Dissolution Test Development for Complex Veterinary Dosage Forms: Oral Boluses

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ABSTRACT Fundamental aspects of electrolyte chemistry were used to design an appropriate dissolution medium with the capacity to maintain sink conditions throughout the test. Dissolution of various bolus dosage forms was studied using USP Apparatus II at various stirring speeds. Complete dissolution of each drug in the designed medium was achieved, and there is evidence that such a dissolution test could be discriminating. This review details the development of potentially discriminating in vitro dissolution tests for veterinary boluses using USP Apparatus II and examines the potential role of such testing during product quality assessments, in the evaluation of postapproval manufacturing changes and for the establishment of the generic equivalence of veterinary products.

KEYWORDS: dissolution, veterinary products, bolus.

Introduction In 1968 a United States Pharmacopeia-National Formulary (USP-NF) Joint Panel on Physiologic Availability directed the identification of candidate articles for the first official dissolution tests. Now, 34 years later, the USP provides for dissolution and drug-release testing in the majority of monographs for solid oral dosage forms. In fact, the official compendium now states: "Dissolution testing is required for all solid oral Pharmacopeial dosage forms in which absorption of the drug is necessary for the product to exert the desired therapeutic effect"¹. It is likely that most pharmaceutical scientists would identify dissolution testing as the in vitro test most likely to correlate with bioavailability and in vivo performance. General information section <1088>, now included in the USP, is entitled In Vitro AND In Vivo Evaluation of Dosage Forms and includes explicit information on in vitro-in vivo correlations. Recently, authors from the Food And Drug Administration have published on the evolving role of dissolution testing².

The Food and Drug Administration Modernization Act (FDAMA) requires, in part, that animal drug manufacturers validate or assess the effects of any manufacturing change on their drug products. A number of guidance documents developed for human drugs, such as the Scale-Up Post-Approval Changes for Immediate Release Solid Oral Dosage Forms (SUPAC-IR), have been published by the FDA and describe the documentation required to validate the effects of manufacturing changes. Comparative dissolution studies on the drug product before and after a change is a key part of the documentation, and dissolution testing is used to determine whether or not additional bioequivalency data are needed to support the manufacturing change.

Within the FDA, the Center for Veterinary Medicine (CVM) approves and regulates animal drug products, including solid oral dosage forms unique to veterinary medicine. Boluses, which are large tablets or for use in animals such as cattle, are generally not quality control tested using a dissolution test. Instead a disintegration test has been used. It is the opinion of these authors that a discriminating dissolution test utilizing conventional methods would enhance quality control and potentially lessen the regulatory burden on the animal drug industry to validate the effects of a manufacturing change on bolus dosage forms. It is also believed that an appropriate dissolution test showing correspondence with an innovator product could be a key factor in a determination of generic product bioequivalence.

Obviously it is necessary to be able to conduct a dissolution test before it is possible to determine if it is discriminating, relevant, and potentially correlative. The widespread availability of the USP dissolution testing apparatus makes it a logical choice for test development, particularly when contrasted with the expense of both equipment and chemicals for larger volume testing. Thus, an initial objective was to see if this apparatus could be employed for testing of boluses. Much of the theoretical background and supporting data included here have recently been reported elsewhere.³⁻⁵

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Figure 1. Volume of dissolution medium required as a function of drug solubility and dosage.

Doses of drugs used in humans, even when the drugs are acidic or basic, represent a relatively small challenge to the buffering capacity of most media. When a 500-mg dose of a drug whose molecular weight is 400 is dissolved in the 900-mL volume in the USP apparatus, the resulting molar concentration of drug is 0.0014 M. If this quantity of drug was dissolved in 900 mL of a 0.1 M phosphate buffer initially prepared at pH 7.2, the pH would change no more than 0.02 pH units.

MATERIALS AND METHODS

Materials

Dissolution tests were conducted in USP Apparatus II (Distek, Dissolution System 2100B, North Brunswick, NJ), at 37°C. Dissolution test data for the following veterinary products are referred to or included in this article: Calf Scour Bolus Antibiotic, 500 mg of tetracycline hydrochloride per bolus, NADA 65-004, manufactured for Durvet, Inc, Blue Springs, MO, by Pharmacia & Upjohn Company, Kalamazoo, MI; Albon, 5 g sulfadimethoxine per bolus, NADA 31-715, manufactured by Pfizer Animal Health, Easton, PA; Aspirin Bolus, 15.6 g acetylsalicylic acid per bolus, manufactured by Agri Laboratories, Ltd, St Joseph, MO. Each dissolution data point represents the average of 6 determinations, and the error bars are based on twice the relative standard deviation. All buffer salts and chemicals used in the preparation of dissolution media met American Chemical Society (ACS) specifications.

