Assessment of the physical compatibility of injectable enrofloxacin with commonly used intravenous fluids and drugs during simulated Y-port administration

Anahita Aghili DVM
Elizabeth J. Thomovsky DVM, MS
Paula A. Johnson DVM
Aimee C. Brooks DVM, MS
Trinna J. Pierce PharmD
Alexandria E. Gochenauer PharmD

OBJECTIVE
To evaluate physical compatibility of small animal (SAE) and large animal (LAE) injectable formulations of enrofloxacin with select IV fluids and drugs.

SAMPLE
162 admixtures containing SAE or LAE with saline (0.9% NaCl) solution, lactated Ringer solution (LRS), Plasma-Lyte A (PLA), 6% hydroxyethylstarch 130/0.4 (HES), metoclopramide, or ampicillin-sulbactam.

PROCEDURES
In the first of 2 simultaneously conducted experiments, admixtures containing enrofloxacin (10 mg/kg) and a volume of IV fluid that would be administered over a 20-minute period when dosed at the maintenance infusion rate (40 mL/kg/d for saline solution, LRS, and PLA and 20 mL/kg/d for HES) were created. In the second experiment, enrofloxacin (10 mg/kg) was admixed with saline solution (40 mL/kg/d) and metoclopramide (2 mg/kg/d) or ampicillin-sulbactam (30 mg/kg). In both experiments, admixture components were infused into a flask over 20 minutes assuming patient weights of 5, 10, and 20 kg. Admixtures were created by use of undiluted SAE and LAE and diluted 1:1 and 1:10 with saline solution. Admixtures were assessed for physical incompatibility at 0, 15, 30, and 60 minutes after completion of mixing. Physical incompatibility was defined as gross precipitation, cloudiness, Tyndall effect, or change in turbidity.

RESULTS
Admixtures containing undiluted SAE or LAE were physically incompatible with saline solution, PLA, LRS, and HES. Because saline solution was used to dilute SAE and LAE, all admixtures containing diluted SAE or LAE were also physically incompatible. Physical compatibility of enrofloxacin with metoclopramide or ampicillin-sulbactam could not be assessed because those admixtures also contained saline solution.

CONCLUSIONS AND CLINICAL RELEVANCE
Enrofloxacin was physically incompatible with all tested solutions. (Am J Vet Res 2021;82:358–366)

A challenge in any ICU is the safe administration of multiple IV medications. Many medications require continuous or prolonged infusions, which can make concomitant administration of fluids and other medications challenging. Medications can be administered simultaneously if data exist to show they are compatible with each other. However, if a medication is incompatible or its compatibility with other medications or IV fluids is unknown, that medication should be administered through a separate IV line or administered before another medication or fluid is administered through the same IV line. This practice can delay administration of some treatments for several hours and may increase the risk for medication errors.

Drug incompatibilities come in 2 types: physical and chemical. Physical incompatibility is defined as interactions between 2 or more substances that result in visible alterations such as precipitation, turbidity, and color change as well as the formation of either visible or subvisible particles. Physical incompatibility is typically evaluated before chemical incompatibility testing. Chemical incompatibilities are caused by interdrug reactions such as oxidation-reduction reactions, complexation, or racemization of the medications. Chemical incompatibilities reduce the effectiveness of the administered substances or can cause toxicoses.

Information regarding the physical and chemical compatibilities of medications is limited in both hu-
man and veterinary medicine. Consequently, incompatible medications are often administered together, despite attempts to avoid doing so. In fact, results of a study involving critically ill children indicate that only 9% of the medications administered concomitantly were known to be compatible, whereas 8% and 29% of medications given concomitantly were known to be incompatible or had unknown compatibilities, respectively. In veterinary medicine, the frequency of concomitant administration of incompatible medications or medications with unknown compatibility is generally unknown but is expected to be as least as common as the frequency of such administration in human medicine.

Results of a meta-analysis of drug incompatibilities following IV administration in critically ill human patients indicate that concomitant administration of incompatible medications increases both morbidity and mortality rates. Clinical signs associated with incompatible drug interactions range from respiratory impairment to death. In some human patients with signs of respiratory dysfunction who subsequently died, pulmonary nodules identified by CT before death were determined to be amorphous calcium-containing material (which was attributed to incompatible drug interactions) that obstructed the pulmonary microvasculature during autopsy. In another study of human neonates who died after concomitant administration of incompatible drugs, crystalline material or white precipitates were frequently found in vascular beds, particularly in the lungs. The veterinary literature lacks data about whether veterinary patients develop similar adverse effects and lesions after receiving incompatible drugs concomitantly.

