The incidence of invasive fungal infections and antifungal treatment failures is increasing in humans, particularly in immunocompromised individuals.\(^1\)\(^-\)\(^3\) During the last decade in human medicine, mortality from systemic mycoses has increased 3-fold.\(^4\) These findings in human medicine suggest that a similar situation may develop in veterinary medicine. Newer, orally administered antifungals that are effective in the treatment of fungal infections and are associated with few adverse effects could improve clinical outcomes in animals.

Fungal infections are commonly diagnosed in companion exotic animal species. Aspergillosis is the most common avian respiratory fungal infection and is reportedly one of the leading causes of death in captive and newly captured free-ranging birds of prey.\(^5\)

**Objective**—To determine the stability and distribution of voriconazole in 2 extemporaneously prepared (compounded) suspensions stored for 30 days at 2 temperatures.

**Sample Population**—Voriconazole suspensions (40 mg/mL) compounded from commercially available 200-mg tablets suspended in 1 of 2 vehicles. One vehicle contained a commercially available suspending agent and a sweetening syrup in a 1:1 mixture (SASS). The other vehicle contained the suspending agent with deionized water in a 3:1 mixture (SADI).

**Procedures**—Voriconazole suspensions (40 mg/mL in 40-mL volumes) were compounded on day 0 and stored at room temperature (approx 21°C) or refrigerated (approx 5°C). To evaluate distribution, room-temperature aliquots of voriconazole were measured immediately after preparation. Refrigerated aliquots were measured after 3 hours of refrigeration. To evaluate stability, aliquots from each suspension were measured at approximately 7-day intervals for up to 30 days. Voriconazole concentration, color, odor, opacity, and pH were measured, and aerobic and anaerobic bacterial cultures were performed at various points.

**Results**—Drug distribution was uniform (coefficient of variation, < 5%) in both suspensions. On day 0, 87.8% to 93.0% of voriconazole was recovered; percentage recovery increased to between 95.1% and 100.8% by day 7. On subsequent days, up to day 30, percentage recovery was stable (> 90%) for all suspensions. The pH of each suspension did not differ significantly throughout the 30-day period. Storage temperature did not affect drug concentrations at any time, nor was bacterial growth obtained.

**Conclusions and Clinical Relevance**—Extemporaneously prepared voriconazole in SASS and SADI resulted in suspensions that remained stable for at least 30 days. Refrigerated versus room-temperature storage of the suspensions had no effect on drug stability. (Am J Vet Res 2009;70:908–914)

Dermatomycoses affecting the skin and mucocutaneous junctions, commonly caused by *Candida* spp, are often detected in captive reptiles.\(^6\) The *Chrysosporium* anamorph of *Nannizziopsis vriesii* is another opportunistic fungus that causes dermatomycoses in reptiles, spreads rapidly in reptile collections, and has potential for zoonotic transmission, particularly to immunocompromised humans.\(^7\)\(^,\)\(^8\) Similar to other animal species, exotic animal species are susceptible to the adverse effects of antifungal drugs. For example, Timneh African grey parrots (*Psittacus erithacus timneh*) are particularly sensitive to itraconazole, and treatment with this drug can result in considerable anorexia and hepatotoxic effects.\(^9\) There is a need for new antifungal drugs that are less toxic for exotic animal species and that can be accurately dosed via oral administration.
Voriconazole is a broad-spectrum, second-generation, triazole antifungal drug approved by the FDA in 2002 for use in humans and is indicated for treatment of candidemia, esophageal candidiasis, and invasive aspergillosis.10–13 Voriconazole has fungicidal activity against some Aspergillus spp., including Aspergillus fumigatus, and fungistatic activity against many Candida spp.10 This antifungal is only labeled for use in humans and is commercially available in formulations that can be administered IV and orally (50-mg tablets,13 200-mg tablets,13 and a suspension10). After voriconazole is administered orally, it is readily absorbed and extensively distributed into tissues.10 In a pharmacokinetic analysis involving healthy humans, the bioavailability of orally administered voriconazole was estimated to be 96%,10 whereas the bioavailability of orally administered itraconazole was only 33%.10 Voriconazole is an alternative to amphotericin B and fluconazole, both of which are sometimes associated with severe adverse outcomes such as nephrotoxic or hepatotoxic effects.14 It has a wide therapeutic index and penetrates well through the blood-brain barrier.

