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▲⟨1001⟩ IN VITRO RELEASE TEST METHODS FOR PARENTERAL DRUG PREPARATIONS

INTRODUCTION

Parenterally administered drugs include injections that are administered through the external boundary tissue with subsequent immediate release or extended release of the drug substance into the circulatory system. Parenteral drugs also include drug preparations that are administered by placement within the body to achieve, for instance, extended release of drug substance at a local area. Immediate and modified-release parenteral drug products exist as injections (solutions, suspensions, emulsions) and implants. Immediately prior to administration, the parenteral drug preparation may be reconstituted from sterile powders to form solutions, suspensions, or emulsions. Such parenteral drug preparations also include drug/device combinations such as stents. Generally, performance tests, as discussed in this chapter, are not required for aqueous solutions.

The definitions and descriptions of dosage forms and drug preparations discussed in this chapter, as well as information about their composition and manufacturing processes, can be found in *Pharmaceutical Dosage Forms* ⟨1151⟩.

The intention of ⟨1001⟩ is to provide guidance on methods that have been demonstrated as useful for the evaluation of product release performance testing of parenteral drug preparations. When reference is made to “dissolution”, “in vitro release”, “in vitro drug release”, “drug release”, and “performance” in this chapter, these terms are intended to have the same meaning. This chapter is not intended to establish new testing requirements for parenteral drug preparations.

COMMON PRINCIPLES

For parenteral dosage forms and parenteral drug preparations, the purpose of both the product quality tests and product performance tests is to assure batch-to-batch quality, reproducibility, reliability, and performance. Product quality tests are performed to assess attributes such as assay, identification, impurities, foreign particulate matter, sterility, bacterial endotoxins, water content, aluminum content, and content uniformity. These tests are part of the compendial monograph (see *Injections and Implanted Drug Products* ⟨1⟩). Method selection can be challenging for many reasons, and each preparation carries its own unique obstacles. *The Dissolution Procedure: Development and Validation* ⟨1092⟩ is an important reference to use when developing an in vitro release test procedure. It is advisable to consult with the appropriate regulatory agency to confirm the adequacy of an in-house in vitro drug release test for a drug product before filing the application.

The drug release test method should be developed early in product development so it can be used to characterize the preparations utilized in safety and efficacy trials. The drug release data for the batches used in these studies support the specifications for the drug release test at product release and expiry. Furthermore, it is important to coordinate the in vitro drug release method strategy for product development with the quality control (QC) method for release of the product. This strategy is useful in product life-cycle management to support possible manufacturing changes.

Each type of parenteral dosage form or preparation is discussed in this chapter, including highlights of the preparation’s unique challenges. Examples of methods for current preparations are provided; these examples come from multiple sources including, but not limited to, the Food and Drug Administration’s Dissolution Methods Database (*1*), workshop reports (*2–3*), *Pharmacopeial Forum* articles (*4–6*), and other scientific literature. For several parenteral drug preparations, procedures described in *Dissolution* ⟨711⟩, *Drug Release* ⟨724⟩, *Mucosal Drug Products—Performance Tests* ⟨1004⟩, or *Semisolid Drug Products—Performance Tests* ⟨1724⟩ may be applicable.

The FDA’s Dissolution Methods Database currently includes several injections and performance test methods for injectable suspensions. When a specific method is not given in this database, the instructions state, “Develop a dissolution method using USP 4 (Flow-Through Cell), and, if applicable, Apparatus 2 (Paddle) or any other appropriate method, for comparative evaluation by the Agency.” The injectable suspensions with methods provided use USP Apparatus 4 and 2, and the test media may include sodium lauryl sulfate (SLS), polysorbate, saline, water, and a small amount of ethanol. The testing time ranges from 45 min to as long as 168 h. Accelerated in vitro release test conditions may be necessary if a performance test method serves as a drug product QC tool as long time frames are generally not practical.

There are many types of extended-release parenteral drug products commercialized in the veterinary industry. The FDA’s Center for Veterinary Medicine (CVM) Guidance for Industry #238, provides guidance and strategies for consideration as part of the development program for drug release testing and product specifications (*7*).