Enrofloxacin is a bactericidal fluoroquinolone antimicrobial commonly administered to veterinary patients treated in ICUs. The bactericidal activity of enrofloxacin is concentration dependent, and the death of susceptible bacteria generally occurs within 20 to 30 minutes after exposure to a lethal concentration of the drug. Enrofloxacin has activity against both gram-negative and gram-positive bacteria and is used to treat respiratory tract, urinary tract, and other generalized infections in animals.

Currently, SAE is approved by the FDA only for IM administration in dogs. However, in clinical practice, we have observed veterinarians routinely administering undiluted and diluted SAE to patients by the IV route. We have also observed LAE being diluted and administered by the IV route, especially in large- or giant-breed dogs, owing to its substantially lower cost relative to SAE. This is despite recommendations that LAE not be diluted and administered to small animals by any route. Anecdotal reports by veterinarians indicate that SAE and LAE are administered to dogs by the IV route following dilution with saline (0.9% NaCl) solution at ratios that range from 1:1 to 1:10 and over periods of time that range from 10 to 45 minutes.

Information regarding the combination of enrofloxacin with other drugs and IV fluids is lacking. To our knowledge, the physical compatibilities of SAE and LAE when combined with divalent cation-containing solutions (eg, LRS and PLA), physiologic saline solution, and HES have not been determined. Plumb’s Veterinary Drug Handbook states that SAE and LAE should not be combined or come into contact with any IV solution containing magnesium owing to the formation of intrapulmonary precipitants. Additionally, although some fluoroquinolones other than enrofloxacin are physically and chemically compatible with various other drugs, the published literature lacks information about the physical compatibility or incompatibility of enrofloxacin with drugs, such as metoclopramide and ampicillin-sulbactam, that are commonly infused IV over time to patients in veterinary ICUs.

In the human medical literature, a Y-port adapter is the most common method used to test the physical compatibility between 2 substances because it allows simulation of the simultaneous administration of 2 or more substances within an IV line. Physical compatibility between 2 substances is typically assessed by visual examination (assessment for color change, particle formation, other visible changes in the admixture, and the presence of a Tyndall effect) and measurement of turbidity by a calibrated laboratory-grade turbidimeter.

Admixtures are considered incompatible if there is a visible change in color or the formation of a haze, gas, or precipitate when an admixture is observed by unaided eyes against white and black backgrounds after mixture or during infusion. The presence of a Tyndall effect is assessed with a laser or fluorescent light and is defined as the visible scattering of light created by the presence of particles (sometimes subvisible) in the path of the primary light source (eg, laser). Admixtures without visible particles are considered compatible, whereas those with any type or amount of particles are considered incompatible. Substances that result in a change in turbidity of > 0.5 NTU when admixed are also considered incompatible.

The objective of the study reported here was to evaluate the physical compatibilities of SAE and LAE with 4 fluid solutions (3 crystalloid solutions [saline (0.9% NaCl) solution, LRS, and PLA] and 1 colloid solution [HES]) and 2 drugs (metoclopramide and ampicillin-sulbactam) commonly administered to small animal patients by the IV route. We hypothesized that both SAE and LAE would be physically incompatible with PLA, LRS, metoclopramide, and ampicillin-sulbactam and physically compatible with saline solution and HES.

Materials and Methods

Study design

The study consisted of 2 experiments. In both experiments, 1 investigator (AA) was responsible for creating the admixtures and therefore was aware of
(ie, was not blinded to) what was in each admixture and 2 other investigators (EJT and AEG) who were unaware of (ie, blinded to) the contents of each admixture were responsible for the physical assessment of each admixture. The blinded investigators assessed the physical attributes of each admixture independently from each other. Each admixture was created 2 separate times by the unblinded investigator during the experimental period. If the unblinded investigator observed substantial interobserver variability in any of the observations, the admixture in question was created a third time during the experimental period and assessed by both blinded investigators. For each admixture, the results for the 2 most similar replicates were averaged, and the resulting means were used for analysis.