Several studies14,15 have been conducted to evaluate the use of voriconazole in humans and other animals. In humans, voriconazole is reportedly superior to amphotericin B for treatment of invasive aspergillosis and is superior to fluconazole for treatment of esophageal candidiasis. In 1 study15 in which the in vitro effects of itraconazole and voriconazole were compared, voriconazole at a concentration of <1 µg/mL inhibited growth of 90% of fungal isolates recovered from humans, whereas itraconazole inhibited only 79% of the isolates at that concentration. In immunocompetent and immunocompromised guinea pigs, compounded voriconazole suspensions (prepared with polyethylene glycol) at 2 dosages (5 or 10 mg/kg, PO, q12 h) were highly effective in treatment of systemic and pulmonary aspergillosis, systemic candidiasis, and pulmonary and intracranial cryptococcosis.16 Antifungal susceptibility testing of Aspergillus spp isolated from the respiratory tracts of falcons before antifungal treatment revealed that 95% of the isolates were susceptible to voriconazole at an MIC ≤0.38 µg/mL, whereas only 79% of the isolates were susceptible to itraconazole at an MIC ≤1 µg/mL.17 A pharmacokinetic study16 of IV and oral administration of a voriconazole in horses revealed excellent absorption (systemic bioavailability, 135.75 ± 18.41%) and a long elimination half-life, which may allow for once-daily dosing in horses. The orally administered drug used in that study consisted of an extemporaneously prepared (compounded) suspension of voriconazole powder (33 mg/mL) in a corn syrup suspension. The stability of the suspension was measured for 48 hours and was stable during that interval when stored at 8°C. The plasma concentrations attained in the horses to which voriconazole was administered orally at 4 mg/kg were also adequate for treatment of any fungal species sensitive to voriconazole at an MIC ≤1 µg/mL.18 In Timneh African grey parrots, oral administration of a voriconazole suspension prepared with a mixture of commercial suspending agent and deionized water (12 mg of voriconazole/kg, PO, q12 h) resulted in plasma concentrations >0.4 µg/mL.9

Many commercially available drugs are not available in concentrations or formulations suitable for use in small exotic animals and therefore must be extemporaneously prepared with formulations and dosages suitable for the animals’ small sizes. However, the stability and integrity of most compounded preparations used in veterinary medicine have not been thoroughly examined. Compounded formulations are commonly assigned expiration dates in veterinary clinics and compounding pharmacies without any scientific evidence to support product stability or without regard to uniformity of distribution of drug molecules within such suspensions. Uniform distribution is important for accurate dosing because inconsistent mixtures can interfere with the ability to measure a precise dose. Before the clinical effectiveness of a compounded suspension is evaluated, the uniformity and stability of that suspension need to be assessed.

In veterinary medicine, voriconazole is an option for treatment of animals with fungal infections; however, certain challenges must be overcome to make the commercially available drug a realistic option for clinical use in small exotic animals including birds. The cost of the existing commercial voriconazole suspension is prohibitively high and is often the primary barrier to use as a treatment. In addition, the commercial suspension for oral administration is only available in a large volume (75 mL) and has a short shelf life (14 days after reconstitution).

The purpose of the study reported here was to determine the stability and variability of distribution of voriconazole in 2 extemporaneously prepared (compounded) suspensions stored for 30 days at room temperature or in a refrigerator. Development of a stable, evenly distributed voriconazole suspension would permit evaluation of the pharmacokinetics and efficacy of voriconazole treatment in avian and small exotic animal species.

Materials and Methods

Determination of optimal method for suspension preparation—Preliminary trials were performed to evaluate modifications of volumes, storage containers, and acidification on voriconazole suspensions to maximize solubility and subsequent recovery of the drug. Two 200-mg voriconazole tablets were pulverized into a uniform powder by use of a mortar and pestle and reconstituted with a 1:1 mixture of an SASS9 or a 3:1 mixture of the same suspending agent in deionized water. A small amount of the designated suspending vehicle (SASS or SADI) was mixed with the powder to form a paste. This process of levigation was important because it created a homogeneous paste to which the remaining measured amount of suspending vehicle was added to form the suspension. After the mortar and pestle were rinsed until visually devoid of remaining paste, the suspensions were diluted with a sufficient volume of SASS or SADI in a graduated cylinder to achieve a concentration of 40 mg of voriconazole/mL in a 10-mL volume. The drug formulations were stored in 200-mL brown glass bottles.