Because of the complex nature of some parenterals, in vitro drug release test methods should be applied on a case-by-case rather than one-size-fits-all basis; however, the inclusion of general approaches and the presentation of options can be useful. Some parenteral drug preparations provide continuous release of the drug substance(s) for weeks, months, or years. The in vitro release test conditions can,

although they are not required to, mimic specific aspects of the intended physiological environment such as the osmolarity, pH, or buffer capacity. Non-sink conditions may be informative in some instances (sink conditions are defined in ⟨1092⟩). The composition of the drug-release media may be kept constant with regard to the physiological parameters for pH (e.g., pH 7.4) and osmotic pressure (e.g., 285 mOsm/kg). Because of the solubility of the drug substance and the requirement for an accelerated test, the addition of surfactants (e.g., polysorbate 80 or SLS) and/or organic solvents may be needed. Accelerated in vitro release testing is a practical solution for QC testing; however, it should be justified as having relevance. This is historically established through clinical trial data along with patient use and may be tied to product attributes that are controlled through validated manufacturing parameters (e.g., excipient quality and preparation, mixing, and time conditions) and batch release testing.

It is well known that the in vitro release of a drug from a drug product is preparation dependent. Therefore, it is unlikely a universal in vitro release test method can be designed to characterize drug release for the wide variety of existing parenteral dosage forms and preparations that exist. Assessing the suitability of a method for a preparation is therefore crucial.

Characteristics of an in vitro drug release test for parenteral drug preparations may include, but are not limited to, the following:

- Distinguishes a compliant batch [where a compliant batch is bioequivalent (BE) to the pivotal batches]
- Mimics the drug release conditions in vivo
- Utilizes early sampling to characterize the initial release

The performance test method may need to discriminate the critical quality attributes, which may include initial release; and any material, process, or product attribute that affects the subsequent release rate. In vitro release testing should be conducted with parenteral drug preparations that are manufactured under target conditions then compared to drug products that are intentionally manufactured with critical attribute variations in preparation and manufacturing parameters (*8–9*).

Multiple components/manipulations make up the drug release methods and are reported in the literature, and their associated equipment (or apparatus), are summarized in *Table 1* (*10*).

Table 1. Examples of Equipment and Techniques that Could be Incorporated into a Drug Release Method

Techniques	Continuous Sampling	Unique Advantages	Limitations
Dialysis	Yes	Filtration usually not required	Dialysis membrane, rather than the preparation, may be rate limiting; nonspecific membrane adsorption
Reverse dialysis/microdialysis	Yes	Filtration usually not required; direct measurement with microdialysis	Dialysis membrane, rather than the preparation, may be rate limiting; nonspecific membrane adsorption
Centrifugation	No	Filtration not required	Preparation dependent; sample may not be resuspendable; nonspecific membrane adsorption
Centrifugal filtration	No	Low centrifugal force possible	Filter clogging/particle deformation
Pressure ultrafiltration	No	Gentle separation at low pressure	Filter clogging/particle deformation
Size-exclusion chromatography	Yes	Selection of filter media	Column presaturation needed
In situ method (fiber optics)	Yes	Direct measurement	Polarography and UV/Vis limited
Continuous flow method	Yes	Flexible media volume	Filter clogging
USP Apparatus 4	Yes	Flexible media volume	Filter clogging/potentially high volume of release media
USP Apparatus 1	Yes	Well-characterized equipment	Defined maximum and minimum volume

Techniques	Continuous Sampling	Unique Advantages	Limitations
USP Apparatus 2	Yes	Well-characterized equipment	Defined maximum and minimum volume

The drug release test for some parenteral dosage forms may require the use of modified compendial or noncompendial equipment. For example, various volumes of dissolution media with or without agitation may be appropriate. The use of a dialysis membrane as well as the use of incubation methods have been shown to be beneficial for some preparations. *Table 2* provides known examples of suitable apparatus for types of preparations.

