

Oil-based compounding flavors more accepted by feline patients

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OBJECTIVE

To evaluate the voluntary acceptance of 10 commercially available compounding flavors in cats.

ANIMALS

46 healthy cats between 1 and 12 years of age.

PROCEDURES

Each cat underwent a 14-day study period consisting of a 4-day acclimation period followed by a 10-day trial period in which each cat was randomly offered 10 different compounding flavors. Owners completed a presurvey along with a daily observation logbook. Kits, including residual amounts of flavors, were returned and weighed to determine residual weight and calculate the amount ingested.

RESULTS

Overall, cats did not voluntarily accept most of the compounding flavors; 58.8% (124/211) and 84.5% (267/311) of offered samples of oil-based and water-based compounding flavors, respectively, were rejected or minimally accepted. Cats were significantly ($P < .001$) more likely to accept oil-based flavors, compared to water-based flavors. The sweet water-based flavors were least accepted, compared to water-based control and water-based savory flavors ($P = .040$ and $P < .001$, respectively). Owner-perceived acceptance was moderately correlated with residual flavor weights (Kendall tau $[\tau] = -0.466$; $P < .001$). Owners were not able to accurately predict which flavors their cats would accept.

CLINICAL RELEVANCE

Cats should be offered oil-based compounding flavorings when available, whereas water-based sweet flavorings should be avoided. Owner perception of acceptance is a valid metric to assess flavor acceptance, which can be used in future studies evaluating flavor acceptance. Owners may not accurately predict their cats' flavor preferences, limiting their ability to guide optimal flavor selection.

The administration of oral formulations of medications to cats is challenging to their caregivers. Owners reported that they were unable to give one-fourth of the prescribed doses of oral medications¹ and < 50% of cats voluntarily accepted conventionally flavored tablets.² As a result, owners may try methods such as manual pilling or “dry swallowing,” which can have deleterious consequences, including negatively affecting the human-animal bond, reducing treatment adherence, or increasing the risk of esophagitis or stricture.² Liquid formulations appear to be more palatable than solid medications (tablets or capsules) and result in improved client adherence.² Due to the substantial challenges involved in medicating feline patients and increased acceptance of liquid medications, veterinarians often use compounding flavors to improve palatability,

ease client administration, and enhance adherence to treatment plans.^{3,4}

Palatability can be defined as the property of being agreeable to taste.^{5,6} One measure of palatability is the voluntary acceptance of a product.^{3,5,6} Voluntary acceptance can depend on many factors, including flavor, texture, consistency, odor, temperature, and color.^{3,5-7} While the FDA Center for Veterinary Medicine currently has no palatability standard, the European Medicines Agency has created a threshold of 70% voluntary acceptance in cats to make a palatability claim on a supplementary protection certificate.⁶ While this applies to species-specific veterinary-approved drug products, the availability of such products is limited.⁴ Additionally, according to these guidelines, acceptance measurements can be obtained in either the field or a laboratory setting,⁶ which could influence

the actual palatability in a real-world setting. Because of the paucity of feline-specific veterinary products, coupled with the difficulty of medicating cats,^{3,4} veterinarians often turn to veterinary compounding to improve palatability and compliance.⁴ Despite the common use of compounding flavors to enhance palatability, no published studies exist evaluating acceptance or preference of compounding flavoring agents in cats. Generally, cats have been found to prefer protein and fat,⁸ with specific preferences toward fish, liver, meat, sour or acidic flavors, yeast, and dairy.³ Despite studies demonstrating that cats lack sweet taste receptors⁹ and do not respond to mono- or disaccharides,¹⁰ other studies have shown feline acceptance of glucose¹¹ and sucrose.^{8,12} It is unclear whether “sweet” acceptance in these studies is related to the sweet flavor or to another aspect of palatability⁷ such as texture, smell, or consistency or whether these findings can translate to medication flavoring. Although the palatability of sweet flavors in cats is controversial, sweetened excipients are often utilized in compounded suspensions even when formulations are not specifically sweet flavored.¹³ Despite our understanding of flavor preferences in cats, analogous compounding flavors have not been evaluated, nor compared, to evaluate which flavors might be the most accepted. Identification of commonly preferred flavors could improve compounding procedures and increase chances of successful treatment. Research is needed to further investigate what compounding flavors cats will accept under normal home conditions to enhance clients’ ability to reliably medicate their cats.