Each drug preparation was vigorously shaken by hand for 30 seconds to promote homogeneity. Immediately afterward, ten 0.2-mL aliquots were withdrawn...
from the center of each suspension by use of a positive-displacement pipette at the middle of the liquid. Each aliquot was expelled into 9.8 mL of acetonitrile-water (1:1) diluent. Diluted aliquots were mixed with a vortex machine for 1 minute and centrifuged at 700 × g for 2 minutes at 20°C. Subsequently, 50 μL of each diluted aliquot was transferred to a 1-mL HPLC vial, diluted additionally with 0.95 mL of acetonitrile-water (1:1), and mixed with a vortex machine for 15 seconds.

Concentrations of voriconazole in aliquots were measured by use of HPLC with UV detection at 263 nm, as described elsewhere. Degradation by-products were not quantitated. A reverse-phase column with octyldecyl packing material was used. An isocratic (constant composition) mobile phase of acetonitrile, distilled water, and trifluoroacetic acid (50:50:0.02) was used at a flow rate of 1 mL/min. Voriconazole analytic standard was dissolved in methanol to a concentration of 100 μg/mL, and stored at approximately −20°C for the duration of the study. For each set of assays, this stock standard solution was dried under nitrogen at 40°C and dissolved in mobile phase to prepare calibration standards over a range of concentrations (2 to 100 μg/mL). A linear correlation between peak height and voriconazole concentration was detected over this range (R² > 0.999). The limit of detection (calculated as the concentration equivalent to a signal-to-noise ratio of 3 determined from background responses in 6 blank samples) was 0.027 μg/mL in SASS and 0.036 μg/mL in SADI. The limit of quantitation (equivalent to a signal-to-noise ratio of 10) was 0.090 μg/mL in SASS and 0.120 μg/mL in SADI.

Mean percentage voriconazole-recovery values for SASS and SADI suspensions (n = 10 aliquots/suspension) stored at room temperature (21 ± 1°C) were 88.4% and 91.9% of the intended concentrations, respectively. These values were near the lower end of the predefined pharmaceutical bioequivalence range (90% to 110%). Therefore, 3 modifications were made to the protocol to increase the percentage of drug recovered from the suspensions. First, the final suspension volume was increased to 40 mL for each formulation. Second, suspensions were not prepared in a graduated cylinder to avoid drug residues remaining in the cylinder; rather, the suspensions were brought to a sufficient volume and strength by use of the volumetric markers on the storage bottles themselves. Third, an acidic diluent was added to potentially improve drug solubility. Other than the aforementioned modifications, new suspensions were then prepared in the same manner as previously described.

Each compounded mixture was transferred from the mortar and pestle to 200-mL brown glass bottles, and the mortar was washed with sufficient suspending vehicle (SASS or SADI) to achieve a final volume of 40 mL. Ten 0.2-mL aliquots of each suspension were diluted with a mixture of acetic acid (1%), acetonitrile (49.5%), and deionized water (49.5%) to acidify the suspension, and ten 0.2-mL aliquots were collected without acidification. The HPLC procedure was repeated with the new suspensions.

A Student t test was used to compare mean percentage voriconazole-recovery values from suspensions prepared at different volumes and with different liquid vehicles; percentage recovery values were considered significantly (P < 0.05) different.

Mean percentage voriconazole-recovery values were significantly higher in the 40-mL SASS suspensions stored at room temperature than in the 10-mL suspensions stored in the same condition. Percentage recovery for the acidic dilution (102.0%) was only marginally different from that of the neutral dilution (101.6%; Table 1). Dried drug residues were visible on the inner surface of the 200-mL glass bottles when the suspensions were stored, which may have led to drug loss. Therefore, in a final modification, 2-oz (60-mL) plastic amber bottles with volume gradations marked by the manufacturer were used to store the 40-mL voriconazole suspensions at 40 mg of voriconazole/mL. Bottles of the same size from the same manufacturer were used for each suspension for consistency. Findings from these preliminary trials suggested that recovery of voriconazole was optimized with 40-mL suspension volumes, smaller (60-mL) amber plastic bottles, and an unacidified acetonitrile-water diluent.

