Understanding the key parameters for water medication

Veterinary antibiotic, anthelminthic and anti-inflammatory products can be administered orally via medicated premixes in feed or via the drinking water. For drinking water administration, either large bulk tanks or highly concentrated stock solutions in combination with a water proportioner are used. These proportioners are increasingly installed worldwide as they provide full control over the product administration.

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Water medication offers several advantages:

- Fast clinical results: Treatment can be initiated immediately after the veterinarian's diagnosis. Prompt treatment in the early stage of a disease outbreak ensures a rapid clinical response.
- Flexible: The dosage and duration of the treatment can be adjusted to each specific field case.
- Sick animals usually continue to drink whilst they may eat less.
- Minimal labour requirements.
- Animal friendly therapy.
- A higher bio-availability of some products can be demonstrated when administered via the drinking water.

After selecting the most appropriate active substance, the choice of the product formulation exhibiting a high solubility and stability in the drinking water is of major importance. Besides the product specific formulation, the quality of the water also largely determines the final clinical outcome.

Formulation

Optimal results in the field can only be achieved when the active substance reaches the infection site in the treated pigs at sufficiently high levels for a sufficiently long time. The formulation should provide maximal solubility and stability to the active compound without any impact on palatability.

The dissolution profiles and stability tests in water of different qualities (low/high pH, 4°C/20°C) are a key part of the product registration. Therefore, Huvepharma formulations for administration in the drinking water are extensively tested before product release.

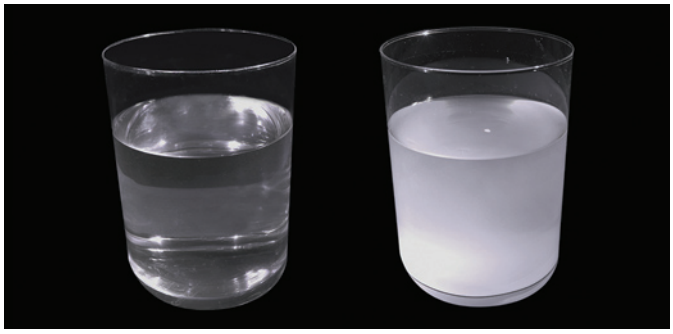
The formulation of specific salts (tylosin tartrate, doxycycline hydrochloride) leads to improved physicochemical properties such as solubility, stability and bio-availability.

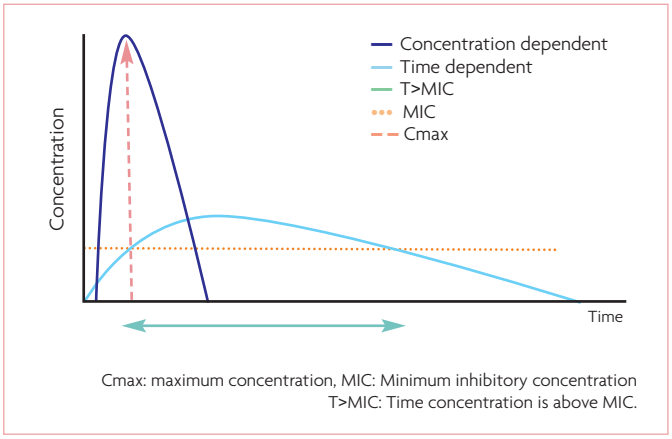
Moreover, crystallised granules of tylosin tartrate (Pharmasin 100% water soluble granules – Huvepharma) demonstrate excellent solubility in combination with a low dust content.

In general, benzimidazoles are difficult to dissolve. Huvepharma developed a unique nanosuspension technology for fenbendazole use in drinking water (Pigfen). This milling technique provides a substantial particle size reduction of the fenbendazole crystals into the nanometer range.

These small particles demonstrate a much larger contact surface with the water molecules, ensuring optimal distribution in the pipelines of the drinking water system. The subsequent higher bio-availability results in maximal efficacy of the implemented deworming programmes on farm.

Fig. 1. Dissolutions of amoxicillin trihydrate at the same concentration. Left: Huvamox (Huvepharma). Right: another amoxicillin based product.





Cmax: maximum concentration, MIC: Minimum inhibitory concentration
T>MIC: Time concentration is above MIC.

Fig. 2. Two types of antibiotics with an ideal pharmacokinetic profile in regards to efficacy.

Solubility

A perfect solubility is characterised by a fast and complete clear dissolution without any undissolved particles in the drinking water or precipitation of the active substance at the bottom of the stock container (Fig. 1). This quality parameter enhances the intestinal absorption and the subsequent bio-availability to achieve an optimal clinical response.

A complete dissolution avoids blocking the filters of the proportioner and the nipples in the pens. Additionally, the risk of residues in the pipelines of the water delivery system, and consequently also in the pig meat, is substantially reduced. This ensures maximal safety with regards to the withdrawal time before slaughter.

Solubility is the key parameter when using medicines in highly concentrated stock solutions. If the maximal solubility is exceeded in the stock solution, the product needs to be dissolved in a larger volume of water and the settings of the proportioner adjusted accordingly. The use of a clean stock container and gently stirring after the preparation of a dissolution is part of good farm management.

For optimal results, concentration dependent antimicrobials like aminoglycosides are preferably administered via pulse dosing. This means that the active substance is administered at a high concentration for a short time period (for example four hours) in the drinking water.

A peak concentration several times higher than the Minimum Inhibitory Concentration (MIC) of the pathogen in the target tissue results in the highest clinical efficacy.

The maximum concentration Cmax/MIC is the most important pharmacokinetic parameter (Fig. 2).