The primary aim of the study reported here was to determine voluntary acceptance of 10 commonly used compounding flavors in cats. Secondary aims were to determine whether owner perception of acceptance is a validated metric based on residual sample weight and whether owners could accurately predict accepted flavors.

Materials and Methods

Healthy cats between the ages of 1 and 12 years old owned by faculty, staff, and students at the University of Wisconsin-Madison (UW-Madison) School of Veterinary Medicine were enrolled in this study on the basis of response to 2 recruitment emails. A paper survey of owners was conducted at the time of enrollment to ascertain their cat’s demographic information, medical history (including their cat’s experience with previously prescribed oral, liquid formulations of medications, if applicable), feeding history (including diet type, feeding regimen, and speed of consumption), and which flavor classes they predicted their cats would enjoy most and least. The survey was developed in partnership with the UW-Madison Survey Center and complied with good practice methodologies (**Supplementary Appendix S1**). Expert review and pretesting of the survey with veterinarians in academia and the field of veterinary nutrition were done to gather feedback on survey content, terminology, and understanding, with the intent of achieving face validity (ie, the degree to which the survey appeared

effective in its objective). Members of the Survey Center then reviewed all survey questions for clarity. Cats were excluded on the basis of age (under 1 year of age and over 12 years of age), health, and administration of any oral formulations of medications in the previous 6 months. A 6-month time frame was chosen to reduce potential bias of recent previous oral medications or medication administration. Protocols were approved by the IACUC at UW-Madison, and this study was found to be exempt by the UW-Madison for an Institutional Review Board.

Procedures

The 10 compounding flavors selected were based on those routinely available for compounding and flavors preferred in cats based on previous studies.^{3,12} Samples were prepared in bulk by the UW-Madison Veterinary Care Hospital Pharmacy using Ora-Blend (Perrigo Co plc) as the base (vehicle) for the water (aqueous) flavors, a fixed oil suspension vehicle (Professional Compounding Centers of America [PCCA]) base for the oil flavors, and commercially available compounding flavors. Identical flavors were not available in both oil and water formulations; thus, similar flavor profiles between the oil and water formulations were selected when possible. The final concentration of the bulk oil-based flavored flavors was 1% and the final concentration of the bulk water-based flavored flavors was 3% on the basis of standard pharmaceutical recommendations. The compounding bases used were an oil oral suspending vehicle, fixed oil suspension vehicle (PCCA), and an aqueous-based oral suspending vehicle, Ora-Blend (Perrigo Co plc). These also served as a control for each group and were included in the flavor consideration. The water-based flavors were liver (Liver, Liquid [Water Miscible]; PCCA), chicken (Chicken Pot Pie; FLAVORx for Pets), tuna (Grilled Tuna; FLAVORx for Pets), marshmallow (Marshmallow, Artificial; PCCA), and vanilla butternut (Vanilla Butternut, Artificial; PCCA). The oil-based flavors were chicken (Chicken Grilled, Natural [Oil Miscible]; PCCA), fish (Fish, Artificial, Liquid [Oil Miscible]; PCCA), and liver (Liver, Artificial, Liquid [Oil Miscible]; PCCA). The pH of all the prepared compounding flavors ranged between 4 and 4.5. Each bulk flavor was assigned a number by the investigators, and samples were identified by number only.