Evaluation of suspensions—Each suspension was extemporaneously prepared (compounded) from eight 200-mg voriconazole tablets that were pulverized into a uniform powder by use of the optimal method determined for suspension preparation. After the mortar and pestle were rinsed, each suspension was diluted with a sufficient volume of vehicle (SASS or SADI) and then poured into the bottle to achieve a final concentration of 40 mg/mL in a 40-mL volume within 60-mL plastic amber bottles. To evaluate variability of voriconazole distribution within each suspension, 2 identical voriconazole suspensions were compounded for each type of suspending vehicle. One bottle of each type of suspension was immediately refrigerated and stored at 3° to 7°C for 3 hours to chill. An aliquot from each of the bottles of the same size from the same manufacturer were used for each suspension for consistency. Findings from these preliminary trials suggested that recovery of voriconazole was optimized with 40-mL suspension volumes, smaller (60-mL) amber plastic bottles, and an unacidified acetonitrile-water diluent.

Table 1—Variability of voriconazole concentrations in extemporaneously prepared suspensions made with 200-mg voriconazole tablets and SASS and SADI liquid vehicles at room temperature (RT; 21 ± 1°C) and after refrigeration (RF; 3° to 7°C) in various conditions in an experiment to determine optimal preparation conditions.

<table>
<thead>
<tr>
<th>Type of suspension</th>
<th>Total volume of suspension (mL)</th>
<th>Voriconazole concentration* (mg/mL)</th>
<th>Percentage recovery</th>
<th>CV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SASS-RTT</td>
<td>10</td>
<td>35.35 ± 0.88</td>
<td>88.4</td>
<td>2.5</td>
</tr>
<tr>
<td>SADI-RTT</td>
<td>10</td>
<td>36.76 ± 0.57</td>
<td>91.9</td>
<td>1.6</td>
</tr>
<tr>
<td>SASS-RTT (pH 3.47)</td>
<td>40</td>
<td>40.80 ± 1.45</td>
<td>102.0</td>
<td>3.6</td>
</tr>
<tr>
<td>SASS-RTT (pH 5.78)</td>
<td>40</td>
<td>40.62 ± 1.01</td>
<td>101.6</td>
<td>2.5</td>
</tr>
<tr>
<td>SASS-RTT</td>
<td>40</td>
<td>36.84 ± 0.93</td>
<td>92.1</td>
<td>2.5</td>
</tr>
<tr>
<td>SADI-RTT</td>
<td>40</td>
<td>41.64 ± 0.08</td>
<td>103.4</td>
<td>0.1</td>
</tr>
<tr>
<td>SASS-RFT</td>
<td>40</td>
<td>39.53 ± 1.43</td>
<td>99.6</td>
<td>3.6</td>
</tr>
<tr>
<td>SADI-RFT</td>
<td>40</td>
<td>43.29 ± 0.90</td>
<td>108.2</td>
<td>2.1</td>
</tr>
</tbody>
</table>

*Values in this column are reported as mean ± SD. n = 10 aliquots. †Prepared for HPLC with unacidified diluent.

Suspensions were originally prepared to contain 40 mg of voriconazole/mL. Room-temperature aliquots were collected immediately after suspension preparation, and refrigerated aliquots were collected approximately 3 hours after refrigeration (to allow aliquots to reach the appropriate storage temperature). Except where indicated otherwise, an acidified (glacial acetic acid) acetonitrile-water (1:1) diluent was used for HPLC measurement of drug concentration.
remaining suspensions was analyzed at room temperature (21 ± 1°C) immediately after suspension preparation. To evaluate the stability of the suspensions, 4 additional voriconazole suspensions were compounded in the same manner as for evaluation of variability of drug distribution. One bottle of each preparation was again immediately refrigerated and stored at 3° to 7°C for 30 days; the remaining 2 preparations were stored at room temperature (21 ± 1°C) for 30 days.

Aliquot collection and analysis—Each drug preparation was vigorously shaken by hand for 30 seconds prior to each aliquot collection to promote homogeneity. Aliquots were then collected and analyzed via HPLC as described for the determination of optimal method of suspension preparation. Voriconazole concentrations were measured in twenty 0.2-mL aliquots of each type of suspension medium to measure variability of drug distribution and accuracy of drug concentration within the suspensions.

