Impact of pH modifiers and drug exposure on the solubility of pharmaceutical products commonly administered through water delivery systems

Paul M. Dorr, DVM, PhD, MACE; Darin Madson, DVM; Spencer Wayne, DVM; Alan B. Scheidt, DVM, MS; Glen W. Almond, DVM, MSc, PhD

Summary

Fifteen antimicrobial powders and aspirin were prepared according to label directions and evaluated for pH and temperature, settling after 5 days, and physical-chemical reactions when pairs of products were mixed. Many products changed state or precipitated when mixed with other products or when the pH was altered.

Keywords: swine, medication, water soluble

Received: June 24, 2008
Accepted: March 4, 2009

Resumen - Impacto de los modificadores de pH y de la exposición a medicamentos en la solubilidad de productos farmacéuticos comúnmente administrados a través de sistemas de suministro de agua

Se prepararon quince polvos antimicrobianos y aspirina de acuerdo a las instrucciones de etiqueta y se evaluaron para pH y temperatura después de 5 días, y reacciones físico químicas cuando se mezclaron productos en pares. Muchos productos cambiaron de estado o se precipitaron cuando se mezclaron con otros productos o cuando se alteró el pH.

Résumé - Impact des modificateurs de pH et de l'exposition des médicaments sur la solubilité de produits pharmaceutiques administrés fréquemment via les systèmes de distribution d'eau

Quinze antibiotiques en poudre et de l'aspirine ont été préparés selon les directives de l'étiquette et évalués pour le pH et la température, la sédimentation après 5 jours, et les réactions physico-chimiques lorsque des paires de produits sont mélangées. Plusieurs produits ont changé d'état ou ont précipité lorsque mélangés avec d'autres produits ou lorsque le pH était altéré.

Large contemporary swine-production systems routinely turn to water delivery systems as a method for administering approved therapeutic agents when circumstances call for mass treatment of entire pig populations. Water medications are used for reasons ranging from the relative ease of the method compared to injectables, to the decreased likelihood of needle-stick injuries and broken needles found in pigs at slaughter, to a desire for a rapid response to therapy. Underlying all decisions to use waterlines for delivering antimicrobials, vaccines, aspirin, vitamins, and electrolytes are assumptions that the medications reach all pigs; that all pigs, including sick pigs, consume the medications; that medications are absorbed; that water delivery systems are functional; and that medicators deliver the desired concentration of medication.

A recently published study challenges many of these assumptions.[1] The author conducted an epidemiological survey investigating the prevalence of problems associated with swine-production drinking systems in North America, Europe, Southeast Asia, and Africa. This study focused on water quality (biological, chemical, or physical contamination), number of drinkers, drinker height, water flow, drinker position, and time spent drinking. The study identified approximately 60 different point-source problems with water administration in these swine-production systems, including antibiotic residues in waterlines that might interfere with the effectiveness of water medication therapy.

Bioavailability, or lack thereof, is also a major concern. Mechanisms of bioavailability interference may include, but are not limited to, a lack of release of the active compound from the pharmaceutical formulation, lack of enterocyte permeability, and gastric or hepatic first-pass effect.[2] Investigators have demonstrated that absorption of orally administered antimicrobials is highly variable.[3-5] While agents such as tiamulin were readily absorbed, others such as spectinomycin and neomycin were poorly absorbed. [3–5] The bioavailability of widely used tetracyclines (oxytetracycline, tetracycline, and chlortetracycline) was low after oral dosing compared to intravenous injection of grow-finish pigs[4,5] Intravenous

PMD: Research and Development, Merial Limited, Duluth, Georgia.

DM: Department of Veterinary Diagnostic and Production Animal Medicine, Iowa State University, College of Veterinary Medicine, Ames, Iowa.

SW: Pipestone Veterinary Clinic, Pipestone, Minnesota.

ABS: Swine Veterinary Services, Pfizer Animal Health, Hampstead, North Carolina.

GWA: Department of Population Health and Pathobiology, College of Veterinary Medicine, North Carolina State University, Raleigh, North Carolina.

Corresponding author: Dr Paul M. Dorr, Merial Limited, 3239 Satellite Blvd, Duluth, GA 30096; Tel: 573-642-5977 ext 1109; Fax: 573-642-0356; E-mail: paul.dorr@merial.com.