Kits were prepared for participating cats and included 10 individual, preweighed, sealed, and numbered plastic bags each containing a shallow, black plastic feeding tray and a numbered syringe containing 5 mL of flavored solution taken from the bulk stock. Owners were blinded to the flavors. Randomized schedules for trials were prepared by the investigators using an online random number generator and provided with kits. Once received, kits were stored in the refrigerator. Instructions for use, a schedule for flavor administration, and an observation logbook were also provided. Four additional feeding trays were provided for use during the acclimation period, 1 tray for each acclimation day. Owners were asked to store the kit in the refrigerator and complete trials within 14 days.

On days 1 through 4 of the study period, owners were instructed to acclimate their cats by placing a fa-

vored treat on one of the black feeding trays once daily. Flavor trials occurred on days 5 through 14 and were conducted using the provided randomized schedule. For each trial, the corresponding bag from the randomized schedule was removed from the refrigerator and the syringe number, date, and time of sample offering were recorded. Owners removed the syringe cap, emptied the contents of the syringe (5 mL) into the feeding tray, offered the feeding tray to their cat for 5 minutes, and then removed the tray. If the cat started eating the flavoring and continued to eat at the end of 5 minutes, the owners were allowed to let the cat finish. If their cat walked away, the owners could bring the cat back to the feeding tray or bring the feeding tray to their cat up to 3 times. If the cat continued to walk away after 3 attempts, owners waited 5 minutes, then concluded the trial. Owners were instructed not to force the cat to eat any of the flavoring.

At the end of each trial, owners recorded the time of removal and perception of their cat's response using a 7-point Likert-type scale (1 = did not like; 7 = loved) as well as any applicable comments. Owners then placed the feeding tray right side up with any remaining liquid and the syringe and cap back into the individual, numbered plastic bag and kept it refrigerated for the remainder of the trial period. A subset of participants (15 owners) was asked to pull sample fluid back into the syringe and recap it after each flavor trial to assess whether the volume returned was consistent with the weighing of kits. All components of the kits were returned after day 14 for reweighing (Adventurer Precision AX423N; Ohaus) of the kit contents and, when applicable, recording of syringe volume (mL) post-trial. Any complications with residual weights such as content leakage and visual inaccuracy of syringe volume were noted. Owners' comments and flavor rankings were transferred into a digital spreadsheet.

Data analysis

Normality of flavor scores and weights were determined by means of visual assessment of Q-Q plots and the Shapiro-Wilk test in which an a priori α level was set at 0.10. The results indicated non-Gaussian distributions for all values, so the nonparametric Wilcoxon-Mann-Whitney test was elected to assess differences among flavor preferences and the influence of pet owner-provided information about their cats' historical preferences. Kendall rank correlation coefficient was employed to compare associations between residual flavor weight, owner perception of enjoyment, and owner-retrieved sample volume. Values of $P < .05$ were considered statistically significant. All statistical analyses were run using an available statistical computing software (R: A Language and Environment for Statistical Computing version 4.0.4; R Foundation for Statistical Computing).

Results

Fifty-six owners enrolled and completed the pre-survey for admission into the study. Of those, 50 completed an initial 14-day trial; however, 3 of those were discarded prior to data analysis for incomplete report-

ing or loss of samples. One research subject dropped out because the cat acquired giardia during the acclimation phase. Forty-six cats in total completed the study and met the requirements for participation. Of the cats that were admissible into the study, 41 had fully completed surveys that could be matched to their acceptance data. The remaining 5 were incomplete, but there was sufficient data regarding age and health status for admission into the acceptance study.

All cats in the study were reportedly healthy and between the ages of 1 and 12 years (mean, 4.60 years; SD, 2.86 years). All were seen by a veterinarian in the last year with the exception of 1 cat that was owned by a veterinarian. The cats included 61% (25/41) spayed females and 39% (16/41) castrated males. There were no sexually intact study participants. Sixteen of the 41 (39%) cats were healthy and reportedly had always been healthy, whereas the remaining 25 (61%) had health problems in the past that were resolved or had been stable for the last 6 months. Eighteen of the 41 (44%) cats had received oral liquid medications in the past, but none had received oral liquid medications in the previous 6 months. Having received oral liquid medication in the past did not produce a statistically significant difference in overall preference.