Five replicates (0.2-mL aliquots) of each suspension at both storage temperatures were collected for stability analysis on days 0, 7, 15, 23, and 30 after preparation. On day 0, room-temperature aliquots of suspensions were collected immediately after suspension preparation; those of refrigerated aliquots were collected 3 hours after refrigeration. Each suspension was inspected by the same investigator (KQN) prior to aliquot collection, and color, odor, opacity, and the existence of visible solids were recorded. The pH of each preparation was also measured at each time point. On days 0, 15, and 30 after suspension preparation, a 0.3-mL aliquot was collected from the center of each by use of a sterile syringe with a 16-gauge hypodermic needle. These aliquots were submitted to the teaching hospital microbiology laboratory for aerobic and anaerobic bacterial culture.

Data analysis—Mean ± SD voriconazole concentrations in aliquots were calculated for each suspension at each collection point and storage temperature. Concentration accuracy was determined by comparing the mean actual voriconazole concentration with the intended drug concentration and calculating the percentage recovery. Variability was determined by calculating the CV, in which the SD was calculated and compared with the actual concentration. For assessment of variability in drug distribution within suspensions, actual voriconazole concentrations measured by means of HPLC analysis were compared with intended concentrations and considered accurate when mean percentage recovery was ≥ 90%. Acceptable variability was defined as a CV < 5%. For assessment of drug stability, a suspension was considered stable when the concentration on day 30 was ≥ 90% of the original concentration on day 0.

Results

Drug distribution—Calculations of mean percentage drug-recovery values and CV were performed from the measurement of mean ± SD voriconazole concentrations for the suspensions. In room-temperature SASS and SADI aliquots, mean percentage voriconazole-recovery values were 92.1% (CV, 2.5%) and 103.4% (CV, 1.6%), respectively (Table 1). Mean percentage voriconazole-recovery values for refrigerated SASS and SADI aliquots were 99.0% (CV, 3.6%) and 108.2% (CV, 2.1%), respectively. Voriconazole suspended in SADI, regardless of whether stored at room temperature or refrigerated, was more viscous than voriconazole suspended in SASS.

Drug stability—The stability of voriconazole in the 2 suspension media was evaluated in 2 experiments. The mean percentage voriconazole-recovery values and CVs for room-temperature SASS and SADI aliquots from day 0 were 90.7% (CV, 2.3%) and 87.8% (CV, 5.1%), respectively (Table 2). The mean percentage drug recovery

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### Table 2—Mean ± SD actual voriconazole concentrations and percentage voriconazole-recovery values in contemporaneously prepared suspensions made with 200-mg voriconazole tablets and SASS and SADI liquid vehicles at RT and after RF, as measured on days 0, 7, 15, 23, and 30 after preparation (n = 5 aliquots/measurement).

<table>
<thead>
<tr>
<th>Day</th>
<th>Voriconazole concentration (mg/mL)</th>
<th>Percentage recovery</th>
<th>Voriconazole concentration (mg/mL)</th>
<th>Percentage recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>36.26 ± 0.84</td>
<td>90.7</td>
<td>35.50 ± 0.70</td>
<td>88.7</td>
</tr>
<tr>
<td>7</td>
<td>40.19 ± 0.79</td>
<td>100.4</td>
<td>38.03 ± 0.95</td>
<td>95.1</td>
</tr>
<tr>
<td>15</td>
<td>40.66 ± 0.59</td>
<td>101.6</td>
<td>38.51 ± 0.53</td>
<td>96.3</td>
</tr>
<tr>
<td>23</td>
<td>39.00 ± 0.76</td>
<td>97.5</td>
<td>38.02 ± 0.59</td>
<td>95.1</td>
</tr>
<tr>
<td>30</td>
<td>39.89 ± 1.02</td>
<td>99.6</td>
<td>38.98 ± 0.99</td>
<td>92.2</td>
</tr>
</tbody>
</table>

### Table 3—Values of pH for contemporaneously prepared suspensions of voriconazole made with 200-mg voriconazole tablets and SASS and SADI liquid vehicles at RT and after RF, as measured on days 0, 7, 15, 23, and 30 after preparation (n = 1 aliquot/measurement) in 2 experiments.