**Experiment 1**

In experiment 1 of the study, PLA was coded as A, saline solution was coded as B, LRS was coded as C, and HES was coded as D. Each fluid was combined with SAE or LAE over a period of 20 minutes to simulate IV infusion of a dose of 10 mg/kg of the drug to patients weighing 5, 10, and 20 kg to determine whether signs of physical incompatibility were dependent on the total dose (amount) of enrofloxacin administered. For each admixture, a fluid pump was used to infuse the IV solution through an IV fluid set and Y-port adapter into a flask. A syringe pump was used to infuse the enrofloxacin through an IV extension set that was attached to another port of the Y-port adapter through which the IV solution was being pumped. Thus, the enrofloxacin was mixed with the IV solution as both fluids passed through the Y-port adapter and into the flask (Figure 1).

Admixtures with SAE were evaluated when the drug was added undiluted and diluted 1:1 with saline solution, and admixtures with LAE were evaluated when the drug was added undiluted and diluted with saline solution at ratios of 1:1 and 1:10. During each 20-minute infusion, the crystalloid (40 mL/kg/d) or colloid (20 mL/kg/d) solution was infused into the flask at a rate sufficient to deliver the 20-minute maintenance volume for a patient with the designated body weight. At the end of the 20-minute infusion period, the total volume of the admixture in the flask was transferred into a glass turbidimeter bottle, which was labeled for

---

**Figure 1**—Schematic illustrations of the experimental setups used to create admixtures to assess the physical compatibility of enrofloxacin at various dilutions with saline (0.9% NaCl) solution, PLA, LRS, HES, metoclopramide, and ampicillin-sulbactam. A—In the first of 2 simultaneously conducted experiments, a fluid pump (not illustrated) was used to infuse 1 of 4 types of IV fluids through an IV set, which was connected to 1 port of a Y-port adapter, into a flask over 20 minutes at the recommended maintenance infusion rate (40 mL/kg/d for saline solution, LRS, and PLA and 20 mL/kg/d for HES). Concurrently, a syringe pump (not illustrated) was used to infuse enrofloxacin through an IV extension set, which was connected to another port of the Y-port adapter. The enrofloxacin was mixed with the IV fluid solution as both solutions flowed through the Y-port adapter into the flask. B—In the second experiment, the apparatus setup was the same as that for the first experiment except a second syringe pump was used to infuse metoclopramide (2 mg/kg/d) or ampicillin-sulbactam (30 mg/kg) through an IV extension set, which was connected to the IV set through which saline solution (40 mL/kg/d) was infused. For both experiments, admixture components were infused into the flask over 20 minutes assuming patient weights of 5, 10, and 20 kg. Enrofloxacin was infused in an amount sufficient to simulate administration of a dose of 10 mg/kg. Admixtures were created by the use of undiluted SAE and SAE diluted 1:1 with saline solution and undiluted LAE and LAE diluted 1:1 and 1:10 with saline solution.
identification purposes (eg, fluid A and undiluted SAE for 5-kg patient), and handed to the blinded investigators for visual inspection.

**Experiment 2**

In experiment 2 of the study, admixtures of enrofloxacin with metoclopramide\(^2\) or ampicillin-sulbactam\(^1\) were evaluated. For each admixture, saline solution was administered as described for experiment 1 to mimic clinical settings in which patients receive IV fluids concurrently with drug treatment. A syringe pump was used to infuse metoclopramide or ampicillin-sulbactam through an IV extension set that was connected to the IV fluid line through which the saline solution was infused before it connected to the Y-port adapter (Figure 1). Metoclopramide is typically administered as a constant rate infusion. Thus, metoclopramide was infused over 20 minutes at a rate sufficient to simulate administration of 0.028 mg/kg of the drug to patients weighing 5, 10, and 20 kg (ie, the dose of metoclopramide that would be delivered over 20 minutes when administered as a constant rate infusion of 2 mg/kg/d).

Ampicillin-sulbactam was infused over 20 minutes at a rate sufficient to simulate administration of a dose of 30 mg/kg of the drug to patients weighing 5, 10, and 20 kg. Admixtures containing undiluted and diluted SAE and LAE as described for experiment 1 were evaluated. Following completion of each 20-minute infusion, the admixture was transferred to a glass turbidimeter bottle for visual evaluation.