One secondary aim of this study was to determine whether owner perception of cat flavor preference would accurately reflect the amount of flavor that was consumed by the cat. The weight of the sample remaining at the end of the trial and the owner's rating of their cat's perceived enjoyment were moderately correlated (Kendall tau $[\tau] = -0.466$; $P < .001$; **Figure 1**). All statistical results were calculated using both weight and owner rating of preference, and in the overwhelming majority of calculations, significance values were aligned. For ease of discussion, all results are given in owner preference values unless sample weight and preference differed. Volume of residual flavors was evaluated in a subset of 15 participants (150 individual sample syringes). Recovering fluid volume into a syringe was more technically difficult for owners, and 16 samples were not sufficiently redrawn into syringes to allow measurement. For the remaining 134 trial samples, residual volume was strongly correlated to residual sample weight ($\tau = 0.688$; $P < .001$).

Comparing the results of the Likert scale results to the question "On a scale of 1 to 7, how much do you think your cat enjoyed this flavor (1 being hated and 7 being loved)," along with review of the corresponding comments, 3 preference groups emerged. Owners reliably chose 6 and 7 from the Likert scale to describe their pet's acceptance when their pets ate the food rapidly and thoroughly (eg, "ate all of it all at once, continued to lick the dish until gone"). Owners chose the ratings 3, 4, and 5 for various stages of semi-interest on their cat's part (ie, "ate about half, then came back to see if [there was anything] better"). Finally, the scores 1 and 2 were chosen to demarcate overt rejection or very mild interest (eg, "sniffed and licked 1 time, then shook its head and ran away"). These groupings are referred to as high, moderate, and low enjoyment ratings in the text

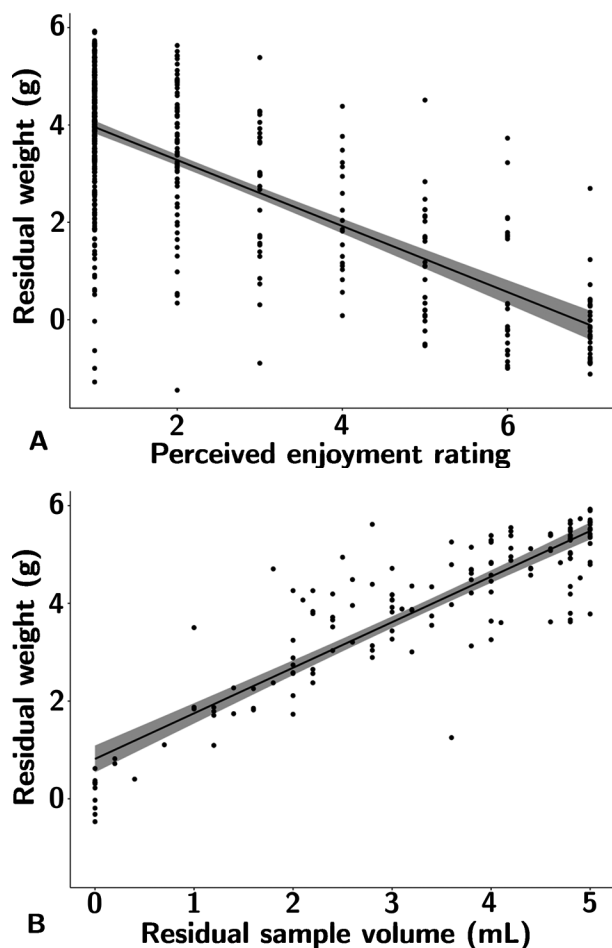


Figure 1—Scatterplots of returned flavor sample residual weight, compared with owner-rated perception of their cat’s enjoyment of the flavor (on a 7-point Likert-type scale; A) and residual sample volume (B) during a study conducted between March 2021 and January 2022 to assess voluntary acceptance of 10 commercially available compounding flavors by healthy cats ($n = 46$) 1 to 12 years of age. Each dot represents 1 cat’s results for 1 flavor, the dotted line represents the line of best fit, and the gray shaded area on the figure demarcates the 95% CI. Sample residual weight moderately correlated with owner perception of flavor preference (Kendall tau $[\tau] = -0.466$; $P < .001$) and highly correlated with sample residual volume ($\tau = 0.688$; $P < .001$).

and figures. Distributions of flavor ratings based on weight of sample remaining after individual trials were compiled (Figure 1).