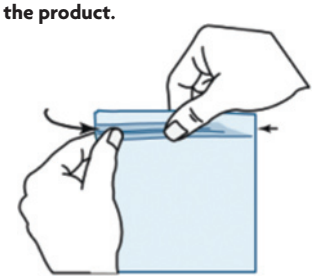
As pulse dosing requires high concentrations of the active compound, perfect solubility is crucial for these concentration dependent antimicrobials.

Several physico-chemical parameters of the drinking water such as temperature, pH, presence of minerals and the water hardness (calcium, magnesium) have an enormous impact on solubility and

stability, hence highly influence the final efficacy.

- Some medications are quite difficult to dissolve, particularly in cold water. Often, a higher speed and rate of dissolution is observed when using water at room temperature.
- Active substances optimally require different pH ranges to completely dissolve and remain in dissolution during the medication period. The pH expresses the acidity or alkalinity of the drinking water, which is region dependent. Water can be classified into three categories: acidic (pH<7), neutral (pH=7) and alkalinic (pH>7).
  - Products based on amoxicillin, tylosin and sulphonamides demonstrate the highest solubility in alkalinic water.
  - On the other hand, antimicrobials belonging to the tetracyclines, trimethoprim and tiamulin optimally dissolve in acidic drinking water. Therefore, some tetracycline based products include citric acid as a carrier to ensure maximal solubility.
  - One of the most common methods used to address these specific requirements is, depending on the pH of the water, to adjust the pH of the medicated stock solution.
- Less absorbable complexes can be formed when antimicrobials belonging to the tetracyclines group are dissolved in water with an elevated concentration of minerals like iron, manganese, calcium and magnesium. These complexes often lead to a blocking of the water delivery system and a substantial reduction of bio-availability. The addition of organic acids in hard water reduces this binding capacity to tetracyclines.
- Combinations of medicines are often incompatible and the effectiveness may be reduced. These combinations need to be avoided unless specifically directed by the veterinarian.

Resealable zipper bags preserve the product.



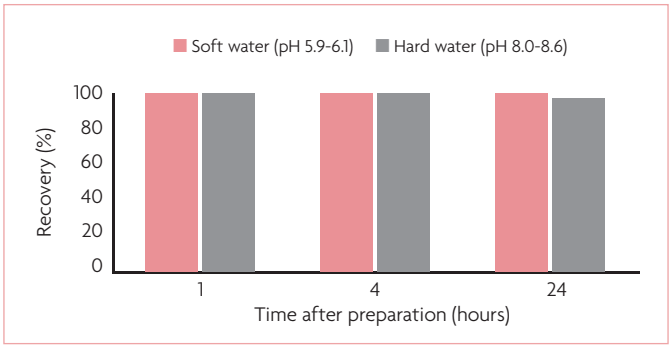


Fig. 3. Recovery of amoxicillin trihydrate in Huvamox as % of the original concentration over 24 hours in two qualities of water.

Stability

The formulation of a water soluble product needs to be stable in the drinking water over a sufficient period of time. Product stability ensures maximal recovery of the original concentration of the active substance after the start of treatment and allows a homogenous dose administration.

Correct dosing of the active compound ensures optimal and fast efficacy of the prescribed treatment. Furthermore, it also fits with the concept of prudent use of antimicrobials, as the susceptibility is not compromised in the long run. Ideally, the stability in drinking water is 24 hours.

However, most veterinary products containing amoxicillin have a limited stability of 12 hours after dissolution in the drinking water. Therefore, these stock solutions should be renewed twice a day. Huvepharma recently launched a water soluble product containing 800mg/g amoxicillin trihydrate (Huvamox).

The well balanced ratio of specific excipients in this formulation and the quality of the active provide a superb stability for 24 hours after dissolution in combination with an excellent solubility (Fig. 3).

Typically, time dependent antimicrobials like amoxicillin, tylosin, tilmicosin and tiamulin demonstrate the highest efficacy when concentrations in the target tissue exceed the MIC of the causative agent for a longer time period. Continuous medication over 24 hours is recommended for this group of antimicrobials. The time period during which the concentration is just above the MIC at the infection site is the most important pharmacokinetic parameter (Fig. 2). Hence, stability is of uppermost importance for time dependent antimicrobials. Packaging features are also crucial for product stability even before administration in the drinking water. Water soluble products marketed by Huvepharma are packed in resealable zipper bags in order to avoid contact with moisture after first opening.

Quality of the drinking water

The quality of the drinking water and the hygiene of the water delivery system play an important role. Some medicines not only contain the active substance, but also sugars like lactose. Organic material, minerals and sugars can create a biofilm in the pipelines. This biofilm impairs the water quality, reduces the delivery rate and may harbour beta-lactamase producing bacteria, which decrease the stability of penicillins.

A clean stock container or bulk tank, free from any organic material is crucial to prepare the stock solution properly. Therefore, regular cleaning and disinfection of the pipelines and storage tanks is highly recommended.

Disinfectants (like chlorine and hydrogen peroxide) and organic acids often interfere with the stability of the medicines in the water, justifying a temporary cessation of the use of these products when antimicrobial treatment is initiated.

An annual quality check of the drinking water for physico-chemical and bacteriological parameters is generally advised. If water quality is not met, product efficacy cannot always be guaranteed and necessary adaptations should be carried out without delay. The use of tap water for drinking water medication should be considered if water of a good quality is not available.

Conclusion

Maximal clinical response following administration of veterinary products in the drinking water can only be achieved if the selected product is highly soluble and stable under the conditions present on the farm.

The use of products demonstrating a high solubility and stability avoids sub-therapeutical concentrations in the target tissue.

Consequently, both solubility and stability contribute to the responsible use of antimicrobials to a large extent. Your veterinary surgeon can advise you on the practical use of medicines in drinking water. ■