For both experiments 1 and 2, all IV fluid lines, extension sets, and Y-port adapters were primed with the designated solution or drug so that the components of all admixtures were mixing together throughout the entire 20-minute infusion period. Both experiments were performed simultaneously and results other than interobserver variability were not assessed until physical compatibility evaluations of all planned admixtures were completed.

### Physical compatibility assessment

The chemical structure, chemical formula, and molecular weight of enrofloxacin,\(^21\) metoclopramide,\(^22\) and ampicillin-sulbactam\(^23\) were summarized (Appendix). Prior to mixing, all IV solutions and drugs (SAE, LAE, metoclopramide, and ampicillin-sulbactam) were visually assessed for color, presence of haze or particles, and Tyndall effect and underwent measurement of turbidity. The turbidimeters\(^6\) were calibrated with manufacturer-provided test solutions daily prior to use on study solutions. All assessments were performed at room temperature (20°C to 25°C) under normal laboratory fluorescent lighting. For all admixtures, visual assessment and turbidity measurements were performed at 0 (immediately; baseline), 15, 30, and 60 minutes after the admixture was placed in a turbidimeter bottle. The assessment times were selected on the basis of the assessment times used in similar studies in the human medical literature.\(^2,11–13,15,19\)

Visual assessment was performed by unaided eyes with the turbidimeter bottle containing the admixture held against white and black backgrounds. The turbidimeter bottle was inverted before visual inspection and measurement of turbidity to mobilize any precipitates before assessment. Visual observation of particles was recorded as yes or no. The Tyndall effect was assessed by use of a laser pointer\(^1\) and was also recorded as yes or no. Turbidity measurements could be performed only when the admixture volume reached or exceeded the fill line of the bottle (ie, ≥ 12 mL of solution). For each admixture with a sufficient volume, each blinded investigator obtained 3 turbidity measurements at each assessment time, and the mean of the 6 measurements was calculated and reported.

### Data analysis

An admixture was deemed physically incompatible if ≥ 1 of the following were observed: gross precipitation, cloudiness, the appearance or disappearance of a Tyndall effect, and a change in turbidity of ≥ 0.5 NTU from baseline.\(^1,2,10–15,17–19\) Objective statis-

<table>
<thead>
<tr>
<th>Component</th>
<th>Color</th>
<th>Presence of particles</th>
<th>Presence of a Tyndall effect</th>
<th>Turbidity (NTU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAE</td>
<td>Colorless</td>
<td>No</td>
<td>No</td>
<td>55.7</td>
</tr>
<tr>
<td>LAE</td>
<td>Yellow</td>
<td>No</td>
<td>No</td>
<td>37.3</td>
</tr>
<tr>
<td>Saline (0.9% NaCl) solution</td>
<td>Colorless</td>
<td>No</td>
<td>No</td>
<td>30.2</td>
</tr>
<tr>
<td>LRS</td>
<td>Colorless</td>
<td>No</td>
<td>Yes</td>
<td>16.0</td>
</tr>
<tr>
<td>PLA</td>
<td>Colorless</td>
<td>Yes</td>
<td>Yes</td>
<td>20.4</td>
</tr>
<tr>
<td>HES</td>
<td>Colorless</td>
<td>No</td>
<td>No</td>
<td>21.1</td>
</tr>
<tr>
<td>Ampicillin-sulbactam</td>
<td>Colorless</td>
<td>Yes</td>
<td>Yes</td>
<td>33.9</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>Colorless</td>
<td>No</td>
<td>Yes</td>
<td>—</td>
</tr>
</tbody>
</table>

Two replicates of each component were visually assessed and underwent measurement of turbidity by 2 independent investigators, who were blinded to the component identity. The turbidity values represent the mean for the 2 replicates. There was no interobserver disagreement for any of the assessed variables.

— = Not measured.
tics were not performed because all visually assessed variables were reported as present or absent.