Results For many human drug products in which the drug is soluble and the dose is relatively low, the design of a dissolution method is largely reduced to selection of the pH of the medium and the stirring speed employed. In contrast, given the large quantity of drug contained in a bolus, it is necessary to consider both the capacity of the medium for the drug and the impact of the dissolving drug on the pH of the medium.

Assumptions

Some basic assumptions are made in the following analysis. First, when the USP apparatus is referred to, this means Apparatus I or II. The constraints placed on

initial development were to use a fixed volume of 900 mL or less of an aqueous dissolution medium at 37°C, with a stirring rate less than or equal to 100. Sink conditions are assumed to be maintained when the system is able to accommodate 10 times the amount of active present.

Capacity of the dissolution medium

If D = dose (mg) of the drug in the bolus dosage form to be tested, S = solubility of the drug (mg/mL), and $V_{\min}$ = the minimum volume (mL) of dissolution medium required to ensure sink conditions when dissolution is complete, then:

$$V_{\min} = [D \times 10 / S] \quad (1)$$

Anytime $V_{\min}$ is 900 mL or less, the USP apparatus can be readily employed. The hyperbolic nature of the relationship between dose and solubility is represented in **Figure 1**. A portion of the response surface generated from Equation 1 is presented in this figure, with solubility values from 0.02 to 20 mg/mL on the x-axis, and selected doses ranging from 1 to 500 mg on the y-axis (note: these axes are not linear). The linear z-axis is truncated at 900 mL, generally taken as the maximum volume employed in the USP apparatus.

To a certain degree, the relatively small amount of drug dissolving and the lack of a dose-solubility restriction provide an opportunity to create test conditions that produce physiologically relevant results, thereby increasing the probability of meaningful discrimination and in vitro-in vivo correlation. Obviously, the situation changes significantly with the large doses of drugs often employed in veterinary products.

The first step in assessing the feasibility of using the conventional USP dissolution apparatus for testing these products is to consider drug solubility. As an example, consider a veterinary bolus with a dose of 5 g. In order to use the USP apparatus and maintain sink conditions throughout dissolution, the solubility of the drug, calculated from Equation 1, would have to be 55.6 mg/mL (ie, 5.56% wt/vol) or higher throughout the run. If solubility, for any reason relevant to dissolution testing, falls below the value of 55.6 mg/mL, then steps must be taken to enhance the capacity of the medium.

Tetracycline Bolus

Dissolution testing of the Calf Scour Bolus is an example of a case in which testing of the animal product can proceed in the same manner as testing of the human drug product⁵. This bolus contains 500 mg of tetracycline hydrochloride in a tablet that weighs approximately 5.8 g. While the bolus is quite large, the amount of active ingredient in this dosage form is not substantially larger than is often found in capsules and tablets made for human use.

The approximate solubility of the tetracycline hydrochloride salt in water is 1 g in 10 mL (100 mg/mL)⁵. Thus, from Equation 1, the minimum volume of water needed

to maintain sink condition during the dissolution

Figure 2. Dissolution of Tetracycline Boluses in water at 37°C.

testing of a 500-mg bolus is 50 mL. This volume is well below that which can be employed in the USP apparatus, indicating that not only can the test be performed, but that water is an acceptable choice for the dissolution medium. Results of dissolution testing of Calf Scour Bolus are presented in **Figure 2**.

Solubility Analysis

Consider a product such as Albon Sulfadimethoxine Bolus 5 g. The solubility of sulfadimethoxine is listed as 4.6 mg in 100 mL at pH 4, and the minimum volume required to conduct a dissolution test under these conditions would be greater than 1000 L. This is a case in which substantial solubility enhancement is required.

As soon as a step must be taken to enhance the solubility of the medium, there is almost always a decision to move away from the ability to achieve complete physiological relevance. The use of solubilizers and cosolvents is an excellent example. While these components can increase apparent solubility, high alcohol and/or surfactant levels are not usually found in the GI tract. In our work conducted to this point, a decision was made that alteration of pH, even outside normal physiological ranges, was preferable to the addition of cosolvents and/or surfactants.