<table>
<thead>
<tr>
<th>Type of suspension</th>
<th>Day 0</th>
<th>Day 1</th>
<th>Day 15</th>
<th>Day 23</th>
<th>Day 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experiment 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SASS-RT</td>
<td>4.67</td>
<td>4.65</td>
<td>4.68</td>
<td>4.69</td>
<td>4.70</td>
</tr>
<tr>
<td>SASS-RF</td>
<td>4.71</td>
<td>4.62</td>
<td>4.67</td>
<td>4.59</td>
<td>4.66</td>
</tr>
<tr>
<td>SADI-RT</td>
<td>4.82</td>
<td>4.80</td>
<td>4.80</td>
<td>4.81</td>
<td>4.85</td>
</tr>
<tr>
<td>SADI-RF</td>
<td>4.81</td>
<td>4.82</td>
<td>4.77</td>
<td>4.82</td>
<td>4.83</td>
</tr>
<tr>
<td>Experiment 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SASS-RT</td>
<td>4.56</td>
<td>4.62</td>
<td>4.56</td>
<td>4.61</td>
<td>4.59</td>
</tr>
<tr>
<td>SASS-RF</td>
<td>4.56</td>
<td>4.61</td>
<td>4.59</td>
<td>4.53</td>
<td>4.66</td>
</tr>
<tr>
<td>SADI-RT</td>
<td>4.67</td>
<td>4.82</td>
<td>4.72</td>
<td>4.77</td>
<td>4.72</td>
</tr>
<tr>
<td>SADI-RF</td>
<td>4.70</td>
<td>4.71</td>
<td>4.69</td>
<td>4.73</td>
<td>4.71</td>
</tr>
</tbody>
</table>

---
values and CVs of refrigerated SASS and SADI aliquots were 88.7% (CV 2.0%) and 93.0% (CV 2.9%), respectively. Day-7 results yielded higher percentage voriconazole-recovery values, compared with day-0 results in which mean percentage voriconazole-recovery values ranged from 95.1% (refrigerated SASS) to 100.8% (refrigerated SADI). Likewise, in subsequent days up to day 30, percentage voriconazole-recovery values were stable and > 90% of the intended voriconazole concentration was maintained for all suspensions (CV < 5%). The pH values of each suspension were consistent throughout the 30-day period (Table 3). Bacterial culture of all suspension aliquots collected on days 0, 15, and 30 failed to yield any bacterial (aerobic or anaerobic) growth. Suspensions prepared with SADI were more viscous than those prepared with SASS; however, no changes in odor or color were detected in any suspension.

Because the measured voriconazole concentrations in suspensions on day 0 were less than those on days 7, 15, 23, and 30 of the first experiment, the experiment was repeated to evaluate the basis for these differences. In this second experiment, an additional set of aliquots collected on day 3 was included to test whether increased solubility may have developed between days 0 and 7 in the first experiment. Mean percentage voriconazole-recovery values for room-temperature SASS and SADI aliquots on day 0 were 96.3% (CV 3.6%) and 112.1% (CV 5.8%), respectively (Table 4). Mean percentage voriconazole-recovery values for refrigerated SASS and SADI aliquots were 104.0% (CV 3.2%) and 107.3% (CV 1.0%), respectively. Drug recovery remained > 90% (CV < 5%) of the intended voriconazole concentration for each formulation for the duration of the second experiment. The pH values during the 30-day period were similar to values identified in the earlier experiment. Bacterial culture of all suspension aliquots collected on days 0, 15, and 30 failed to yield any bacterial (aerobic or anaerobic) growth. Again, suspensions prepared with SADI were more viscous than those prepared with SASS; however, no changes in odor or color were detected in any suspension. Calculation of the combined mean percentage voriconazole-recovery values from both experiments yielded datum points for each aliquot collection point that were within our pharmaceutical bioequivalence range of ± 10% of the intended concentration (Figure 1).

Table 4—Mean ± SD actual voriconazole concentrations and percentage voriconazole-recovery values in extemporaneously prepared suspensions made with 200-mg voriconazole tablets and SASS and SADI liquid vehicles at RT and after RF, as measured on days 0, 5, 7, 15, 23, and 30 after preparation (n = 5 suspension aliquots/measurement).