Overall, most cats declined to voluntarily consume individual flavor samples, with 74.2% (391/527) of trials receiving a low preference rating, 14.0% (74/527) receiving a moderate preference rating, and 11.2% (62/527) receiving a high preference rating. When evaluating preferences of each flavor, it was found that the primary determinant of whether cats more or less commonly accepted the flavor was whether it was based in oil or water. Flavors in an oil base were more commonly enjoyed (median, 2; IQR, 1 to 4) than flavors in a water base (median, 1; IQR, 1 to 2; $P < .001$; **Figure 2**).

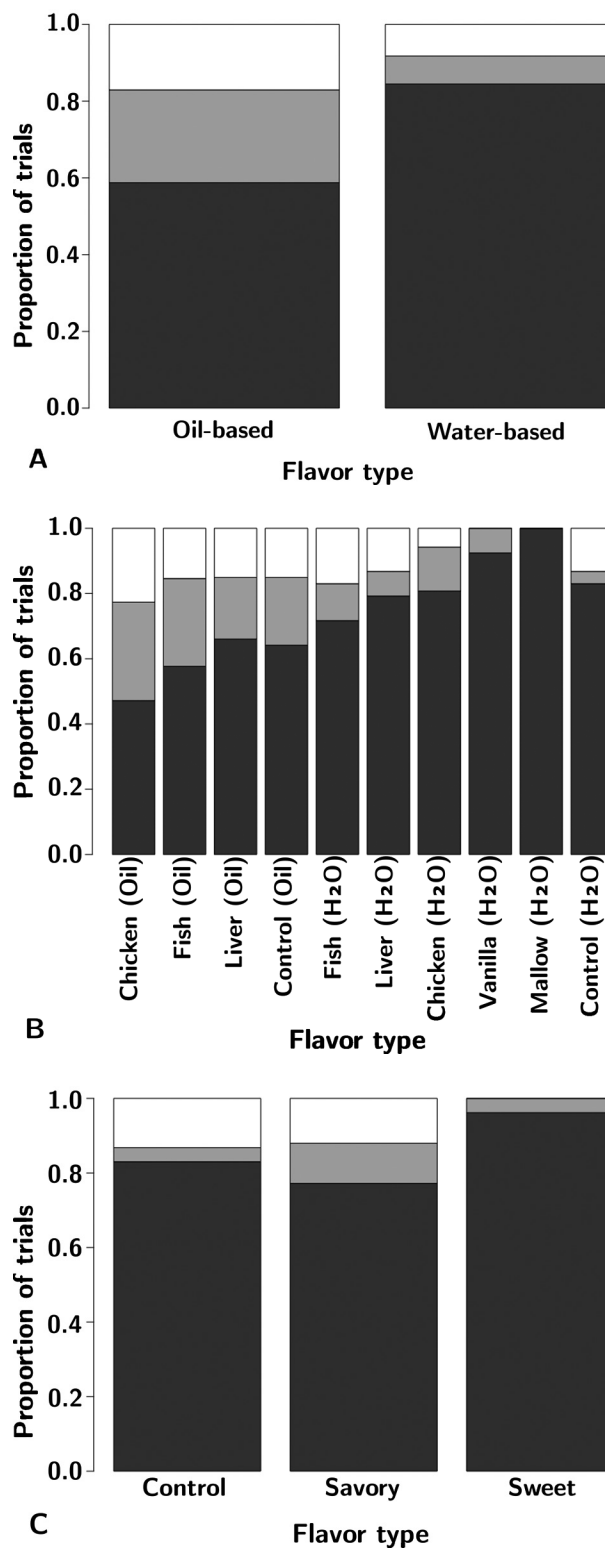


Figure 2—Stacked bar graphs of the proportions of flavor trials described in Figure 1 reported by owners on a 7-point Likert scale to have low (score of 1 or 2; dark gray), moderate (score of 3 to 5; light gray), or high (score 6 or 7; white) enjoyment by their cats, with samples grouped by flavor types, as follows: oil-based vs water-based samples (A), flavor and base (B), or flavor category (ie, control, savory, or sweet; C).