Table 2. Known Examples of Apparatus Used for In Vitro Release for Parenteral Preparations

Preparations	Apparatus
Nonaqueous solutions/oily preparations	Apparatus 2
Suspensions	Apparatus 2, Apparatus 4, reduced volume apparatus, dialysis cell
Nanosuspensions	Apparatus 2, Apparatus 4, dialysis cell, reduced volume
Liposomes	Apparatus 1, Apparatus 2, Apparatus 4, dialysis cell
Microparticles	Apparatus 2, Apparatus 4, incubation jar, dialysis cell
Powders for suspension	Apparatus 2, Apparatus 4, reduced volume apparatus, dialysis cell
Emulsions	Apparatus 2, reduced volume apparatus, vertical diffusion cell
Implants	Apparatus 2, Apparatus 4, Apparatus 7, incubation jar
Drug-eluting stents (DES)	Apparatus 7, Apparatus 4, modified flow-through cell
In-situ forming preparations	Apparatus 2, Apparatus 4, Apparatus 7, incubation jar

When long-term in vitro release tests are needed, special attention should be paid to the evaporation of the test media, microbial growth, and chemical degradation of the released/dissolved drug as discussed below:

- **Evaporation:** Sealed containers (e.g., jars or vials) and Apparatus 4 help prevent test media evaporation. Where justified, it may be possible to include an internal standard to correct for test media volume changes due to evaporation. An appropriate internal standard would be chemically stable, nonvolatile, and possess suitable chromatographic or spectral properties so that it can be quickly and reliably quantified independently of the active ingredient. If a poorly sealed apparatus is used for real-time tests (e.g., Apparatus 2) with an internal standard, consideration should be given to whether the reduction in volume over time will affect the sink conditions of the test media.
- **Microbial growth:** Microbial growth may be limited by using preservatives in the test media. Concentrations between 0.1% and 0.01% w/v sodium azide are reported in the literature (*11–12*). It should be noted that sodium azide is toxic to humans and may be a carcinogen, so alternative antimicrobials should be considered.
- **Chemical degradation:** Degradation of the released or dissolved drug in the test media may be partially or wholly addressed by using a nonspecific measurement technique such as UV-Vis spectroscopy, HPLC with class separation (the drug and all solution-phase degradants coelute), or summing of all drug-related peaks (with appropriate justification). The latter approach is predicated on the common observation that solution-phase chemistry tends to be much faster than solid-phase. In other words, the drug likely degrades after dissolution, so summing all degradation products and the parent compound in solution is likely a good indication of the quantity of drug that dissolved. In some cases, the addition of an antioxidant to the dissolution media or the use of an alternate pH where the drug is more stable may also be useful. Lastly, the use of Apparatus 4 in open loop mode may help mitigate degradation, because a dissolved drug does not remain in the system for the duration of the test, but open loop may create challenges for detection sensitivity.

In the case of accelerated in vitro release methods, many of the same considerations described above apply, i.e., elevated temperature can promote evaporation and chemical degradation.

Although desirable, in vitro and in vivo correlations may not be possible for modified-release parenteral dosage forms due to the complexity of the release mechanisms and the lack of knowledge about in vivo release conditions. However, the in vitro release method should reflect the route of administration. An in vitro drug release method with proven IVIVC potential would have a long-term advantage in terms of serving as a surrogate for in vivo BE testing required to qualify higher level scale-up and post approval changes for modified release (SUPAC-MR).

The following sections provide performance test guidance that is unique to parenteral dosage forms and parenteral preparations discussed in this chapter.

SOLUTIONS

One recent example reported by Priddy et al. describes the work conducted for a veterinary drug product consisting of a lipophilic drug dissolved in a low-viscosity oily matrix (*13*). This publication describes important considerations such as the identification of a suitable medium that dissolves the drug over time without degrading it and the development of a system and methodology that can be used as a QC lab tool and as a way to discriminate a quality drug product from one that was formulated or processed incorrectly.

SUSPENSIONS

Suspension dosage forms are solids suspended in a suitable liquid. Examples of suspensions include liposomes, microparticles, poorly water-soluble drug substances, and drug substances deliberately formulated to achieve prolongation of their release compared to that observed or anticipated for an immediate-release dosage form. Nanosuspensions consist of solids with any dimension inside and outside the nanoscale range of 1–100 nm but with properties attributed to its dimension (less than 1000 nm), suspended in a suitable liquid, typically water with other components (*6,14–15* and *Drug Products Containing Nanomaterials* ⟨1153⟩).

The FDA provides guidance on in vitro performance testing of modified-release parenteral dosage forms and drug preparations containing nanomaterials (*14*). Ideally in vitro drug release testing should be performed using compendial instruments described in ⟨711⟩ and ⟨724⟩. However, use of compendial instruments is not required.