**Results**

Results of the visual assessment and turbidity measurements of the individual components of the admixtures prior to mixing were summarized (Table 1). One hundred sixty-two admixtures were created and assessed, of which interobserver disagreement was recorded for 18. For each of those 18 admixtures, the disagreement was related only to the density of particles or magnitude of Tyndall effect present; the observers agreed that particles or Tyndall effect were present in all 18 admixtures. For each of the 18 admixtures with interobserver disagreement, a third replicate was evaluated, and results were reported for the 2 replicates that were in closest agreement. A fourth replicate was not required to ensure reproducibility of any results for any admixture.

Interobserver disagreement was not recorded for turbidity measurements. Because an admixture volume of at least 12 mL was required to measure turbidity, the turbidity could not be measured for all admixtures created for simulated patients with a body weight of 5 kg (5-kg patients) and most admixtures created for simulated patients with a body weight of 10 kg (10-kg patients).

### Physical compatibility of enrofloxacin with commonly administered IV fluids

Admixtures of undiluted SAE with saline solution created for 5- and 10-kg patients were visually compatible at all assessment times. Admixtures of undiluted SAE with saline solution created for simulated patients with a body weight of 20 kg (20-kg patients) were deemed physically incompatible owing to the presence of visible particles at 30 and 60 minutes and changes in turbidity of ≥ 0.5 NTU from baseline beginning at 15 minutes after completion of mixing (Table 2). It is important to note that even though the SAE-saline solution admixtures created for 20-kg patients appeared visually compatible prior to 30 minutes after mixing, turbidity measurements at 15 minutes after mixing revealed incompatibility; thus, we assumed that all SAE-saline solution admixtures were incompatible, although turbidity measurements were not available to prove this for admixtures created for 5- and 10-kg patients. Therefore, results were not reported for any admixtures containing diluted SAE.

All admixtures of LAE and saline solution were visually incompatible at all assessments (Table 2). Turbidity measurements could not be obtained for LAE-saline solution admixtures created for 5- and 10-kg patients. Turbidity measurements could not be obtained for LAE-saline solution admixtures created for 20-kg patients.

### Table 2—Changes in visual appearance and turbidity relative to baseline for admixtures containing undiluted SAE or LAE and saline solution, PLA, LRS, or HES that were created for simulated patients with body weights of 5, 10, and 20 kg.

<table>
<thead>
<tr>
<th>Admixture</th>
<th>Simulated patient weight (kg)</th>
<th>Change in color or presence of particles or cloudiness</th>
<th>Change in Tyndall effect</th>
<th>Change in turbidity (NTU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAE and saline solution</td>
<td>5</td>
<td>No</td>
<td>No</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>No</td>
<td>No</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>Yes (30)</td>
<td>No</td>
<td>9.5</td>
</tr>
<tr>
<td>LAE and saline solution</td>
<td>5</td>
<td>Yes (0)</td>
<td>Yes (0)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>Yes (0)</td>
<td>Yes (0)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>Yes (0)</td>
<td>Yes (0)</td>
<td>2.5</td>
</tr>
<tr>
<td>SAE and PLA</td>
<td>5</td>
<td>No</td>
<td>No</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>Yes (30)</td>
<td>Yes (60)</td>
<td>15.2</td>
</tr>
<tr>
<td>LAE and PLA</td>
<td>5</td>
<td>Yes (60)</td>
<td>Yes (60)</td>
<td>13.7</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>Yes (0)</td>
<td>Yes (0)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>Yes (0)</td>
<td>Yes (0)</td>
<td>4.6</td>
</tr>
<tr>
<td>SAE and LRS</td>
<td>5</td>
<td>Yes (0)</td>
<td>No</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>Yes (0)</td>
<td>Yes (15)</td>
<td>8.9</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>Yes (0)</td>
<td>Yes (0)</td>
<td>7.6</td>
</tr>
<tr>
<td>LAE and LRS</td>
<td>5</td>
<td>Yes (0)</td>
<td>Yes (0)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>Yes (0)</td>
<td>Yes (0)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>Yes (0)</td>
<td>Yes (0)</td>
<td>8.1</td>
</tr>
<tr>
<td>SAE and HES</td>
<td>5</td>
<td>Yes (30)</td>
<td>No</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>Yes (0)</td>
<td>No</td>
<td>20.1</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>Yes (0)</td>
<td>Yes (0)</td>
<td>10.2</td>
</tr>
<tr>
<td>LAE and HES</td>
<td>5</td>
<td>Yes (0)</td>
<td>Yes (30)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>Yes (0)</td>
<td>Yes (15)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>Yes (0)</td>
<td>Yes (15)</td>
<td>2.7</td>
</tr>
</tbody>
</table>

