

T E C H N I C A L

Overview

Stability of NUFLOR® 2.3% Concentrate Solution When Exposed to Common Water Line Chemicals or Agents

*US Swine Technical Services
Schering-Plough Animal Health Corp.*

NUFLOR is highly stable in stock solutions and post-medicator water lines, even in the presence of other common chemicals or agents.

I N T R O D U C T I O N

Veterinarians and managers of integrated swine production systems often encounter herd treatment situations (e.g., respiratory disease outbreaks) that are best remedied by administering approved chemicals/agents through water lines. Antimicrobial treatment of swine via drinking water has long been recognized as a fast, convenient, and labor-saving method of mass-medication compared to parenteral treatments. Furthermore, drug administration through drinking water helps ensure delivery of effective doses of antimicrobial agents to pigs that are off feed.

Agents appropriate for drinking water administration include antimicrobials, non-steroidal anti-inflammatory agents (NSAIDs), and vitamins (and a variety of chemicals are also routinely used in swine facilities to disinfect and clean water lines). Unfortunately, physical factors (e.g., variation in pH,

stock solution solubility/precipitation, line cleanliness, water chemistry, dietary composition, and ambient temperature) as well as biological factors (e.g., presence of disease and palatability) can interfere with the delivery of intended dosages of water medications to swine.

Research has been conducted to evaluate the stability and reactivity of water-soluble NUFLOR®, a powerful antimicrobial, in the presence of other common water line chemicals and compounds used in swine production facilities.

NUFLOR 2.3% Concentrate Solution

Nuflor 2.3% Concentrate Solution is a fast-acting water medication containing florfenicol, a novel broad-spectrum antibiotic. Florfenicol was discovered and developed by

Schering-Plough, culminating a search for a new therapeutic agent with an efficacy and safety profile that would be superior to that of chloramphenicol.¹ Since its discovery, florfenicol has been the subject of several years of intensive world-wide research.

Florfenicol, the active ingredient of NUFLOR®, is highly lipophilic, a feature that enhances penetration and concentration in tissues and helps the drug widely distribute into serum, lungs, and the gastrointestinal tract of pigs. Florfenicol is effective against a broad range of Gram-positive and Gram-negative, aerobic and anaerobic bacteria isolated from domestic animals. In the U.S., NUFLOR 2.3% Concentrate Solution is approved for administration in the drinking water for 5 consecutive days (400 mg/gallon or 100 ppm, providing 10 mg florfenicol/kg body weight/day) for the treatment of swine respiratory disease associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Salmonella choleraesuis*, and *Streptococcus suis*.¹

Experimental Design

A laboratory study was conducted to evaluate the effects of pH modifiers, line sanitation solutions, NSAIDs, and various water-soluble supplements on the stability and reactivity of NUFLOR 2.3% Concentrate Solution administered through the drinking water.² The study evaluated the following water-soluble agents for pH changes, temperature changes, and chemical reactivity with florfenicol:

Medicinals/NSAIDs

- acetylsalicylic acid (aspirin)*
- sodium salicylate (liquid aspirin)
- ibuprofen

Sanitation/Chelating Agents

- ammonia
- bleach
- citric acid*
- hydrogen peroxide
- sodium thiosulfate*

Nutritional Agents

- milk replacer
- vitamin supplement
- Solutein™ (plasma protein)*

*=solids; all others in liquid form

All agents were evaluated and mixed based on manufacturer recommendations (pre-medicator stock solutions) for dosing through a medicator set at a ratio of 1:128 (except milk replacer), and at the resulting concentrations that occur in the drinking water (post-medicator water lines). Pre-medicator interactions were assessed by preparing a stock solution of NUFLOR antibiotic and adding appropriate amounts of stock solutions of the various agents. Similarly, post-medicator water line concentrations of each agent were mixed with post-medicator NUFLOR concentrations for analysis. All NUFLOR stock and post-medicator solutions were mixed in glassware with deionized water and evaluated for changes in pH, temperature, and appearance (precipitate). Florfenicol concentrations were assessed by HPLC at 3 time points (0, 5, 24 h) after mixing.

