pH and the Solubility of Antimicrobials in Drinking Water

Dual Consideration of the Stock Bucket *and* the Drinker Lines Using Continuous Water Treatment

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Delivering medication through the waterlines for swine and livestock is not a new practice and can be one of the most efficient methods of providing a true therapeutic dose. However, there can be challenges with solubility of medications in the stock bucket and inside the water lines depending on the pH of the source water. Certain medications (powdered antibiotic formulations) will dissolve and then remain dissolved differently, sometimes depending on the acidity or alkalinity (or pH) of the drinking water. There are many factors other than pH that can also influence solubility, stability, bioavailability, and therapeutic potential. These include other water contaminants (such as iron and manganese), solubility of the molecule (the raw drug dispersion actually prefers oil vs water), particle size of the drug and carrier, other "non-active" ingredients in the drug bucket/packet, cleanliness of the stock bucket, physical attributes of the product (like coatings or encapsulation) and water temperature.

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Certain medications or certain classes of medications optimally require different pH ranges to completely dissolve and remain in solution during the medication process. Water can generally be broken down into three categories: acidic (pH <7), neutral (pH =7) and basic (pH >7). Therapeutic medication's preferred solubility can also be separated into the same three categories (or buckets) **[See Table 1]**.

TABLE 1. RANGE OF RELATIVE pH OF WATER-ADMINISTERED MEDICATIONS (COMMON TRADE NAME AND MANUFACTURER)[1]

Acid (pH below 7)

Amprolium (Amprol® – Huvepharma), (AmproMed™ P – Bimeda)
Chlortetracycline (Chloronex® – Huvepharma), (Pennchlor 64® – PharmGate)
Gentamicin (Gentamed™ – Bimeda), (Gen-Gard® Soluble – AgriLabs)
Lincomycin hydrochloride (Lincomycin™ Soluble – Huvepharma) (Linxmed-SP® – Bimeda)
Lincomycin + Spectinomycin (SpecLinx-50® – Bimeda), (L-S 50 Water Soluble® – Zoetis)
Oxytetracycline (Oxytet® Soluble – Huvepharma), (Tetroxy® – Bimeda), (Pennox 343® – Pharmgate)
Spectimomycin (Spectam®/SpectoGard® Water Soluble – Bimeda)
Tetracycline (Tet-Sol™ – Huvepharma), (TetraMed® 324 – Bimeda), (Tet TC Vet 324 – VetOne)
Tiamulin (Denagard® 12.5% liquid – Elanco), (Triamulox™ – Zoetis)
Tilmicosin (Pulmotil® AC – Elanco)
Tylvalosin (Aivlosin® – PharmGate)

Neutral (pH = 7.0)

Neomycin Sulfate (Neo-Sol® 50 – Huvepharma), (NeoMed® – Bimeda)
Penicillin G Potassium (R-Pen® – Huvepharma), (PenAqua Sol-G® – Bimeda)

Basic (pH above 7)

Bacitracin Methylene Disalicylate (BMD® Soluble – Zoetis)
Erythromycin (Galimycin® PFC – Bimeda)
Sulfadiomethoxine (SDM – VetOne), (SulfaMed G® – Bimeda)
Sulfamethazine (SMZ-Med® – Bimeda)
Sulfamethazine + Sulfamerazine + SQ (PoultrySulfa – Huvepharma)
Sulfaquinoxaline; SQ (34% Sul-Q-Nox – Huvepharma)
Tylosin (Tylan® – Elanco), (Tylovet® – Huvepharma), (Tylosin – VetOne), (Tylosin Tartrate – Bimeda)

One of the most common methods used to address these specific pH requirements is sometimes, depending on the pH of the incoming water, to adjust the pH of the medication stock solution. Generally, there are three methods: The first method is using a weak acid (like citric acid) to create slightly more acidic water with a target solution that has a pH target below 6.5. The second method is to add sodium bicarbonate (baking soda) to drive the pH up to a maximum of 8.4. The third method is to add ammonia to borrow a proton from water and produce more hydroxide, making the water more alkaline. All of these methods work to address the solubility concerns in the stock solution container (delivery step 1), but what about the source water inside the waterlines being dosed by the medicator from the stock solution (delivery step 2)?

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More often than not, the stock solutions will be dosed at a ratio of 1:128 or 0.78% by volume, so the pH alteration that has been done to this water is quickly going to be nullified (i.e., "buffered") by well water in the waterline, as it will comprise greater than 99% of the mixture. If the pH of the source water is not pH-aligned for a specific medication, there are two risks for the grower and integrator/processor: 1) there is an under-dosing risk via the medication precipitating out of the water into the bottom curvature of the PVC waterline pipe and biofilm/gunk, and 2) there is a drug residue risk by delaying drug delivery to the hog due to settling and delayed release caused by physical dislodging/slugging of antibiotic during high water

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flow times (i.e., older and larger animals consuming more water at a greater rate, hotter weather).