The profound influence that pH has on the solubility of weakly acidic and weakly basic substances provides a basis for enhancing the solubility of drugs in these categories. To proceed in this direction, it is necessary to explicitly determine the relationship between pH and solubility for the candidate compound. Determining this relationship requires real solubility data and the ability to interpolate and/or extrapolate these data to drug dissolution data generated under other sets of test conditions. Real solubility data often may be obtained from the literature or, preferably, determined experimentally. Theoretical solubility relationships based on consecutive equi-

libria are well recognized. For simplicity, this discussion will focus on a monoprotic weakly acidic drug, represented as DH, where

$$\text{St} = (\text{DH}) + (\text{D}^-) \quad (3)$$

$$K_{a,\text{DH}} = [\gamma_{\text{D}^-} (\text{D}^-) a_{\text{H}^+}] / [\gamma_{\text{DH}} (\text{DH})] \quad (4)$$

$$K_{a',\text{DH}} = [\gamma_{\text{DH}} K_{a,\text{DH}}] / \gamma_{\text{D}^-} = [(\text{D}^-) a_{\text{H}^+}] / (\text{DH}) \quad (5)$$

$$\text{St} = \text{So} [1 + K_{a',\text{DH}} / a_{\text{H}^+}] \quad (6)$$

and where DH and D⁻ refer to the acidic (undissociated) and ionized (dissociated) forms of the drug, respectively. The designations (DH) and (D⁻) refer to the molar concentrations of these species, and St = total drug solubility. The dissociative equilibrium is characterized in Equation 4, where $K_{a,\text{DH}}$ = dissociation constant for the drug, and a_{H^+} refers to the activity of the hydronium ion in solution. The terms γ_{DH} and γ_{D^-} are the activity coefficients for the acidic and ionized forms of the drug, respectively. $K_{a',\text{DH}}$ = the functional dissociation constant for the drug that governs the relative concentrations of chemical species in solution as a function of pH. In this analysis, an assumption is made that the activity coefficient ratio $\gamma_{\text{SDMH}} / \gamma_{\text{SDM}^-}$ is constant, so that $K_{a',\text{DH}}$ is also constant. With regard to Equation 6, So = intrinsic solubility of the drug, which in this case is (DH), is constant in the portion of the pH-solubility profile where the solid phase is the weak acid. Since deviations from ideal behavior are expected (and are significant), it is necessary to fit real data to Equation 6. Usually, an acceptable approach is to iteratively vary So and pK_{a'} until the theoretical relationship converges with that of the real data. A more unbiased approach, however, is to vary the final parameters such that the residual sums of squares are minimized within the pH range corresponding to the collected data.

Sulfadimethoxine Bolus

The case for sulfadimethoxine has been presented in **Figure 3**, where real data for drug solubility were obtained from the literature¹. **Figure 2** is a pH-solubility profile for sulfadimethoxine, which includes the real drug solubility data and compares them to a theoretical profile based on Equation 6, with the following parameter values: pK_{a',\text{DH}}} = 5.54 and So = 0.0349 g/L.

Table 1. Species concentrations of the USP Borate Buffer System

pH	(H ⁺)	(OH ⁻)	(H ₂ Bor ⁻)	b(calc)	b(USP)
8	1.00E-08	1.00E-06	3.38E-03	0.0034	0.0039
8.2	6.31E-09	1.58E-06	5.15E-03	0.0052	0.0060
8.4	3.98E-09	2.51E-06	7.70E-03	0.0077	0.0086
8.6	2.51E-09	3.98E-06	1.12E-02	0.0112	0.0118
8.8	1.58E-09	6.31E-06	1.57E-02	0.0157	0.0158
9	1.00E-09	1.00E-05	2.10E-02	0.0210	0.0208
9.2	6.31E-10	1.58E-05	2.67E-02	0.0267	0.0264
9.4	3.98E-10	2.51E-05	3.23E-02	0.0323	0.0321
9.6	2.51E-10	3.98E-05	3.71E-02	0.0372	0.0369
9.8	1.58E-10	6.31E-05	4.10E-02	0.0411	0.0406
10	1.00E-10	1.00E-04	4.39E-02	0.0440	0.0437

Figure 3. pH Solubility profile for Sulfadimethoxine.

For a 5-g sulfadimethoxine bolus, complete dissolution in 900 mL water corresponds to a concentration of 5.56 g/L (0.0179 M). To achieve sink conditions the solubility of the drug must be at least 55.6 g/L. Based on Equation 5, a pH of 8.74 would produce a system in which the solubility is 55.5 g/L. Thus, the buffer system for dissolution must be designed so that the pH remains at or above 8.74.

