copolymers. In *Biodegradable Polymers as Drug Delivery Systems*, Chasin M, Langer R (eds). Marcel Dekker Inc.: New York, 1990; 71–120.
55. Park K, Shalaby WSW. Biodegradation. In *Biodegradable Hydrogels for Drug Delivery*, Park K, Shalaby WSW, Park H (eds). Technomic Publishing Co., Inc.: Pennsylvania, 1993; 13–34.
56. Stenken JA, Reichert WM, Klitzman B. Magnetic resonance imaging of a tissue/implanted device biointerface using *in vivo* microdialysis sampling. *Anal Chem* 2002; **74**: 4849–4854.
57. Wisniewski N, Klitzman B, Miller B, Reichert WM. Decreased analyte transport through implanted membranes: differentiation of biofouling from tissue effects. *J Biomed Mater Res* 2001; **57**: 513–521.
58. Folley SJ. 'Ghost' formation in subcutaneously implanted tablets of synthetic estrogens. *Nature* 1942; **150**: 403–404.
59. Bishop PMF, Folley SJ. Implantation of testosterone in cast pellets. *Lancet* 1944; **1**: 434–435.
60. Lewin J, Huidobro F. On the absorption mechanism of pellets. *Acta Physiol Latinoamericana* 1953; **3**: 17–24.
61. <1088> *In vitro* and *In vivo* Evaluation of Dosage Forms. USP24/NF19. The United States Pharmacopeial Convention. Rockville, MD, 2000; 2051–2056.
62. <1225> Validation of Compendial Methods. USP24/NF19. The United States Pharmacopeial Convention. Rockville, MD, 2000; 2149–2152.
63. FDA. Draft Guidance for Industry: Waiver of *In Vivo* Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms containing certain Active Moieties/Active Ingredients based on Biopharmaceutical Classification System, 1999.
64. Kasim NA, Whitehouse M, Ramachandran C, et al. Molecular properties of WHO essential drugs and provisional biopharmaceutical classification. *Mol Pharm* 2004; **1**: 85–96.
65. Rohrs BR, Skoug JW, Halstead GW. Dissolution assay development for *in vitro*–*in vivo* correlations. In *In Vitro–In Vivo Correlations*, Young D, Devane JG, Butler J (eds). Plenum Press: New York, 1997; 17–30.
66. Lin S, Chao PY, Chien YW, et al. *In vitro* and *in vivo* evaluations of biodegradable implants for hormone replacement therapy: effect of system design and PK–PD relationship. *AAPS Pharm Sci Tech* 2001; **2**: article 16.
67. Siewert B, Siewert M. Dissolution tests for ER products. Dissolution Technologies website: <http://www.dissolutiontech.com/Dtresour/1198art/Nov98Art1.html> [4 February 2004].
68. FIP Guidelines for Dissolution Testing of Solid Oral Products, 1997.
69. FDA. Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms, 1997.
70. Moore JW, Flanner HH. Mathematical comparison of curves with an emphasis on *in vitro* dissolution profiles. *Pharm Technol* 1996; **20**: 64–74.
71. Shah VP, Tsong Y, Sathe P, Liu JP. *In vitro* dissolution profile comparison—statistics and analysis of the similarity factor. *J Pharm Res* 1998; **15**: 889–896.
72. Sathe P, Tsong Y, Shah VP. *In vitro* dissolution profile comparison: statistics and analysis, model dependent approach. *Pharm Res* 1996; **13**: 1799–1803.
73. Burgess DJ. Presentation: new apparatus design: dispersed systems, stents and other implantable devices. *AAPS Workshop on Dissolution: New Technologies and Regulatory Initiatives*, Bethesda, MD, March 2004.
74. Rackley RJ. Examples of *in vitro*–*in vivo* relationships with a diverse range of quality. Figure 3. In *In Vitro–In Vivo Correlations*, Young D, Devane JG, Butler J (eds). Plenum Press: New York, 1997; 1–15.

75. Hwang SS, Bayne W, Theeuwes F. *In vivo* evaluation of controlled-release products. *J Pharm Sci* 1993; **82**: 1145–1150.
76. Gray V. Controlled release society annual meeting report: dissolution highlights. *Diss Tech* 2004; **11**: 30–31.
77. Skelly JP, Yau MK, Elkins JS, Yamamoto LA, Shah VP, Barr WH. Topographical dissolution characterization for controlled release products—a new technique. *Drug Dev Ind Pharm* 1986; **12**: 1159–1175.
78. Skelly JP, Yamamoto LA, Shah VP, Yau MK, Barr WH. *In vitro* topographical characterization as a predictor of *in vivo* controlled release quinidine gluconate bioavailability. *Drug Dev Ind Pharm* 1986; **12**: 1177–1201.
79. Young D, Chilukuri D, Becker R, Bigora S, Farrell C, Shepard T. Approaches to developing a Level-A IVIVC for injectable dosage forms. Website: www.globomaxservice.com/resource/LevelAIVIVCPoster.pdf [30 October 2004].
80. Shameem M, Lee H, DeLuca PP. A short-term (accelerated release) approach to evaluate peptide release from PLGA depot-formulations. *AAPS Pharm Sci* 1999; **1**: article 7.
81. Zackrisson G, Östling G, Skagerberg B, Anfält T. Accelerated dissolution rate analysis (ACDRA) for controlled release drugs. Application to Roxiam. *J Pharm Biomed Anal* 1995; **13**: 377.
82. Burgess DJ, Hussain AS, Ingallinera TS, Chen ML. Assuring quality and performance of sustained and controlled release parenterals: workshop report. *AAPS Pharm Sci* 2002; **4**: article 7.
83. Quist PO, Östling G. Accelerated dissolution testing for improved quality assurance. *J Pharm Biomed Anal* 2002; **28**: 1081–1089.
84. Scott P. Process analytical technology: applications to the pharmaceutical industry. *Diss Tech* 2002; **9**: 6–9.
85. Makino K, Arakawa M, Kondo T. Preparation and *in vitro* degradation properties of polylactide microcapsules. *Chem Pharm Bull* 1985; **33**: 1195–1201.
86. Storey DE. The role of dissolution testing in the design of immediate release dosage forms. *Drug Inf J* 1996; **30**: 1039–1044.
87. FDA. *Summary Progress Report: Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach*. Website: <http://www.fda.gov/cder/gmp/21stcenturysummary.htm> [31 August 2004].
88. Wood JH. Dissolution rediscovered. In *Pharmaceutical Dissolution Testing*, Swarbrick J (ed.). Marcel Dekker Inc.: New York, 1992; 420.