The good news is this problem can easily be corrected. Most progressive farms today have been retrofitted with a metering pump system for water treatment and continuous waterline disinfection. This is usually a two-part system: one with a chlorine (i.e., chlorine dioxide precursor–chlorite) and one with an acid to activate the chlorine via acidification. The acid is the piece we are interested in for the purpose of assisting antibiotic solubility. The acid, in this case, is going to be used both for activation of the ClO_2 precursor *and* for pH alteration of the water for acid soluble antibiotics. As discussed and depicted in **Table 1**, pH certainly impacts solubility of antimicrobial medications in water.

If a tool has already been installed that has the ability to alter the pH of the water, why not use it? There are a few pieces of information that need to be known for this to be effective. The process to optimize solubility for oral antimicrobials is:

1. **What is the starting pH of the source/well water?** You can determine this with a simple pH meter or good, high-color contrast pH strips.
2. **Match the medication.** The second piece will be to match the medication that is going to be (prescribed) administered with the pH range that is needed for solubility of the medication in the stock bucket. Once these are known and a general, desired pH has been established from **Table 1**, it may be as simple as using the acidified water to make the stock bucket solution. There are going to be circumstances where you do *not* want to be lowering the pH of the water (i.e., basic or alkaline antibiotics). For example Sulfadimethoxine, or SDM, requires basic (pH > 7) water to remain optimally soluble. In a situation where SDM has been chosen as the infection treatment, and the site has an acid dosing pump as part of continuous water treatment, it would be advised for *the acid to be turned off for the duration of the medication process* to ensure the maintained solubility of the product. In this case, it is assumed that the well water is slightly or significantly alkaline, which is usually the case for most well water. For neutral pH antibiotics, the acid levels in continuous water treatment may simply be temporarily turned down for water treatment and stock bucket filling, to achieve a neutral pH.

With a few pieces of information and proper, comprehensive water treatment tools, the pH of the water can be tailored to the medication to help solubility and stability of the drug not only in the stock solution but throughout the barn's waterlines as well.

See the next page for a quick guide to pH and soluble medication.

A Quick Guide for pH and Soluble Medication

1. **Sulfas, BMD soluble, erythromycin, and tylosin (like basic pH) + acidified water = likely precipitants**
   - i. Sulfonamides will precipitate out of solution and possibly plug the medicator and/or drinker system, or settle in the water line/scale/biofilm in acidic pH. Also, erythromycin, BMD, and tylosin can precipitate in acidic conditions.
   - ii. Do not mix with and turn off any acid you are using for water treatment while running any of the sulfa drugs (SMZ, SDM, SQ, or sulfa combinations), BDM, erythromycin, or tylosin (Tylan, Tylovet, or Tylosin Vet One).
   - iii. If you turn off the acid and chlorine system, turn it back on immediately after medication has been delivered.
2. **Tetracyclines, Linco/Specto, or Gentamicin, Amprol, Tiamulin, Tilmicosin, or Tylvalosin (like acidic pH) + alkaline well water = likely precipitants**
   - i. Tetracyclines (oxytetracycline, chlortetracycline, tetracycline), lincomycin, spectinomycin, gentamicin, tiamulin, tilmicosin, tylvalosin, and amprolium can precipitate out of solution and possibly plug the medicator and/or drinker system, or settle in the water system's delivery lines/bioscale/biofilm.
   - ii. If you are treating drinking water continuously with acid and chlorine, leave the acid running and you may or may not be instructed by your technician/flock supervisor to turn off the valve from the chlorine bucket.
   - iii. If you are not treating water continuously, add acid because most stock solutions in the bucket will dissolve and not precipitate (stabilize) with pH below 6. Always check the label for presence of powdered acid already on the product.
   - iv. If you turn off the chlorine during acid + medication, do not forget to turn the chlorine valve back on immediately after the bucket is empty.
3. **Penicillin and neomycin are near-neutral pH chemistries. There is no need to adjust pH to maintain solubility in the stock bucket if farm water is near neutral. Adjust pH of well water in the stock bucket by buffering with baking soda, in the case of very high or low pH. Follow manufacturer's recommendations.**
4. **Do not co-mix other soluble products with the antibacterial solution in the stock bucket (other OTC, natural extract, or prescription medications, iodine, milk-based products, aspirin, vitamins, electrolytes, etc.).**
5. **In the rare case that farm well water is naturally acidic and you are using sulfonamides, BMD, erythromycin, or tylosin in medicators, the addition of ammonia to raise the pH of the stock solution may increase the stability and availability of these antimicrobials. Follow manufacturer's recommendations.**
   - i. To improve solubility, add 2-4 ounces of household or sudsy ammonia per gallon of stock solution + medication.
   - ii. Do not add any acid (including citric acid) to sulfas, BMD, erythromycin, or tylosin in the stock bucket.

**Flush waterlines after medicating to minimize risk of residual carryover in waterlines, and always follow instructions and recommendations on the product label.*

Reference

[1]Derived from "Medicating Mistakes: Proper Steps when Medicating", Stephen Clark, DVM, version 1.3, 2008