This project was supported by private agricultural industry.

This article is available online at http://www.aasv.org/shap.html.

Dorr PM, Madson D, Wayne S, et al. Impact of pH modifiers and drug exposure on the solubility of pharmaceutical products commonly administered through water delivery systems. *J Swine Health Prod.* 2009;17(4):217–222.

or intramuscular injections provided more rapid increases in blood levels of antimicrobials, and greater blood levels, than water medication.[5]

Research conducted at North Carolina State University identified problems in water delivery systems that could potentially result in subtherapeutic dosing.[6] Due to clogged lines (eg, residues from previous treatments, sludge), inconsistent water pressure, and many other variables, flow rate varied with medication delivery and among farms, barns within a farm, pens within a barn, and drinker types.[6] Variation in flow rate at individual drinkers was a factor affecting uniform antimicrobial uptake by pigs. Differences in plasma tetracycline concentrations were attributed to the differences in drinker flow rates and to the dissimilar quantities of antimicrobials consumed by pigs. Another problem associated with ineffective delivery of antimicrobials was medicators that apportioned inconsistently due to sludge, residues, stock-solution solubility, and sediment formation (Figure 1).[6]

The common conclusion of these various research projects is that multiple challenges are associated with mass treating pigs by administering therapeutic agents through waterlines. In situations where antimicrobials are administered for disease control, producers and veterinarians should consider the potential harmful effects of subtherapeutic dosing. First, the possibility exists that little or no medication is provided to the pigs, resulting in little to no benefit to the animal, especially in units where waterlines, medicators, or both are obstructed. Second, subtherapeutic dosing may make subsequent treatment modalities more difficult or ineffective due to selection of subpopulations of resistant bacteria, which in turn may result in a food-safety issue. Also, the emergence of resistant strains may compromise conventional treatment options, which can result in increased or extended morbidity and mortality, increased treatment time, and increased treatment cost.

Because of the many variables involved in the treatment process in field situations, it is often difficult to troubleshoot treatment failure due to waterline problems and subtherapeutic dosing when water-soluble agents are used. Often, however, the following common complaints are registered by producers and service providers in operations where an apparent treatment failure has occurred: the pigs do not drink the medicated water, the pharmaceutical settles out in stock solution, the pharmaceutical does not go into solution at the recommended dose, and the stock solution does not run efficiently through the medicator or waterlines.

Figure 1: Water-soluble product precipitation in stock-solution containers that resulted in clogged medicator input lines. A: Container completely lined with crystals and black sludge. B: Container completely lined with white crystals, with precipitated product floating. C: White precipitate throughout the solution. D: Precipitated product floating.

To determine whether exposure to pH modifiers or pharmaceuticals in water delivery systems contribute to potential pharmaceutical delivery problems, a study was conducted to quantify the solubility and reaction potentials of several commonly used therapeutic products. The overall study objective was to evaluate whether exposure to pH modifiers and other water-soluble products are factors that may interfere with the effectiveness of delivery of water-medication therapy.[7]

Materials and methods

The following 15 commonly administered, commercially available water-soluble therapeutic agents were included in the study: sodium salicylate (Uni-sol; Animal Science Products Inc, Nacogdoches, Texas), acetylsalicylic acid (Aqua Source Water Soluble Aspirin; Paragon, Rainsville, Arkansas), amoxicillin (Amoxil; Smith-Kline Beecham, King of Prussia, Pennsylvania), sulfamethoxazole-trimethoprim (Sulfamethoxazole and Trimethoprim Oral Suspension USP; Hi-Tech Pharmacal Co, Inc, Amityville, New York), potassium penicillin G (AmTech Penicillin G Potassium USP; IVX Animal Health, Fort Dodge, Iowa), gentamicin (Gen-Gard; AgriLabs, St Joseph, Missouri), lincomycin (AmTech Lincomycin Hydrochloride Soluble Powder; IVX Animal Health), neomycin (Neomycin Oral Solution; AmTech IVX Animal Health), neomycin (Neomycin 325 Soluble Powder; Bimeda Inc, LeSueur, Minnesota), tetracycline (Tet Sol 324; Alpharma Inc, Fort Lee, New Jersey), oxytetracycline (Tetroxy HCA-280; Bimeda Inc), chlortetracycline (Penchlor 64; Pennfield Oil Co, Omaha, Nebraska), chlortetracycline-sulfamethazine (Aureomycin Sulmet; Fort Dodge Animal Health, Overland Park, Kansas), sulfamethazine (Sulmet; Fort Dodge Animal Health), tiamulin (Denagard; Boehringer Ingelheim, Ingelheim, Germany), and tylosin (Tylan; Elanco, Greenfield, Indiana).