It should be noted that in this case the determination of the functional dissociation constant is not only required for the generation of a complete profile, it is also required in subsequent proton balance equations developed to describe the dissolution system. When pH adjustment is used to increase solubility, it is essential that the pH be both established and maintained within some critical range. Since sulfadimethoxine is a weak acid, and since a large quantity of drug will be dissolved, dissolution will drive the pH in a direction that corresponds with a decrease in overall solubility.

Therefore, the selected buffer medium must be capable of compensating for such changes.

While fluctuations in pH are inevitable, it is desirable to minimize these changes. For this work, an arbitrary maximum change of 0.5 pH units was selected. With the corresponding need for a high buffer capacity, a buffer system must be chosen that has a pK_a very close to that of the target pH. Even so, it is necessary to utilize relatively high buffer concentrations to achieve this design goal. Once again, substantial deviations from ideal behavior are to be expected. Also, if possible, buffers that absorb light should be avoided so that simple analysis may be accomplished using UV/VIS spectroscopy.

In developing an appropriate dissolution medium for sulfadimethoxine, a borate buffer system was selected. The USP Alkaline Borate buffer system was employed² as a set of real solution data that allows for an estimate of the functional pK_a of the buffer as represented by the following equilibrium:

where H_3Bor and H_2Bor^- refer to boric acid and the monobasic borate ion.

A corresponding proton balance equation for a borate buffer system resulting from the combination of boric acid and sodium hydroxide³ would be

$$(H^+) = (OH^-) + (H_2Bor^-) - b \quad (8)$$

where (OH^-) = hydroxide ion concentration, (H_2Bor^-) = borate ion concentration, and b = concentration of strong base (ie, NaOH). In this equation, (OH^-) and (H_2Bor^-) concentrations correspond to the concentrations of hydronium ion contributed by water and boric acid, respectively, while b corresponds to the concentration of hydronium ion neutralized by the addition of the strong base.

Considering the respective equilibrium relationships, Equation 8 may be rewritten as

$$(\text{H}^+) = K_w/(\text{H}^+) + C_t (\text{H}^+)/[(\text{H}^+) + K_{a'}_{\text{BOR}}] - b \quad (9)$$

with K_w = dissociation constant for water, C_t = buffer concentration, and $K_{a'}_{\text{BOR}}$ = functional dissociation constant for boric acid. Once again, the real data may be used to estimate $K_{a'}_{\text{BOR}}$ by iteratively varying parameters in Equation 9 until convergence of the real and theoretical data is achieved. These iterations are easily executed using a spreadsheet format. **Table 1** represents the results of such a procedure, where $C_t = 0.05$ M.

In this case, the pH values used are those specified in the USP. Once the pH is stipulated, (OH^-) and (H_2Bor^-) can be determined from the equilibrium relationships and b can be calculated from Equation 9. The calculated values for b (ie, $b(\text{calc})$) can be compared with values of b determined from the alkaline borate buffer recipes in the USP. The values for $b(\text{calc})$ in the table were obtained with a $\text{pK}_{a'}_{\text{BOR}} = 9.14$, and these compare very well with $b(\text{USP})$. Once again, the sum of the squares of the residuals was minimized to obtain the $\text{pK}_{a'}_{\text{BOR}}$ estimate.

Now that functional $\text{pK}_{a'}$ values have been determined for both the drug and the selected buffer, it is possible to proceed to the actual design of the buffer system. Since the $\text{pK}_{a'}$ for sulfadimethoxine is 5.54, and the dissolution process will necessarily be conducted at or above pH 8.74, sulfadimethoxine will be at least 2 pH units above its $\text{pK}_{a'}$. It will behave like a strong acid, contributing its available protons to the solution. The concentration of undissociated sulfadimethoxine (DH) present at pH 8.8 or above will be essentially zero.

Thus, the dissolution of DH in the borate buffer system could be represented by the following proton balance equation:

$$(\text{H}^+) = (\text{OH}^-) + (\text{Bor}^-) - b + (\text{D}^-) \quad (10)$$

where, because of the relatively low $\text{pK}_{a'}$, (D^-) = concentration of sulfadimethoxine dissolved.

By stipulating an initial pH and concentration of a buffer system and by solving Equation 10 for (D^-) at various pHs, it is possible to estimate the pH that will result as sulfadimethoxine. **Figure 4** represents a theoretical plot of pH versus amount dissolved in a 0.15 M pH 9.0 Borate buffer system. The graph also includes data from an actual dissolution test described below. It can be seen that the pH resulting after the dissolution of a 5-g bolus will be about 8.75. This corresponds well to the target established in the pH – solubility analysis.

