

Dissolution Testing of Veterinary Products

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Dissolution Testing of Aspirin Boluses

Background

Aspirin is used orally as an aid in reducing fever and in relief of minor muscular aches and joint pain in cattle and horses. Aspirin boluses examined in this study (i.e., Lot# 990664, manufactured for Agri Laboratories, Ltd., St. Joseph MO and Lot# 990843 manufactured for The Butler Company, Columbus OH) contain 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 significant dissolution challenge for conventional methodology.

The general objectives of this work are addressed in the preceding article on Sulfa drugs, and the development of the dissolution method presented below will follow that format. An additional complication to the development of this dissolution method is the relatively rapid hydrolysis of aspirin that is base catalyzed in the dissolution medium.

Solubility

Aspirin [ASAH] is a weak acid, and its solubility can be characterized using the following relationships:



$$St = (\text{ASAH}) + (\text{ASA}^-) \quad \text{Eq. (2)}$$

$$St = So \left[1 + K_a'_{\text{ASAH}} / a_{\text{H}^+} \right] \quad \text{Eq. (3)}$$

where ASAH and ASA⁻ refer to the acidic (undissociated) and ionized (dissociated) forms of the drug, respectively. The designations (ASAH) and (ASA⁻) refer to the molar concentrations of these species, and St = total drug solubility. As discussed previously, $K_a'_{\text{ASAH}}$ = the functional dissociation constant for the drug which governs the relative concentrations of aspirin chemical species in solution as a function of pH. With regard to Eq.3, So = intrinsic solubility of the drug, which in this case is (ASAH) and which is constant in the portion of the pH-solubility profile where the solid phase is the weak acid.

Real data for ASAH solubility were estimated by adjusting the pH of dispersions of aspirin in water

to specific pH values in the range of 2-5, and letting these systems equilibrate at room temperature for approximately 4 hours. The dispersions were filtered, the pH of the filtrate was determined, and the concentration of the saturated solution was determined using the UV method described below. Figure 1 is a pH-solubility profile for ASAH which includes that data and compares it to a theoretical profile based on Eq.3, with the following parameter values: $pK_a'_{\text{ASAH}} = 3.9$ and $So = 6.31 \text{ g/L (0.035 M)}$.

For the ASAH bolus dissolution, 15.6 g of drug in

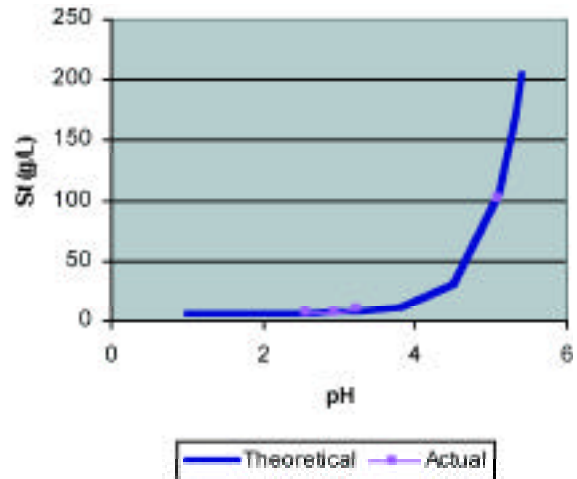


Figure 1. Solubility of Aspirin as a function of pH.

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

Buffer System

A 0.05 M pH 4.5 acetate buffer system is employed in the USP (1) dissolution test for aspirin tablets. 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, the acidic character of the

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drug will drive the pH to an even lower value. If the functional pK_a' of aspirin is indeed 3.9, and an acetate buffer is desired, it was determined by proton balance equation analysis that a 0.5 M sodium acetate solution could be used. After complete dissolution of 15.6 g of aspirin, this medium would end up at a pH of 5.34, which is sufficiently high to reflect sink conditions. However, the starting pH of this solution would be 9.2, and there would be a pH change of about four units during the dissolution process.

To demonstrate the limitations of the acetate buffer system, a preliminary study of the dissolution of Aspirin boluses was conducted in 0.5 M pH 4.75 acetate buffer in USP Apparatus 2 at 75 RPM. The results of this study are presented in Figure 2.

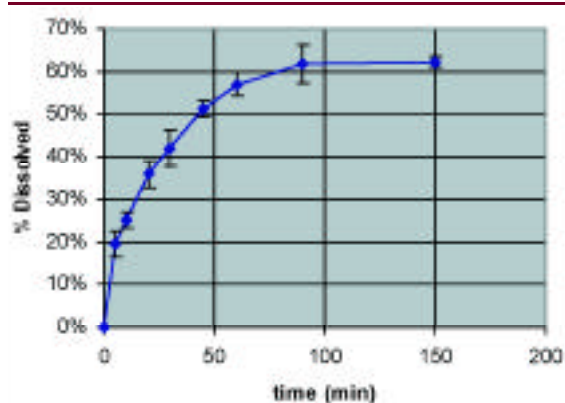


Figure 2. Dissolution of Aspirin Boluses in 0.5 M pH 4.75 Acetate Buffer at 75 RPM.