Each compound was reconstituted to 400 mL of stock solution using distilled water and according to package recommendations for therapeutic dosing through a medicator set at a ratio of 1:128. The following parameters were observed: pH and temperature at the time of mixing the stock solution, settling at 5 days after mixing, observation of a visible chemical or physical reaction when the pH of 20-mL aliquots of the stock solutions were altered with citric acid (Citric Acid Anhydrous, USP/FCC; Archer Daniels Midland Co, Decatur, Illinois; 54.16 gm per L of stock) and household ammonia (10%; 7.9, 15.7, and 31.5 mL per L of stock). The glass thermometer and pH meter were cleaned with alcohol and distilled water between measurements. The pH meter was recalibrated to read a pH of 7 using distilled water between measurements.

After baseline observations were made, new stock solutions (400 mL) were prepared at room temperature in standard laboratory glass beakers and divided into 20-mL aliquots in plastic cups. All aliquots were observed for approximately 30 minutes for reactions to the plastic cups. Each agent was then evaluated for its reactivity with every other agent by pouring a 20-mL aliquot of one product into a 20-mL aliquot of a second product and observing for reactions. If no immediate reaction was observed, the compounds were gently mixed by swirling the cup for approximately 10 to 20 seconds and observing for delayed reactions over the course of 1 day.

Results

pH and reactivity

The range in stock solution pH (Figure 2) was very wide (3.1 to 10.5). After 5 days in solution, film was observed on the surface of the glass beakers containing solutions made with seven of the therapeutic agents: acetylsalicylic acid, amoxicillin, sulfamethoxazole-trimethoprim, potassium penicillin G, tetracycline, oxytetracycline, and chlortetracycline.

Percent reactivity (the proportion of product-product combinations resulting in the formation of a precipitate) ranged from 0% to 53% (Figure 2). Direct compound-by-compound reactions are shown in Figure 3. Although the most acidic substances accounted for a majority of the reactions, precipitation occurred throughout the whole range of pre-test pH values. Examples of reactions are shown in Figure 4.

Acid-base reactions

When the solutions were exposed to pH modifiers (citric acid and ammonia), reactions occurred with nine of the 15 solutions. Acetylsalicylic acid, amoxicillin, sulfamethoxazole-trimethoprim, potassium penicillin G, and sulphamethazine all reacted with citric acid, forming white precipitate or crystallizing. Tetracycline, oxytetracycline, chlortetracycline-sulphamethazine, and tiamulin all reacted with ammonia, forming yellow precipitate or crystallizing.

Discussion

This report presents the results of an in vitro study that examined the fate of water-soluble drug formulations when stock solutions were exposed to other products (pH modifiers and pharmaceuticals) that are commonly administered through drinking-water distribution systems. Results of this study underscore the importance of maintaining clean stock-solution buckets and medicators. The addition of citric acid and ammonia for purposes of pH modification caused residue reactions to occur with nine of the 15 therapeutic agents evaluated. For this reason, when lines are flushed with substances such as chlorine (sodium hypochlorite) or sodium thiosulfate for purposes of cleaning, disinfection, or chelating, the prudent course of action is to complete a fresh-water flush before administering any water-soluble therapeutic product. Failure to do so potentially could result in formation of residue that could clog medicators, waterlines, and nipple drinkers, impeding delivery of therapeutic doses to sick pigs. Whether residue-forming reactions occur through a range of pH values when therapeutic agents are added to water is a question remaining to be addressed.