Figure 4. Effect of dissolution of sulfadimethoxine from a bolus containing 5 g of drug on pH using a 0.15 M borate buffer system medium with an initial pH of 9.0.

Once an acceptable medium has been identified or developed, the design of the dissolution test turns to issues such as stirring rate, sampling times, and analytical methods. Just as the medium design for boluses requires special consideration, so does this aspect of the process.

First of all, it may be necessary to adjust the paddle height normally used in the apparatus. A large bolus will not fit under the paddle at its normal height. Instead, the bolus will be swept around the bottom of the vessel until disintegration occurs. For rapidly disintegrating boluses, like sulfadimethoxine, this is not a significant issue. However, for a bolus that does not disintegrate rapidly, failure to raise the paddle height could create an exposure characterized by unrealistic or irreproducible mechanical erosion and degradation.

There also can be a considerable amount of undissolved substance in the vessel. As a result, sampling can be problematic. Testing performed with 0.45-micron in-line filters was unsuccessful because several lines became clogged during the run. Manual sampling using a 0.45-micron syringe filter was ultimately necessary.

Results from an analysis of the sulfadimethoxine boluses conducted at RPMs of 50, 75, and 100 are presented in **Figure 5**. Each profile is based on averages of 6 boluses. The error bars included in the figures are based on ± 2 standard deviations. The relationship between average percent dissolved versus RPMs suggests that this method is discriminative and may serve as an acceptable in vitro quality control method.

Figure 5. Dissolution of Sulfadimethoxine Boluses in 0.15 M pH 9.0 Borate Buffer at 37°C.

In addition to sulfadimethoxine, where each bolus contains 5 g of sulfadimethoxine, this dissolution medium has been employed for sulfachlorpyradazine, where each bolus contains 2 g of sulfachlorpyradazine, and for sulfamethazine, where each bolus contains 5 g of sulfamethazine.

Aspirin Bolus

A similar approach has been taken in the design of a dissolution test for Aspirin boluses containing 15.6 g (240 grains) of acetylsalicylic acid in a large tablet that weighs approximately 18.5 g. These boluses were chosen because the large dosage presents a dissolution challenge for conventional methodology.

Figure 6 is a pH-solubility profile for aspirin, which includes actual data and compares them to a theoretical profile based on Equation 6, with the following parameter values: $pK_{a'}_{ASAH} = 3.9$ and $S_o = 6.31$ g/L (0.035 M) (4).

Figure 6. Estimated Solubility of Aspirin as a function of pH.

For the aspirin bolus dissolution, 15.6 g of drug in 900 mL corresponds to a concentration of 17.3 g/L (0.0963 M). At 100% dissolution, the pH where St is 10 times the maximum is 5.32. Thus, the buffer system must be designed so that a pH of no lower than 5.32 will exist at the conclusion of the dissolution process.

A 0.05 M pH 4.5 acetate buffer system is employed in the USP dissolution test for aspirin tablets¹. While this system is adequate for the dissolution of 325 mg tablets of aspirin in 900 mL, the analysis above shows that it is grossly insufficient when the goal is complete dissolution of a 15.6-g dose of aspirin. Not only is the starting pH of 4.5 too low to accommodate the drug, but the acidic character of the drug will also drive the pH to an even lower value.

In a dissolution test with a 0.5 M acetate buffer at pH 4.75, approximately 62% of the 15.6 g of aspirin dissolves in 150 minutes, and the pH is at 3.87 at the end of the test. From the solubility profile presented earlier, a concentration of 12.2 g/L (11.0 g/900 mL) is the maximum amount of aspirin that can be dissolved at pH = 3.87. If a saturated solution were achieved, one would predict that only about 70% of the 15.6-g dose would be dissolved.

One of the basic tenets of dissolution testing is that all of the dose must be capable of dissolving. However, it may be possible to have a discriminating dissolution test even when the dissolution process is capacity limited. All of the factors that influence the rate of dissolution in the traditional approach to complete dissolution (eg, disintegration, particle size, diffusion layer thickness, rate of surface renewal) also influence the rate of dissolution in the approach to saturation of the medium. There is increased sensitivity inherent in the situation in which all of the drug is capable of dissolving. However, there may be sufficient sensitivity associated with a test in which complete dissolution is not possible. In situations where solubility adjustment is not feasible, incomplete dissolution may be an acceptable alternative.