Determination of the test media composition is the first key step to setting up an in vitro performance test (e.g., choice of organic solvent(s), surfactant, buffer, and pH).

Addition of the suspension test article to the test vessel or cell is another key step. For example, addition of suspension test articles into the test media may significantly alter the inherent drug release and/or dissolution characteristics of the suspension depending on the composition and volume of the test media and how the suspension test article is diluted prior to dissolution.

Another key step is sampling from the test media, including separating the test article from the dissolved drug (*16*). Many isolation techniques are employed to separate the test article from the released drug. Two major filtration technologies are used to isolate test samples. One is dead-end filtration, where particles are collected on the surface of the filter device. The second type of filtration is cross-flow filtration, where the suspension flows across the surface of a membrane filter with minimal particle buildup on the filter. Filters with a particle pore size smaller than 100 nm may be considered. In situ fiber optics combined with derivative spectroscopy allow quantification of the dissolved drug substance in the presence of the bound or encapsulated drug substance associated with the nanoparticle (*17–18*).

Compendial instruments with a basket, paddle, or flow-through cell can accommodate a bag or pouch (e.g., dialysis tubing clamped at both ends) that contains the suspension test article. The bag or pouch can consist of a dialysis membrane with a defined molecular weight cut-off. Another dialysis technique (known as reverse dialysis) uses a dialysis bag or pouch with only test media inside. This pouch is placed in the test media containing the suspension test article. Samples of released drug are taken from inside the pouch. This technique allows for placement of test article in the bulk media to, for example, minimize the agglomeration and aggregation effects.

Nanosuspensions or suspensions can be deliberately formulated to prolong or accelerate the rate of release of a drug based on the poor water solubility of the drug and on the in vivo diffusion dynamics of the drug in the biological fluid or matrix. In such cases, dissolution of the suspension in a typical performance testing apparatus may be very rapid. The provision of full solubility is typically required in order to meet regulatory expectations (able to meet $Q = 80$, for example), and biologically relevant diffusion barriers are difficult to construct. For such suspensions, the most likely product attribute for which the performance test must discriminate (most likely to affect pharmacokinetics) may be the specific surface area (SSA) of the drug substance particles, for which drug substance particle size is often a good surrogate. As such, any in vitro release test that measures the impact of variations in SSA or particle-size distribution may be appropriate for performance control, regardless of the speed of dissolution. Consideration should also be given as to whether a direct measurement of particle size (e.g., via light scattering) may be a better measurement of likely in vivo product performance.

LIPOSOMES

Liposomes are submicron to micron-sized vesicles composed of a single lipid bilayer surrounding an aqueous core or a concentric series of multiple bilayers separated by aqueous compartments. The bilayers are formed by amphipathic molecules, such as phospholipids and cholesterol. Generally, liposome drug products comprise the drug substance and lipid components, as well as non-lipid inactive ingredients.

In liposomal drug products, the drug substance can be encapsulated within the aqueous compartment(s) [hydrophilic drugs], intercalated within the lipid bilayer(s) [hydrophobic drugs], or associated with the surface(s) of lipid bilayer(s) [charged and/or amphiphilic drugs]. Drug release is not a consequence of dissolution of the liposomes. It is dependent on a combination of factors including the following:

- Lipid composition
- Nature of the drug (hydrophilic, hydrophobic, charged or uncharged)
- Location in the liposomes
- Molecular state (e.g., precipitated in the aqueous compartment or independent from environmental factors such as pH, counter ions, etc.)
- Liposome manufacturing/drug loading process (can affect the molecular state of the drug as well as the state of the bilayer)

In vitro drug release testing is performed to characterize the functionality of the lipid bilayer. Such drug release testing can also test for uncontrolled leakage (“dose-dumping”). In vitro release test conditions are chosen to discriminate changes that can occur in the drug product (the state of the lipid bilayer or the associated drug) during manufacturing or storage or in vivo. In vitro drug release tests are used

for lot release and stability testing. Examples of in vitro release techniques include flow-through cells with dialysis membranes (USP Apparatus 4) and other dialysis methods. Furthermore, separation methods, such as ultracentrifugation or filtration, can be employed.