Results

No changes in appearance (precipitation) were observed when NUFLOR was mixed with the other test

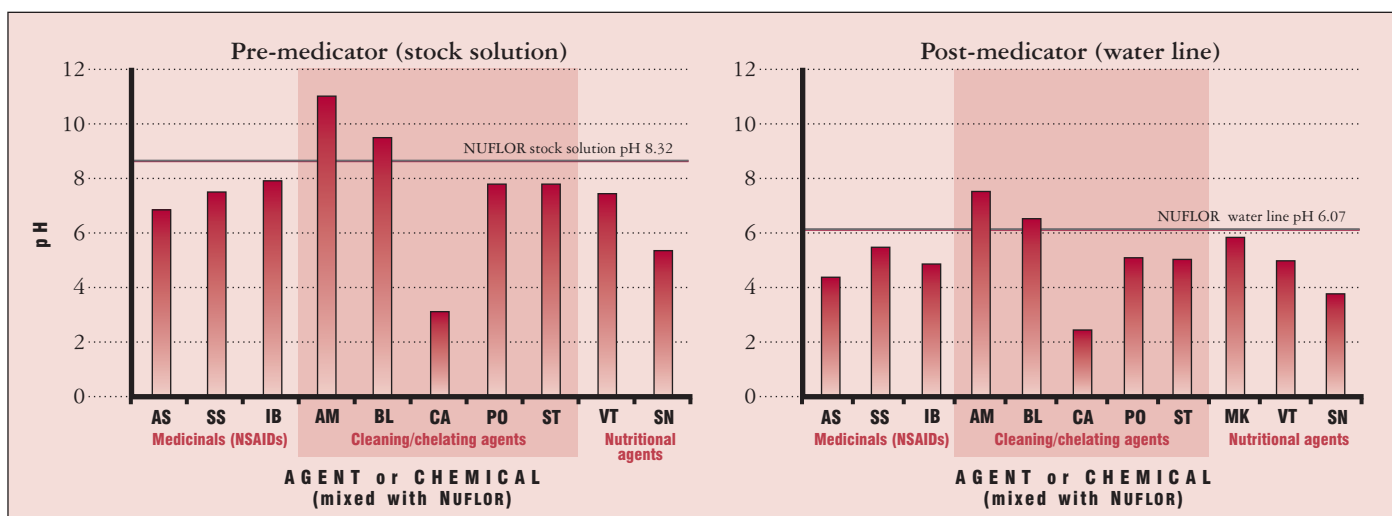


Figure 1. Average pH of pre-medicator stock solutions and post-medicator water line solutions of various common chemicals/compounds in the presence of Nufloor. (AS=acetylsalicylic acid; SS=sodium salicylate; IB=ibuprofen; AM=ammonia; BL=bleach; CA=citric acid; PO=hydrogen peroxide; ST=sodium thiosulfate; MK=milk replacer; VT=multivitamin supplement; SN=Solutein)

substances at the pre-medicator stock concentrations or post-medicator water line concentrations, and no significant temperature changes were observed after mixing. Substantial pH modifications were detected in many of the NUFLOR[®]/agent mixtures for both pre-medicator stock solutions as well as the post-medicator water line solutions (Figure 1). pH changes were likely a characteristic of the additive and not a result of interaction with NUFLOR. Citric acid, Solutein, and ammonia exerted the greatest effects on pH when mixed with NUFLOR.

The impacts of the various chemicals/agents on florfenicol concentrations are summarized in Figures 2 and 3 for the pre-medicator stock solutions and post-medicator water line concentrations, respectively (Tables 1 and 2 contain the numerical values). High florfenicol concentrations (as a percent of the theoretical target concentration) were retained in the presence of all test agents over the 24 hours of testing, indicating little degradation of activity or interference with florfenicol. The greatest impact was exerted by bleach, which was expected due to the moderate degree of reactivity known to exist between florfenicol and chlorine. The NUFLOR 2.3% Concentrate Solution label instructs that chlorinators should be turned off during administration.

These various physico-chemical observations demonstrate that NUFLOR 2.3% Concentrate Solution is highly stable in the presence of agents commonly administered to pigs in drinking water. NUFLOR can be expected to provide appropriate levels of effective antimicrobial activity to pigs even when other common agents used in swine production facilities are present in the water distribution system.