Keeping within the stipulated objectives (900-mL volume, sink conditions, and not more than a 0.5-unit change in pH), a phosphate buffer system was ultimately selected for the dissolution medium. From the solubility perspective, any pH in the effective range of this phosphate buffer system could be chosen for the dissolution testing. However, if the objective is to maintain a constant pH during the dissolution process, it is desirable (for a weakly acidic drug) to identify a pH that is greater than the functional pK_a of the buffer system. By selecting a starting pH that exceeds the pH of maximum buffer capacity, the dissolving aspirin (which lowers pH) actually increases the buffer capacity of the system. Thus, the system becomes progressively more resistant to pH change during the drug dissolution process.

After analysis, a 0.5 M pH 7.4 phosphate buffer was selected as the dissolution medium for this dissolution study. In 900 mL of this medium, sink conditions exist, and it is expected that complete dissolution of 15.6 g of aspirin would occur within a system with a pH of 7.0.

Figure 7. Dissolution of Aspirin Boluses in 0.5 M pH 7.4 Phosphate Buffer at 37°C.

Dissolution testing of aspirin boluses was initially conducted using USP Apparatus II at 50 rpm and a medium consisting of 0.5 M Phosphate Buffer (pH 7.4, 37°C). An automatic sampler collected 3.5 mL at each of the following time points: 5, 10, 20, 30, 45, 60, and 90 minutes. At this stirring rate, there was a large mound of solid located at the center of the bottom of each flask, and dissolution was not complete at 90 minutes of testing. After the 90-minute sample, the stirring rate was elevated to 100 rpm, and an additional sample was withdrawn at 120 minutes. When the test was repeated at 75 rpm, dispersion of the undissolved solid was enhanced, and complete release was obtained in less than 60 minutes. The results of the dissolution test are summarized in **Figure 7**. Liquid from vessels was withdrawn at the end of the dissolution, and a pH of 7.11 was measured. Approximately 3% of the aspirin degraded to salicylic acid during the dissolution test.

The aspirin boluses disintegrated quickly, and the resulting quantity of dispersed solids in the dissolution flask was quite large. Initial testing was performed with 0.45-micron in-line filters. However, several lines became clogged during the run, and manual sampling was periodically necessary. In all cases, samples were cloudy and were filtered after collection using a 0.45-micron syringe filter. These results suggest that the dissolution medium works well, and that the boluses tested display very little variation in drug release at the time points tested.

Discussion Given the large doses of drug administered in veterinary products, there are only 2 options for limited volume testing: modification of the medium to enhance solubility or removal of the drug during dissolution testing. The approach taken here was to enhance solubility using buffer design principles. For the aspirin bolus, a 0.5 M pH 7.4 phosphate buffer was employed. While this is a relatively high buffer concentration, the pH of the medium and the chemical character of the buffer argue in favor of its physiological relevance. On the other hand,

for sulfadimethoxine, a 0.15 M pH 9.0 borate buffer was employed. The physiological relevance of this medium could certainly be questioned.

The essential question being addressed here is: To what extent can dissolution testing be used as a surrogate for testing in animals? The added dimensions for veterinary products are the large amounts of drug per dosing unit, product use in multiple animal species, and the absence of previous well-controlled in vitro test procedures.

Of what good is a test that accepts, rejects, or more subtly discriminates between dosage forms but does not correlate with in vivo outcomes? The default justification for dissolution testing requirements has always been that it is a good quality-control test. With this argument, there is an inherent inference that any change in the in vitro performance of the dosage form reflects a therapeutically important change from the approved product. While regulators often embrace this view, it may not be feasible. In truth, no 2 products will ever perform exactly the same, and differences in a test result may not translate into meaningful differences in in vivo performance.

The design requirements discussed in this review may not fall within a physiologically relevant range of conditions. Nevertheless, this does not necessarily indicate that the results of these test methods will fail to correlate with in vivo outcomes. The next step in the process is to document the ability of the dissolution test in these designed media to provide meaningful discrimination.

CONCLUSIONS It appears that potentially discriminating in vitro dissolution testing of veterinary boluses containing drugs that are weakly acidic or weakly basic, can be accomplished using USP Apparatus II and conventional fluid volumes. Stirring rates and aqueous buffer systems can be designed to provide and maintain sink conditions. Subsequent to demonstrating that the test is discriminating, it can serve as a useful quality-control tool for the regulated industry and may qualify as a mechanism for demonstrating the impact (or lack thereof) of a postapproval change.

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