Development of in vitro drug release assays can be challenging due to the complex dependence of release on the specific nature of the liposome preparation and drug. Standardized in vitro release techniques do not exist. Existing guidance documents refer to specific drug products on the market. An FDA guidance document on chemistry, manufacturing, and control (CMC) aspects of liposomes is available (19). At present, developers of liposomal drug preparations have proprietary in vitro drug release methods for use in the QC of their preparations. More collaborative efforts among academia, industry, and regulators are needed to standardize in vitro drug release testing of liposomes (20).

MICROPARTICLES

Microparticles, or microspheres, (⟨1151⟩) are larger than 100 nm and are typically incorporated into suspensions for injection. Often microparticles are powders containing extended-release particles that just prior to administration are suspended in a suitable liquid. There are two distinct challenges when performing an in vitro drug release test on microparticles. First, if microparticles do not wet well, as observed by floating or aggregating, then the test media can be modified by adding a small quantity of surfactant to the media to reduce the surface tension. Secondly, microparticles may require a prolonged testing time, which could cause extensive evaporation of the dissolution media and chemical degradation of the released drug in the media. See the *Common Principles* section on chemical degradation for additional recommendations. Methods that use dialysis membranes with microparticles have been reported in the literature (21).

EMULSIONS

For emulsions, the drug substance is typically trapped within a water-in-oil or oil-in-water dispersed phase; however, the majority of parenteral emulsions are oil-in-water emulsions. When assessing the drug release of these type of emulsions, the apparatus described in ⟨711⟩, ⟨1004⟩, and ⟨724⟩ may be appropriate; these apparatus include USP Apparatus 2, dialysis cell, USP Apparatus 4, a vertical diffusion cell, and reduced-volume equipment.

IMPLANTS

For extended-release implants, the in vitro drug release test should include a procedure to ascertain whether the drug releases as intended and to prove the robustness of the drug product. There may be a regulatory expectation for real-time (long-term) in vitro drug release tests used along with accelerated in vitro drug release tests. Some acceleration strategies include elevated temperatures, non-neutral pH to increase the hydrolysis of rate-controlling polymers and/or to increase the drug solubility, and organic cosolvents used to increase drug solubility and/or to increase the permeability of rate-controlling polymers. Both real-time and accelerated performance tests should be well studied and justified in their predictive ability (clinical relevance) and/or discriminatory power for QC.

In the *USP* monograph *Goserelin Implants*, the apparatus is a sealed jar that is incubated. Apparatus 4 and Apparatus 7 are also used (5–8). The FDA database provides three implant methods: the goserelin implant uses an incubation method, the dexamethasone implant uses Apparatus 7, and the buprenorphine hydrochloride implant uses Apparatus 2.

DRUG-ELUTING STENTS

Drug-eluting stents (DES) are a combination of a device and a drug, where the drug is usually within a polymeric matrix that coats the stent. As with implants and extended-release microparticle suspensions, the long-acting nature of the DES makes long in vitro release tests (up to 6 months in some cases) necessary to fully characterize the drug release profile. Long tests come with the challenges of media evaporation and stability of drug substances within the media. The possibility of accelerated conditions is an important consideration, as the in vivo release may occur over a long period of time. Other considerations are the positioning of the DES in the apparatus for adequate mixing and the use of a small volume of media due to the low drug concentration.

There are performance test methods suggesting the use of a reduced-volume paddle apparatus—USP Apparatus 4 or USP Apparatus 7 with stent holders—where small volumes of media are used (4). For the approved DES, sirolimus, USP Apparatus 4 (flow rate of 25 mL/min) was used with an elution media (50 mL) of 2% SLS and 10% acetonitrile at a pH of 4.5 and a temperature of 37° (22). This is a closed-loop configuration.

The method needs to reflect the transport forces that are predominant in vivo (23). This has been demonstrated in methods using a blood vessel-simulating flow-through cell apparatus (24). Other apparatus that have been used for in vitro drug release testing of DES are as follows: incubation cells of different volumes, agitation at 250–300 rpm at 37°, and USP Apparatus 7 with small-volume reciprocating holders in 10-mL glass cells at dip rates of 5 or 40 DPM (25).

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