Residue-forming reactions can also occur when one water-soluble therapeutic agent comes into contact with another. In this study, percent reactivity for the 15 compounds ranged from 0% to 53%, covering an entire range of primary stock-solution pH measurements. The mechanisms by which this happened were not investigated, a limitation of this study. These findings not only further illustrate the importance of cleaning medicators and waterlines between treatments, but also point to the wisdom of restrictions against mixing therapeutic compounds. Another potential health risk to the pigs may involve the accumulation of residues or reaction products throughout the delivery system, which may compromise effectiveness of oral modified-live vaccines administered through the water.

Figure 2: Therapeutic product pH range of water-soluble medications and percent reactivity with other compounds. The dotted line represents pH 7. Bars represent pH, whereas the background area graph (blue) represents the percent reactivity of each compound with the other compounds. For example, chlortetracycline-sulfamethazine had a stock solution pH of 3.1 and reacted with 35% of the other test solutions. Chlor-S = chlortetracycline-sulfamethazine; tet = tetracycline; chlortet = chlortetracycline; oxytet = oxytetracycline; tiam = tiamulin; gent = gentamicin; ASA = acetylsalicylic acid; Na sal = sodium salicylate; amox = amoxicillin; neo1 = neomycin #1; Smz-Tmp = sulfamethoxazole-trimethoprim; PotPen = potassium penicillin G; neo2 = neomycin #2; linc = lincomycin; Sulfa = sulfamethazine.