Values in parentheses represent the number of minutes after baseline at which the change was first noted. Admixture components were infused and mixed together through a Y-port adapter and into a flask over 20 minutes. The designated fluid solution was infused at the recommended maintenance infusion rate (40 mL/kg/d for saline solution, PLA, and LRS and 20 mL/kg/d for HES), and enrofloxacin was infused in an amount sufficient to yield a dose of 10 mg/kg assuming patient weights of 5, 10, or 20 kg. Two replicates of each admixture were assessed independently by 2 investigators who were blinded to the admixture components at 0 (immediately, baseline), 15, 30, and 60 minutes after completion of mixing. An admixture was deemed physically incompatible if ≥ 1 of the following were observed: gross precipitation, cloudiness, the presence of a Tyndall effect, and a change in turbidity of ≥ 0.5 NTU from baseline.

— = Admixture volume was insufficient for measurement.
10-kg patients owing to insufficient volume. Turbidity measurements obtained for the LAE-saline solution admixtures created for 20-kg patients varied from baseline by > 0.5 NTU at 15 minutes after mixing, which was also consistent with physical incompatibility. Thus, results were not reported for admixtures containing diluted LAE.

Physical assessment results for the admixtures of undiluted enrofloxacin with PLA, LRS, and HES were summarized (Table 2). The PLA contained particles and had a Tyndall effect and the LRS had a Tyndall effect (Table 1) prior to mixing with enrofloxacin, which made visual evaluation of the admixtures that contained those 2 solutions difficult. For all admixtures with a volume sufficient for turbidity measurement, the turbidity varied by > 0.5 NTU from baseline over time. Therefore, enrofloxacin was deemed physically incompatible with PLA, LRS, and HES.

**Physical compatibility of enrofloxacin with metoclopramide and ampicillin-sulbactam**

We could not draw any conclusions regarding the physical compatibility of enrofloxacin with metoclopramide or ampicillin-sulbactam because admixtures containing those components also contained saline solution (to simulate concurrent administration of saline solution through the IV lines) and enrofloxacin was deemed physically incompatible with saline solution.

**Discussion**

Results of the present study indicated that, when undiluted, both SAE and LAE were physically incompatible with saline solution, PLA, LRS, and HES. Additionally, because saline solution was used to dilute SAE and LAE, all admixtures containing diluted SAE or LAE were also deemed physically incompatible. Saline solution was also included in all admixtures with metoclopramide and ampicillin-sulbactam, which precluded our ability to assess the physical compatibility between enrofloxacin and those 2 drugs. These findings were not surprising, because **Plumb's Veterinary Drug Handbook** states that enrofloxacin should not be mixed with IV fluids or administered by the IV route. The present study was conducted because, in small animal clinical practice, it is common for SAE and LAE to be diluted with saline solution prior to infusion through IV lines and catheters concurrently with other fluids and drugs. Our findings suggested that this practice should be discontinued and investigated further to avoid administration of physically incompatible admixtures containing enrofloxacin to patients and potential adverse effects.

The present study was designed to evaluate another common clinical practice: the preparation or dilution of enrofloxacin hours or minutes before administration and storage of the diluted drug in a syringe before and during extended IV infusion. Diluted and undiluted enrofloxacin is commonly administered through an IV line with various other drugs and fluids over periods ranging from 10 to 45 minutes. In the present study, many indicators of visual incompatibility were not detected until ≥ 30 minutes after an admixture was created; turbidity measurements, when possible, were consistent with physical incompatibility sooner than that. However, owing to the lack of visual changes, those indicators of incompatibility would likely go unnoticed by someone administering the admixture to a patient in a clinical setting. Regardless, the results of this study supported the manufacturer's recommendation to administer the entire dose of enrofloxacin undiluted, IM (dogs) or SC (cattle and pigs), and as a single bolus rather than as a slow infusion over time.