Each data point represents the average of six determinations, and the error bars are based on twice the relative standard deviation. The pH of the medium started at 4.75, and was at 3.87 at the end of this test. From the solubility profile presented earlier, a concentration of 12.2 g/L (11.0 g/900 mL) is the maximum that can be achieved at pH = 3.87. If a saturated solution were achieved, then one would expect about 70% of the 15.6 g dose to be dissolved. This test resulted in approximately 62% dissolved in 150 minutes, which corresponds well with expectations.

One of the basically unquestioned tenets of dissolution testing is that all of the dose must be capable of dissolving. Indeed, here we have established an ambitious objective of sink conditions. While this basic tenet will not be challenged here, it

can be pointed out that it may be possible to have a discriminating dissolution test even when the dissolution process is capacity limited. All of the factors which influence the rate of dissolution in the traditional approach to complete dissolution (e.g., 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 where all the drug can dissolve, but there may be sufficient sensitivity in the case where complete dissolution is not possible. This is supported in this case by the fact that over 60% of the aspirin dissolved in 90 minutes under capacity-limited conditions.

Keeping within the stipulated objectives, a phosphate buffer system was ultimately selected for the dissolution medium. The USP Phosphate buffer system was employed as a set of real solution data that allow an estimate of the functional pK_a' of the buffer representing the following equilibrium:



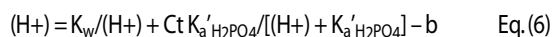
where $H_2PO_4^-$ and HPO_4^{2-} refer to monobasic and dibasic phosphate ions, respectively.

A proton balance equation (2) for a phosphate buffer system made by combining monobasic potassium phosphate and sodium hydroxide would be:



where $[OH^-]$ = hydroxide ion concentration, $[HPO_4^{2-}]$ = dibasic phosphate ion concentration, and b = concentration of strong base (i.e., NaOH)

Considering the respective equilibrium relationships, Eq. 5 may also be written as:



with K_w = dissociation constant for water, Ct = buffer concentration, and $K_a'_{H_2PO_4}$ = functional dissociation constant for monobasic phosphate. Once again, the real data may be used to estimate $K_a'_{H_2PO_4}$ by sequentially varying parameters in Eq. 6 until data from the theoretical relationship converges with the real data. These variations can be done easily on a spreadsheet, and the following table represents the results of such a process where $Ct = 0.05$ M.

Aspirin Bolus testing ... continued

Table 1. Species concentrations of the USP Phosphate Buffer System

pH	(H+)	(OH-)	(HPO4=)	b(calc)	b(USP)
5.8	1.58E-06	6.31E-09	3.84E-02	0.038	0.036
6.0	1.00E-06	1.00E-08	5.82E-02	0.058	0.056
6.2	6.31E-07	1.58E-08	8.64E-02	0.086	0.081
6.4	3.98E-07	2.51E-08	1.24E-01	0.124	0.116
6.6	2.51E-07	3.98E-08	1.72E-01	0.172	0.164
6.8	1.58E-07	6.31E-08	2.27E-01	0.227	0.224
7.0	1.00E-07	1.00E-07	2.84E-01	0.284	0.291
7.2	6.31E-08	1.58E-07	3.38E-01	0.338	0.347
7.4	3.98E-08	2.51E-07	3.84E-01	0.384	0.391
7.6	2.51E-08	3.98E-07	4.20E-01	0.420	0.424
7.8	1.58E-08	6.31E-07	4.46E-01	0.446	0.445
8.0	1.00E-08	1.00E-06	4.65E-01	0.465	0.461

In this case, the pH values used are those specified in the USP. The calculated values for base [b(calc)] in the table were obtained with a $pK_{a'}_{H_2PO_4} = 6.88$, and these compare very well with the values from the USP [b(USP)]. Once again, the sum of the squares of the residuals was minimized to obtain the $pK_{a'}_{H_2PO_4}$ estimate.

Since the $pK_{a'}$ for ASA is 3.9 and the dissolution process will be conducted at or greater than 2 pH units above its pK_a , aspirin will behave like a strong acid, contributing its available protons to the solution. Thus, the dissolution of ASA in the phosphate buffer system could be represented by the following proton balance equation:

$$(H^+) = (OH^-) + (HPO_4^{2-}) - b + (ASA^-) \quad \text{Eq. (7)}$$

where, because of the low pK_a , (ASA^-) = concentration of ASA dissolved.