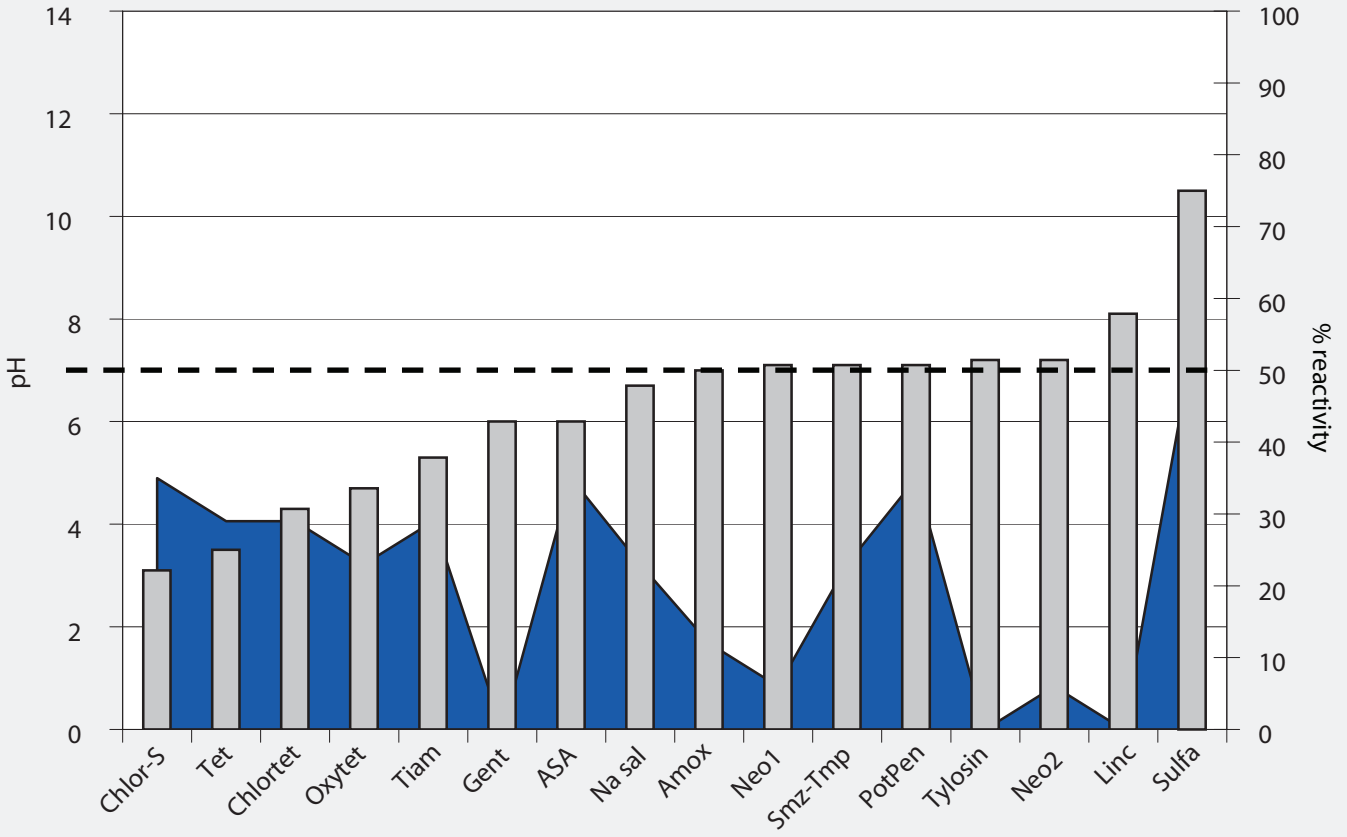
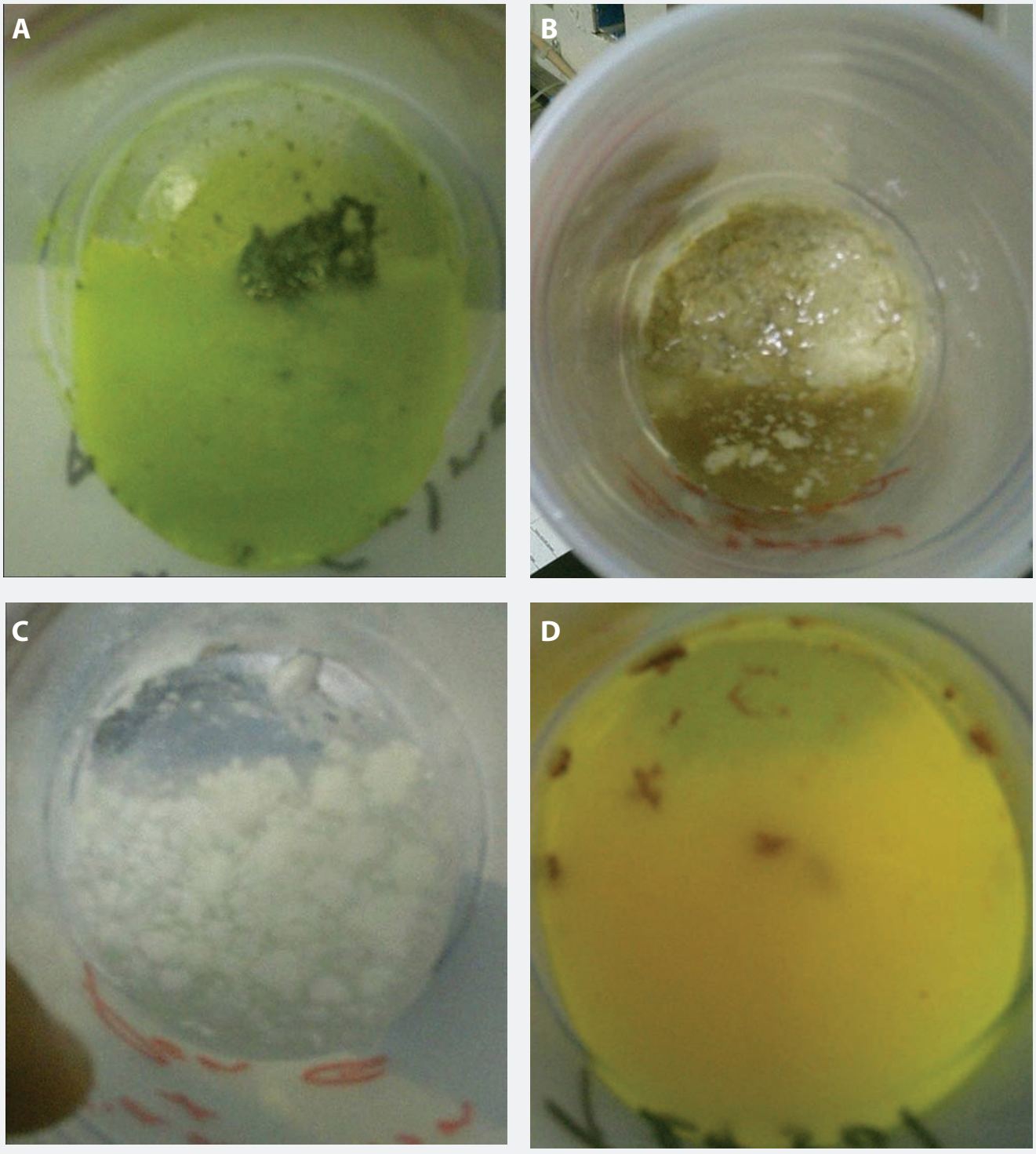