<table>
<thead>
<tr>
<th></th>
<th>Sass-RT</th>
<th>Sass-RF</th>
<th>Sadi-RT</th>
<th>Sadi-RF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day</td>
<td>Voriconazole concentration (mg/mL)</td>
<td>Percentage recovery</td>
<td>Voriconazole concentration (mg/mL)</td>
<td>Percentage recovery</td>
</tr>
<tr>
<td>0</td>
<td>38.50 ± 1.38</td>
<td>96.3%</td>
<td>41.62 ± 1.33</td>
<td>104.0%</td>
</tr>
<tr>
<td>5</td>
<td>38.17 ± 1.23</td>
<td>90.4%</td>
<td>37.42 ± 0.68</td>
<td>93.5%</td>
</tr>
<tr>
<td>7</td>
<td>40.58 ± 0.72</td>
<td>101.4%</td>
<td>42.53 ± 0.96</td>
<td>106.3%</td>
</tr>
<tr>
<td>15</td>
<td>36.67 ± 0.68</td>
<td>92.2%</td>
<td>37.70 ± 0.56</td>
<td>94.3%</td>
</tr>
<tr>
<td>23</td>
<td>37.43 ± 0.38</td>
<td>93.6%</td>
<td>37.10 ± 0.51</td>
<td>92.7%</td>
</tr>
<tr>
<td>30</td>
<td>38.66 ± 0.47</td>
<td>96.6%</td>
<td>36.25 ± 0.48</td>
<td>90.6%</td>
</tr>
</tbody>
</table>

See Tables 1 and 2 for key.

Discussion

Extemporaneously prepared suspensions of voriconazole in SASS and SADI at 40 mg/mL in 40-mL volumes stored in 60-mL plastic amber bottles resulted in acceptable drug stability (> 90% voriconazole recovery) when maintained for 30 days at room and refrigeration temperatures.

The decision to use 40-mL volumes was made after preliminary trials were conducted to determine the minimum volume that could be used to yield a stable 40 mg/mL suspension. Preliminary attempts to compound a 10-mL volume of suspension were made to minimize the cost of suspension preparation because for many small exotic animals, a 10-mL volume containing 40 mg of voriconazole/mL would be sufficient for a 30-day treatment period. Working with the lower 10-mL volumes of suspending vehicles in the present study resulted in less voriconazole being recovered from suspension aliquots because of a limitation associated with the volume of base solution used to completely wash out residual drug in the mortar. In addition, the 200-mL glass bottles were too large for the 10-mL vol-
umes, and drug residues were adhering to the inner surface of the glass, potentially reducing the amount of drug available to be recovered from suspension aliquots. In general, veterinarians and pharmacists attempt to minimize cost of medications extemporaneously prepared. This is done by using less amounts of drug and suspending vehicle to yield a low total volume of the medication. However, the results of the present study indicated that minimizing the volume of the suspension yielded a product with a lower concentration of voriconazole than that in a higher suspension volume. If such a low-concentration suspension of drug were prescribed, then inaccurate dosing and compromised treatment outcomes could result.

Variability in the dispersion of drug molecules within suspensions was also evaluated in the study reported here. The low CVs indicated that the distribution of voriconazole throughout the suspending vehicle was uniform. Reduction of the diluent pH had a negligible effect on increases in drug solubility. Some azole antifungal medications such as ketoconazole and itraconazole have improved solubility and bioavailability in humans and animals when acidic fluid such as citrus juice or cola is ingested at the time of drug administration.\(^\text{19,20}\) Results of our preliminary trials indicated that pH did not influence drug solubility, and >90% of suspended voriconazole was recovered whether aliquots were prepared for HPLC analysis with neutral or acidic diluent.

In the first experiment of the present study, lower percentage voriconazole-recovery values were identified at day 0, compared with values obtained every 7 days afterward for 30 days. These low values were most likely attributable to differences in standard calibration curves or experimental variability. It is also possible that voriconazole gradually dissolved in the suspension vehicles, which could have led to the finding of more dilute aliquots collected on day 0 versus other days. However, when the experiment was repeated and aliquots of suspensions were obtained and measured at an additional time point (day 5), a decrease from the percentage of voriconazole recovered on day 0 was detected, although values were still within the expected range of ±10% of the intended concentration. If drug solubility changed with time, then one would have expected an increase in voriconazole concentrations as duration of storage increased; however, such an increase was not identified. Therefore, the reduction in the percentage of voriconazole recovered from suspensions between day 0 and the other time points in the preliminary trials was most likely attributable to interassay variability. The combined results from the 2 subsequent experiments likely reflected that which would be obtained if multiple suspensions that vary in methods of extemporaneous preparation are compounded. When the results were combined, all values were within ±10% of the intended concentration, which is an acceptable pharmaceutical standard.\(^\text{21}\)