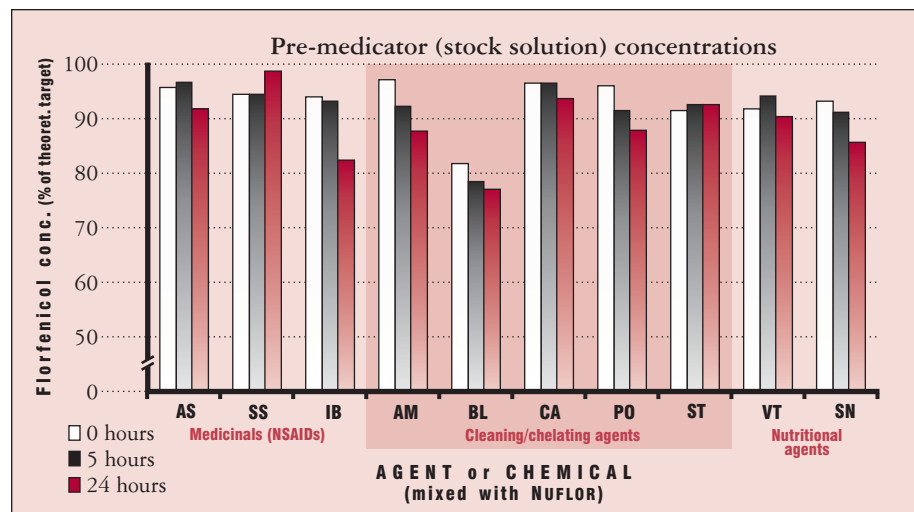


Figure 2. Florfenicol concentration (as % of initial theoretical target) in pre-medicator stock solutions measured in the presence common chemicals/agents at 0, 5, and 24 h after mixing.

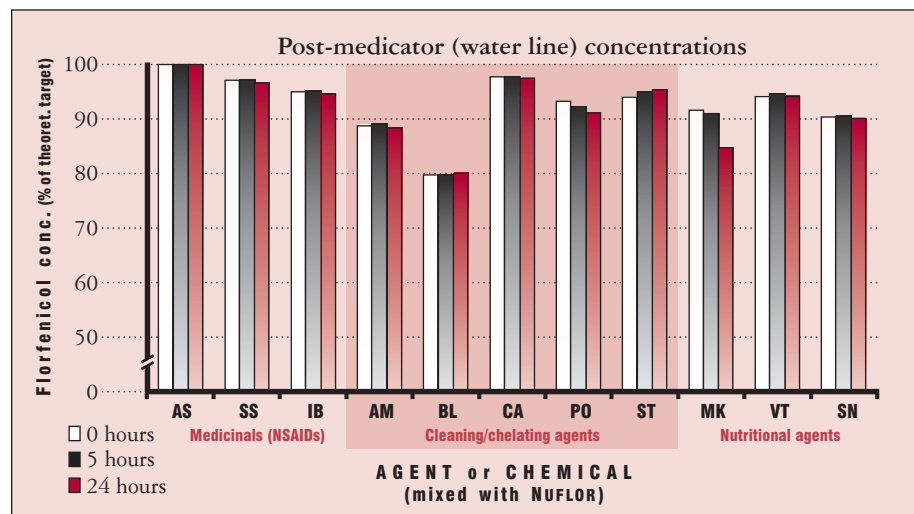


Figure 3. Florfenicol concentration (as % of initial theoretical target) in post-medicator water line solutions measured in the presence common chemicals/agents at 0, 5, and 24 h after mixing.

NUFLOR Administration Characteristics and Recommendations

NUFLOR 2.3% Concentrate Solution is safe and easy to administer to swine through either proportioners or bulk-tank systems. Stability research has been conducted to provide information regarding compatibility with

various types of water at different levels of pH, water hardness, and extent of chlorination.³

Several conditions related to water quality may affect the final concentration of florfenicol delivered to the pigs being treated. In regard to chlorination, studies found a drop of about 10 ppm florfenicol immediately after addition of 0.5 ppm chlorine to the

Chemical/Agent	Florfenicol concentration (% of theoretical target)		
	0 hours	5 hours	24 hours
<i>Medicinals/NSAIDs</i>			
Acetylsalicylic acid	95.7%	96.6%	91.8%
Sodium salicylate	94.4%	94.5%	98.7%
Ibuprofen	94.0%	93.2%	82.4%
<i>Cleaning/Chelating</i>			
Ammonia	97.1%	92.3%	87.7%
Bleach	81.8%	78.5%	77.1%
Citric acid	96.5%	96.5%	93.7%
Hydrogen peroxide	96.0%	91.4%	87.8%
Sodium thiosulfate	91.5%	92.6%	92.6%
<i>Nutritional</i>			
Vitamin supplement	91.8%	94.1%	90.4%
Solutein	93.2%	91.2%	85.6%

