Solubility and stability

Introduction

This is the fourth in a series of articles on how to optimize water medication. Previous articles dealt with a general overview and descriptions of the requirements for water quality and the drinking water system. In this article we will cover the chemical characteristics that will make a product suitable for water medication: solubility and stability.

Solubility

Of course a water medication product has to be soluble. To be more specific it has to dissolve in water in sufficient quantities to get the required dose into the animals given their water intake.
Solubility can be measured in two ways:

1. maximum solubility: the maximum amount of product that can be dissolved in 1 litre of water
2. solubility rate: the time it takes to completely dissolve a product

The first one is critical because if maximum solubility is too low it will not be possible to give the correct dose. The second one mainly has an impact on convenience.

Solubility of a product is depending on the solubility of the active ingredient and temperature, pH and constitution of the water.

Active ingredient

Amoxicillin, trimethoprim, and chlortetracyclin have a low or very low solubility while sodium salicylate, phenoxymethyl-penicillin and tiamulin are very easy to dissolve. For example, it is possible to dissolve more than 1 kg of sodium salicylate in 1 litre of water!

Water

The physical and chemical characteristics of the water have a big impact on solubility. As we all know solubility tends to be lower when water is colder. Solutions should be prepared in cold to lukewarm water to avoid inactivation of the molecule by high temperatures (amoxicillin!).

What is less known is the fact that also pH is important. This opens up the possibility to increase the solubility of an active by including acid or alkaline additives in the formulation in order to create the optimal pH for the active molecule in a solution.

Finally some elements in the water can bind to active ingredients and form complexes that do not dissolve. For example high levels of calcium and/or magnesium (hard water) or iron can prevent tetracyclines from dissolving and trimethoprim/sulfonamide can bind to organic substances in the water.

Stability

Stability is not as well-known but is as important as solubility: once a product is dissolved the active ingredient should stay active and dissolved long enough to get to the animals.

Stability is determined by comparing the concentration at any time point with the concentration at the beginning. According to European standards a solution is stable as long as the concentration of the active ingredient is more than 90% of the concentration right after the solution has been prepared. If for example the concentration of the active in a solution after 12 hours is 92%, the solution is considered “stable for 12 hours”.

Like solubility, also stability depends on temperature, pH and constitution of the water.
The active ingredient can disappear because of either precipitation or degradation.

Precipitation
When a product initially dissolves but over time a deposit becomes visible again this is called precipitation. Again this is depending on temperature, pH and constitution of the water.

Precipitation may occur after cooling down of a solution that has been prepared in hot water. This is another reason not to use hot water for preparing stock solutions.

Also pH is critical: you need the right pH to dissolve a product, but it is also important to maintain that pH for a longer period of time. In other words, it is important to have sufficient buffering capacity in the solution to prevent a change in pH over time due to exposure to oxygen. Without the right buffers in sufficient quantities the pH will not remain below 6,5. This means doxycycline concentrations in the solution will decrease and the solution will show severe dark brown precipitation within 24 hours (see Figure 1 and 2).

Finally some elements can cause precipitation as well. If a farm has (galvanized) iron pipes the product may dissolve without problems but will precipitate once it gets into the pipes where the iron levels are much higher.
In general precipitation is reversible: increasing the temperature or changing the pH will resolve the precipitation.

Degradation
This is the process where an active molecule is broken down to substances that do not have the desired effect anymore (or even sometimes are harmful).
It should be noted that degradation often is not visible. Amoxicillin solutions for example will stay perfectly clear even if all active has been degraded.

Degradation may occur when using hot water (60 °C). It has been demonstrated that when dissolving amoxicillin in hot water immediately 20% of the active ingredient is destroyed.

Degradation may also be seen if the pH of a solution is too low or too high. Amoxicillin for example will degrade completely within a couple of hours if the pH exceeds 8 (Figure 3).
Degradation by definition is irreversible.

Optimal balance

Unfortunately the pH required for the best solubility and the best stability are not always the same (Figure 3). For example the solubility of amoxicillin can be increased significantly by increasing the pH, but when the pH will be higher than 8 the stability will decrease rapidly (the active ingredient is degraded).
This again demonstrates the importance of including the right buffers in the right amounts in the product to maintain the optimal pH. Adding acid or basic ingredients on your own is nothing more than a wild guess.

Summary
Of course a water medication product has to be soluble to a level that allows adequate

dosing of the animals given their water intake. Stability however is equally important to make sure that the molecule remains active and dissolved long enough to get to the animals. Both characteristics are depending on the active ingredient and temperature, pH and constitution of the water.

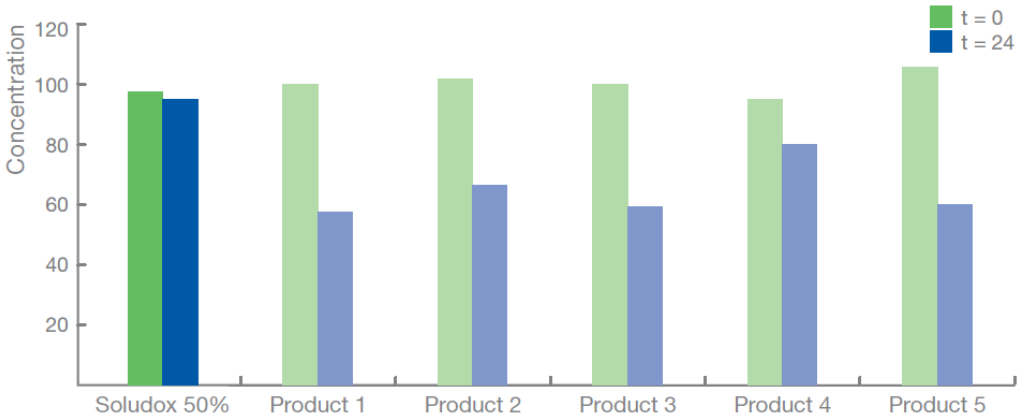

Figure 1 Stability of different doxycycline products.

Figure 2 Dark brown precipitation of doxycycline after 24 hours if pH is too high.

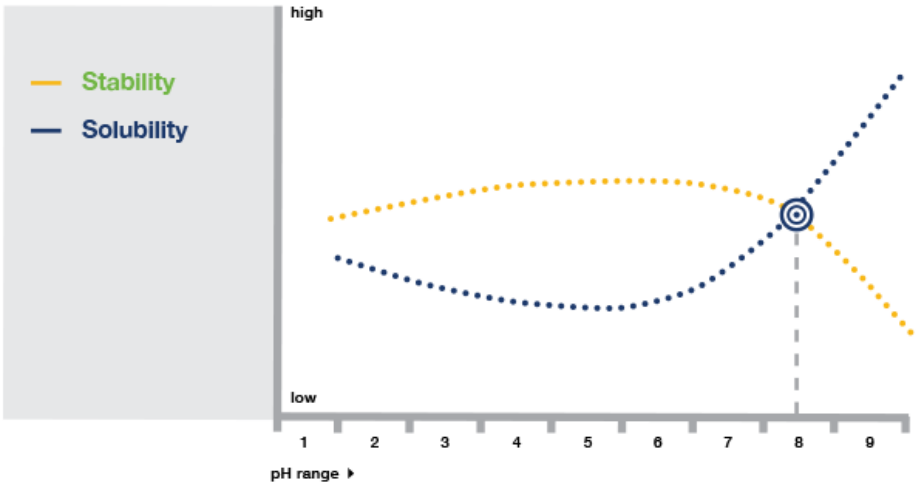

Figure 3 solubility and stability of amoxicillin depending on pH