The viscosity of room-temperature SADI and refrigerated SASS aliquots increased with time without a change in color and seemed to obscure the fragments of suspended voriconazole and tablet excipients more than the viscosity of SASS did during the same period. Deionized water may have helped dissolve the fragments of the voriconazole tablet to an extent greater than it was dissolved in SASS, or the increased viscosity may have simply yielded a physical barrier that obscured detection of suspended fragments. Although not statistically confirmed, percentages of voriconazole recovery were slightly higher in SADI versus SASS suspensions, but were still within ±10% of the intended concentration during each 30-day experiment.

The commercial suspending vehicle\(^\text{c}\) contains preservatives that may become too dilute to maintain antimicrobial properties after dilution with deionized water. Lack of preservatives can encourage bacterial overgrowth, which in a drug suspension may not only change the pH of the solution and alter drug solubility, but may also alter the integrity of the active drug in the suspension.\(^\text{22,23}\) In the present study, there was no evidence of bacterial growth in any voriconazole suspensions during the 30-day period.

Dilution of the suspending vehicle with deionized water did not appear to reduce the percentage of voriconazole recovered during the study period. Voriconazole concentrations did not appear to decrease with time, and voriconazole in the opaque SADI did not degrade to an appreciable amount with time. In general, compounded drugs may be inactivated by oxidation, reduction, and other chemical reactions that may make them ineffective.\(^\text{24}\) Whereas other orally administered azole antifungals such as itraconazole and ketoconazole already have limited to poor oral absorption,\(^\text{25}\) it is often difficult to distinguish whether a poor treatment outcome is attributable to inactivated, unstable drug or lack of drug absorption. However, it has been suggested that the use of a suspending vehicle is better than sterile water alone because a suspending vehicle can improve the bioavailability of extemporaneously prepared voriconazole suspensions.\(^\text{9}\) The suspending vehicle may do so by yielding a more uniform suspension, thereby likely increasing solubility of the drug in the suspending vehicle or reducing gastrointestinal transit time to allow for higher drug absorption.\(^\text{26}\)

Results of the study reported here indicated that extemporaneously prepared voriconazole (40 mg/mL) suspensions made with 200-mg voriconazole tablets and SASS or SADI stored in 40-mL volumes in plastic amber bottles were stable for 30 days. Storage at room temperature or in a refrigerator did not affect drug solubility or concentration. Such suspensions may be stored for 30 days, thereby reducing the cost of treatment for small exotic animals and birds and allowing treatment for 30 days with only 1 suspension.

\begin{itemize}
  \item \textbf{a.} Voriconazole (Vfend), 10 mg/mL, IV injectable solution, Pfizer Inc, Groton, Conn.
  \item \textbf{b.} Voriconazole (Vfend), 50-mg tablets, Pfizer Inc, Groton, Conn.
  \item \textbf{c.} Voriconazole (Vfend), 200-mg tablets, Pfizer Inc, Groton, Conn.
  \item \textbf{d.} Voriconazole (Vfend), 40 mg/mL oral suspension, Pfizer Inc, Groton, Conn.
  \item \textbf{e.} Ora-Plus, Paddock Laboratories Inc, Minneapolis, Minn.
  \item \textbf{f.} Ora-Sweet, Paddock Laboratories Inc, Minneapolis, Minn.
  \item \textbf{g.} Transferpettor, BrandTech Scientific Inc, Essex, Conn.
  \item \textbf{h.} Zorbax RX-C8, 5 µm, 4.6 × 150-mm reverse-phase column with a 4.6 × 12.5-mm guard column, Agilent Technologies, Wilmington, Del.
\end{itemize}
i. Pfizer Inc, Groton, Conn.

j. Glacial acetic acid, HPLC grade, EMD Chemicals Inc, Darmstadt, Germany.

k. Waters 501 and 510 pumps, 717 autosampler, and 996 PDA detector, Waters Corp, Milford, Mass.

l. pH meter 340, Corning Inc, Corning, NY.

References