Figure 3. Formation of precipitates when 20-mL aliquots of commonly used water-soluble medications prepared according to label directions were combined in pairs and observed for 24 hours. Medications included in precipitation reactions were aspirin (ASA), sodium salicylate (Na sal), amoxicillin (amox), sulfamethoxazole-trimethoprim (Smz-Tmp), potassium pencillin G (PotPen), neomycin (Neo1 and Neo2), tetracycline (tet), oxytetracycline (oxytet), chlortetracycline (chlortet), chlortetracycline-sulfamethazine (chlor-S), sulfamethazine (sulfa), and tiamulin (tiam). Gentamicin, lincomycin, and tylosin were also tested with other products with no observation of precipitate formation. ■ – precipitate; □ – no precipitate

	Tet	Oxytet	Chlortet	Chlor-S	Sulfa	Tiam
ASA	■	□	■	■	□	■
Na Sal	□	■	□	■	□	□
Amox	□	□	■	□	□	□
Smz-Tmp	■	□	■	■	□	□
PotPen	■	■	□	■	□	■
Neo1	□	□	□	□	■	□
Neo2	□	□	□	□	■	□
Tet	□	□	□	□	■	□
Oxytet	□	□	□	□	■	□
Chlortet	□	□	□	□	■	□
Chlor-S	□	□	□	□	■	□

Figure 4: Examples of reactions that occurred when pairs of certain water-soluble products prepared according to label directions were mixed together. A: Acetylsalicylic acid (aspirin) × chlortetracycline-sulphamethazine: an immediate reaction causing black precipitate formation. B: Oxytetracycline × sulfamethazine: an immediate reaction which resulted in a beige-colored precipitate the consistency of oatmeal. C: Potassium penicillin G × tiamulin: immediate crystallization of product. D: Tetracycline × sodium salicylate: immediate formation of a brown precipitate.



Implications

- Some water-soluble compounds react with each other, potentially clogging medicators and waterlines.
- The use of pH modifiers in drinking water affects the composition of stock solutions of some water-soluble antimicrobials.
- The occurrence of reactivity between water-soluble medications is not clearly explained by pH differences among products.

References

*1. Carr J. Water systems – troubleshooting common mistakes. *Proc ISU Swine Dis Conf Swine Pract.* 2002;99–110.

2. Iwamoto K, Takei M, Watanabe J. Gastrointestinal and hepatic first-pass metabolism of aspirin in rats. *J Pharm Pharmacol.* 1982;34:176–180.

3. Plumb DC. *Veterinary Drug Handbook*. 3rd ed. Ames, Iowa: Iowa State University Press; 1999.

4. Mevius DJ, Vellenga L, Breukink HJ, Nouws JF, Vree TB, Driessens F. Pharmacokinetics and renal clearance of oxytetracycline in piglets following intravenous and oral administration. *Vet Q.* 1986;8:274–284.

5. Nielsen P, Gyrd-Hansen N. Bioavailability of oxytetracycline, tetracycline and chlortetracycline after oral administration to fed and fasted pigs. *J Vet Pharmacol Therap.* 1996;19:305–311.

6. Dorr PM, Nemechek M, Scheidt AB, Baynes RE, Gebreyes WA, Almond GW. Pharmacoepidemiology of water flow variation and pharmaceutical delivery in swine finishing facilities. *JAVMA.* In press.

*7. Dorr P. Residue and pH effects on therapeutic products administered through the water. Abstract presented at Healthy Hogs Seminar; October 2005; Sampson Community College, Clinton, North Carolina.

* Non-referred references.