When assessing the physical compatibility of 2 or more substances in an admixture, it is important that objective analytic measures, such as turbidity, are assessed as well as visual indices (ie, color and presence or absence of particles and a Tyndall effect) because visual indices are subjective and can be missed. For example, in the present study, the SAE-saline solution admixtures for 20-kg patients appeared visually compatible but were deemed physically incompatible on the basis of changes in turbidity > 0.5 NTU over time.

The PLA solution assessed in the present study contained visible particles and was positive for a Tyndall effect before it was mixed with enrofloxacin (Table 2). Therefore, we were surprised that particles were not observed in the undiluted SAE–PLA admixtures at baseline (0 minutes after completion of mixing). However, all undiluted SAE–PLA admixtures created for 10- and 20-kg patients were positive for particles and a Tyndall effect at 30 and 60 minutes after completion of mixing, respectively. Although that observation was not investigated further, we suspected it was the result of dilution or dissociation of PLA particles in the admixtures. It was unclear whether the particles in the undiluted SAE–PLA admixtures observed 30 and 60 minutes after baseline were the particles initially present in the PLA or new particles created by mixing enrofloxacin with PLA.

Newly formed particles in the undiluted SAE–PLA admixtures might have been the result of ionic or acid-base reactions between the drug and PLA. Enrofloxacin contains both acidic (amine) and basic (carboxylic) groups and has a betaine structure. Injectable formulations of enrofloxacin have a pH of approximately 11. At a pH > 5.0, carboxylates are negatively charged and capable of forming ionic bonds with cations such as magnesium or calcium. Because PLA contains polyvalent anions and cations (eg, magnesium) that have multiple electrons in their outer shells, those ions could form low-solubility salts with the carboxylate groups in enrofloxacin and produce visible particles.

Precipitation is another possible reason for the development of particles in admixtures containing
divalent cations, such as magnesium (eg, PLA) and calcium (eg, LRS).\textsuperscript{25} When combined with organic acids, the solubility of calcium and magnesium salts decreases, resulting in the formation of precipitates.\textsuperscript{27} In the present study, the combination of enrofloxacin with PLA or LRS likely led to ionic reactions and precipitation, which contributed to the particle formation and increases in turbidity observed. It is also possible that the greater amount of enrofloxacin in admixtures for 10- and 20-kg patients, relative to those for 5-kg patients, facilitated visual detection of particles over time; however, changes in turbidity were detected immediately.

A dose-dependent effect likely contributed to the ability to determine physical incompatibility of many admixtures evaluated in the present study. For example, admixtures for 20-kg patients that contained undiluted LAE and PLA and undiluted LAE and HES were visually assessed as cloudy throughout the observation period, whereas those for 5- and 10-kg patients were clear. Also, among the undiluted SAE-saline solution admixtures, particles were observed only in those created for 20-kg patients. Although further investigation is required to characterize the respective relationships between enrofloxacin and the fluids assessed in the present study, we believe that physical incompatibility noted in any admixture at any dose negates the use of that combination in patients.

In the present study, experiments 1 and 2 were conducted simultaneously, and the investigators responsible for conducting the physical compatibility assessments remained blinded to the content of the admixtures throughout the observation period. Thus, it was only after the physical compatibility assessments were completed and the results were evaluated that it became evident that enrofloxacin was physically incompatible with saline solution. Consequently, we were not surprised that both SAE and LAE were physically incompatible with HES because saline solution is the carrier for HES. Additionally, we could not determine whether SAE and LAE are compatible with metoclopramide and ampicillin-sulbactam because the drugs were concurrently admixed with saline solution during experiment 2. Future studies should evaluate the physical compatibility of injectable enrofloxacin with metoclopramide and ampicillin-sulbactam in the absence of saline solution.

After data collection in the present study was completed, the ninth edition of Plumb’s Veterinary Drug Handbook\textsuperscript{2} was released in which an extra-label protocol for IV administration of SAE to dogs is provided (SAE diluted 1:10 with saline solution infused IV over a period of 30 to 45 minutes [original source, anecdotal]). We did not simulate that protocol in the present study; however, given the findings of the present study, we doubt that further dilution of the SAE with saline solution and administration of the admixture over a longer duration will make the 2 solutions physically compatible for safe concomitant administration to patients.