Table 1. **Pre-medicator (stock solution) concentrations of florfenicol (% of initial theoretical target) when mixed with various chemicals/agents.**

Chemical/Agent	Florfenicol concentration (% of theoretical target)		
	0 hours	5 hours	24 hours
<i>Medicinals/NSAIDs</i>			
Acetylsalicylic acid	100.0%	100.0%	100.0%
Sodium salicylate	97.1%	97.1%	96.7%
Ibuprofen	95.0%	95.1%	94.6%
<i>Cleaning/Chelating</i>			
Ammonia	88.8%	89.1%	88.4%
Bleach	79.7%	79.7%	80.0%
Citric acid	97.7%	97.8%	97.4%
Hydrogen peroxide	93.2%	92.2%	91.2%
Sodium thiosulfate	94.0%	95.0%	95.4%
<i>Nutritional</i>			
Milk replacer	91.6%	91.0%	84.8%
Vitamin supplement	94.1%	94.6%	94.1%
Solutein	90.4%	90.5%	90.0%

Table 2. **Post-medicator (water line) concentrations of florfenicol (% of initial theoretical target) when mixed with various chemicals/agents.**

water, but this drop in concentration did not continue over time. Thus, chlorinators should not be operated while administering NUFLO[®] antibiotic. The performance of NUFLO has not been tested under conditions where water hardness (calcium carbonate) exceeds 275 mg/L (ppm). Therefore, the product is not recommended for use in automatic proportioners if water hardness surpasses this level. In acidic (pH 6.5) or alkaline conditions (pH 8.5), some tested samples had slightly reduced florfenicol levels at 24 hours. Additional research evaluated the stability of NUFLO 2.3% Concentrate Solution in the presence of zinc and copper ions in water, common nutrient additives for swine diets. NUFLO was found to be stable in the presence of 3000 ppm of Zn (II) and 250 ppm Cu (II) ions.

NUFLO antibiotic should not be stored or dispensed in galvanized metal watering systems, as the zinc-coated surfaces of galvanized materials can react with florfenicol (in contrast to the research showing no reactivity with dissolved zinc ions). In studies with galvanized pipes, severe reductions in florfenicol concentrations were detected after 24 hours, but florfenicol concentrations in plastic pipes, copper pipes, or rusty carbon steel pipes were not significantly affected.

To avoid any potential impact that local water chemistry might impose on the performance of NUFLO, distilled water and plastic buckets should be used for preparation of stock solutions. This simple strategy removes much of the potential for any problems mixing or metering

NUFLO. Some heating of the stock solution (exothermic reaction) may occur when the product is added to water; this is normal and not a cause for concern.

Automatic proportioners should be set to deliver 1:128 (0.8%); do not use NUFLO at any other proportioner setting as precipitation of the product may occur. Other important points for using NUFLO include the fact that stock solutions must be made *fresh daily*, and adding *excessive water* to a stock solution may cause the product to precipitate. Therefore, when using proportioners, add water to the NUFLO container until the 1-gallon fill line is reached, and do not dilute further. Closely follow mixing and administration directions on the product label.

Conclusions

NUFLOR® 2.3% Concentrate Solution is highly stable in both stock solutions and post-medicator non-galvanized water lines. In the presence of multiple chemicals or agents commonly used in swine production facilities, no florfenicol precipitation and no substantive loss of florfenicol activity were observed during a 24-hour evaluation period. NUFLOR 2.3% Concentrate Solution can be used in swine drinking water medication systems with full confidence that appropriate concentrations of drug are delivered to pigs, providing fast, convenient, and effective treatment of swine respiratory disease.

References

¹ NADA 141-206. US FDA.

² Data on file. Schering-Plough Animal Health Corporation.

³ Hayes JM, Eichman J, Katz T, Gilewicz R. Stability of florfenicol in drinking water. *Journal of the Association of Official Analytical Chemists* 2003; 86:22-29.

Swine intended for human consumption must not be slaughtered within 16 days of the last treatment. The effects of florfenicol on swine reproductive performance, pregnancy, and lactation have not been determined. Do not use in swine intended for breeding.

Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

**For more information about
Schering-Plough Animal Health Corp. and
its swine products, call 1.800.211.3573
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