From the solubility perspective, given the data presented earlier, it is evident that any pH in the effective range of this phosphate buffer system could be chosen for the dissolution testing. However, if the objective is to keep pH constant during the dissolution process, it is desirable, for a weakly acidic drug, to identify a medium pH that is greater than the functional pK_a of the buffer system.

For example, the theoretical buffer capacity of a 0.5 M phosphate system, computed by numerical analysis, is presented in Figure 3. As expected, maximum buffer capacity is observed when the pH of the medium is 6.9, corresponding to the estimated $pK_{a'}_{H_2PO_4}$. By selecting a starting medium pH greater than the pH of maximum buffer capacity, the dissolving aspirin, which lowers pH, actually produces an increase in the buffer capacity of the system. Thus, the system becomes progressively

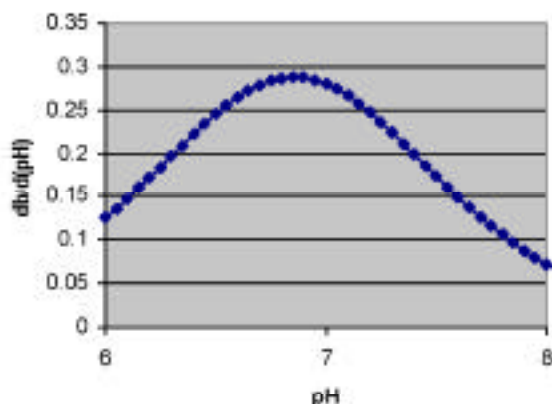


Figure 3. Theoretical buffer capacity vs pH for 0.5 M phosphate buffer system.

more resistant to pH change during the dissolution process.

After analysis using the preceding proton balance equations, 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 result in a system with a pH = 7.0.

Dissolution of Aspirin Boluses

A UV method was used to determine the amount of aspirin dissolved, accounting for the hydrolysis that takes place during the dissolution testing process. Analysis of samples and standards was conducted by simultaneously acquiring absorbance values at 276 and 296 nm, the respective maxima for salicylic acid and aspirin, using 0.01 cm path length cells. Absorptivities were determined for each solute at each wavelength, and the molar concentrations of salicylic acid and aspirin were determined by solving simultaneous equations. The amount of aspirin dissolved was calculated from the total molar salicylate concentration present at each measurement.

Dissolution testing of aspirin boluses was initially conducted using USP Apparatus 2 at 37°C and 50 RPM, with the 0.5 M pH 7.4 Phosphate Buffer as the medium. An automatic sampler was employed, and programmed to collect 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. After the 90 minute sample, the stirring rate was elevated to 100 RPM,

and an additional sample was withdrawn at 120 minutes. The test was repeated at 75 RPM, where dispersion of the undissolved solid was enhanced, and complete release was obtained in less than 60 minutes. Results of the dissolution test are summarized in Figure 4. Liquid from Vessel 3 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 tested disintegrated quickly, and the

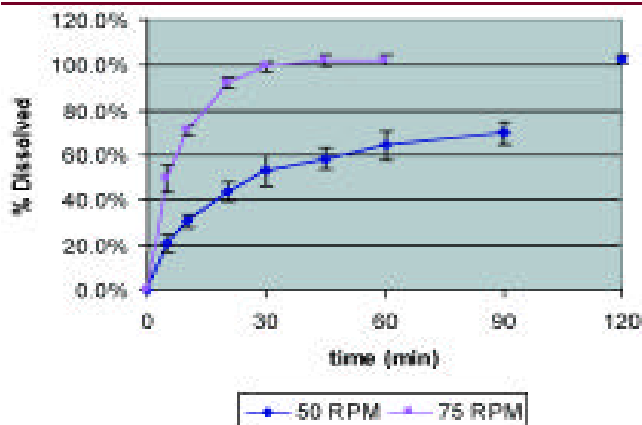


Figure 4. Dissolution of Aspirin Boluses in 0.5 M pH 7.4 Phosphate Buffer at 37 °C.

resulting quantity of solid in dispersion 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.

Conclusions

Dissolution testing of veterinary boluses containing 15.6 g of Aspirin was accomplished using USP Apparatus 2 with conventional volume and stirring rates in an aqueous medium specially designed to provide and maintain sink conditions. A 0.5 M pH 7.4 phosphate buffer system was employed in this analysis and complete dissolution was accomplished in less than 1 hour at 75 RPM. Based on the studies performed here, the bolus dosage forms tested appeared to be of high quality presenting relatively rapid dissolution with little variability.

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