Injectable drugs can be diluted with diluents other than physiologic (0.9%) saline solution such as sterile water, 5% dextrose in water, and 0.45% saline solution. Because we believe that ionic bonds or other chemical reactions (eg, precipitation) were the cause of the physical incompatibility of the enrofloxacin-containing admixtures evaluated in the present study, it is possible that use of a less concentrated saline solution such as 0.45% saline or a solution that does not contain NaCl such as 5% dextrose in water or sterile water might not cause physical incompatibility reactions. Further research is necessary to determine whether enrofloxacin is physically compatible with 0.45% saline solution, 5% dextrose in water, and sterile water.

The present study had several limitations. The turbidity could not be measured for several of the admixtures evaluated because they had an end volume < 12 mL, which was the minimum volume required for measurement by the turbidimeter used in this study. Our conclusions, particularly those for admixtures created for 5- and 10-kg patients, would have been stronger had turbidity been consistently measured. However, because our study was aimed at a clinical population with the goal of providing information about drug safety, finding physical incompatibility at any body weight on the basis of changes in visual appearance or turbidity was sufficient to conclude that a particular drug combination is incompatible.

The manufacturer of the turbidimeter used in the present study states that the accuracy of the device is within ± 2 NTU for measurements < 25 NTU and ± 5 NTU for measurements ≥ 25 NTU.\textsuperscript{28} Review of the turbidity measurements recorded in the present study indicated that, for all admixtures except 1, the magnitude of change from baseline turbidity was sufficiently large that measurement bias did not affect our conclusions regarding the physical compatibility of the admixtures. The undiluted LAE-saline solution admixture was the only admixture for which the inherent measurement bias of the turbidimeter might have affected the physical compatibility classification. However, that admixture was also deemed physically incompatible on the basis of the presence of particles and a Tyndall effect, so the potential inaccuracy of the turbidimeter was irrelevant.

Another limitation of the present study was the fact that our supplies were finite. Consequently, although the scientific literature\textsuperscript{1,2,10-15,17,18} suggests that 3 replicates is the optimal number of replicates for assessment of the physical compatibility of admixture components, only 2 replicates of each admixture were assessed in this study unless there was disagreement between the 2 blinded reviewers, in which case a third replicate was evaluated. We believe our results are still valid because there was interobserver agreement for both replicates of all admixtures evaluated. Furthermore, when interobserver disagreement was present, it was only in regard to particle density, not whether there were particles or a Tyndall effect present.
Finally, the present study was designed to assess only the physical compatibility between enrofloxacin and select IV fluids and drugs. It was not designed to evaluate the degradation, chemical characteristics, or chemical compatibility of the admixtures created. That area requires further research.

Findings of the present study indicated that both SAE and LAE were physically incompatible with saline solution, LRS, PLA, and HES. Thus, those 2 products should be administered as recommended by the manufacturer (ie, IM in dogs and SC in cattle and pigs) and not administered by the IV route until the risks associated with that practice have been more thoroughly investigated.

Acknowledgments

The authors declare that there were no conflicts of interest.

Footnotes

a. Baxter, Deerfield, Ill.
b. VetStarch, Zoetis, Parsippany, NJ.
d. Smiths Medical, Dublin, Ohio.
e. ICU Medical Inc, Lake Forest, Ill.
g. Vernier, Beaverton, Ore.
h. Hospira Inc, Lake Forest, Ill.
i. Meitheal Pharmaceuticals, Chicago, Ill.

References


The appendix appears on the next page
### Appendix

Chemical structures and formulas and molecular weights of enrofloxacin, ampicillin-sulbactam, and metoclopramide.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Chemical formula</th>
<th>Molecular weight (g/mol)</th>
<th>Reference No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrofloxacin</td>
<td>C₁₁H₁₂FN₃O₃</td>
<td>359.4</td>
<td>22</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>C₁₄H₂₂ClN₃O₂</td>
<td>299.80</td>
<td>23</td>
</tr>
<tr>
<td>Ampicillin-sulbactam</td>
<td>C₂₅H₃₁N₇Na₂O₁₄S₂</td>
<td>625.6</td>
<td>24</td>
</tr>
</tbody>
</table>

For the chemical structure of ampicillin-sulbactam, the ampicillin component appears in blue font and the sulbactam component appears in red font.