Individual flavor acceptance of oil-based flavors was significantly higher than water-based flavors. No flavor stood out as being significantly more favored than another; however, oil-based chicken (median, 3; IQR, 1 to 5) was the most preferred followed by oil-based fish (median, 2; IQR, 1 to 4). Water-based marshmallow flavor (median, 1; IQR, 1 to 1) was the least preferred flavor followed by water-based vanilla butternut (median, 1; IQR, 1 to 1).

This study did not include oil-based sweet flavors; however, there were 2 water-based sweet flavors. When enjoyment ratings of the water-based control (median, 1; IQR, 1 to 2) were compared to the water-based savory flavors (median, 1; IQR, 1 to 2), there was no significant difference between the two. However, when water-based sweet flavors (median, 1; IQR, 1 to 1) were compared to both the control and savory flavors, the sweet flavors were significantly less preferred than either ($P = .040$ and $P < .001$, respectively;

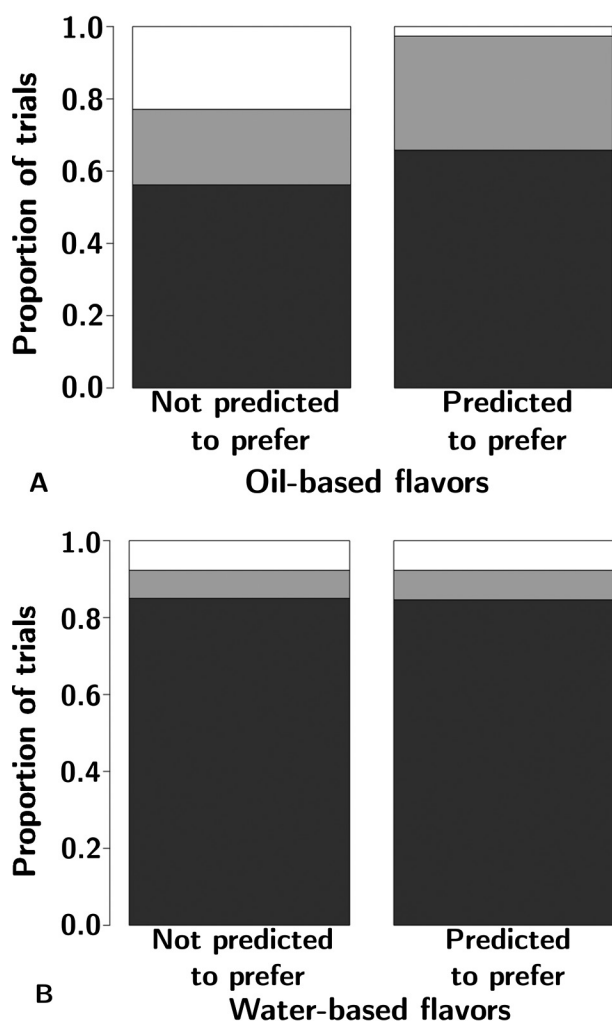


Figure 3—Stacked bar graphs of the proportion of flavor trials described in Figure 1 reported by owners on a 7-point Likert scale to have low (score of 1 or 2; dark gray), moderate (score of 3 to 5; light gray), or high (score 6 or 7; white) enjoyment by their cats, with samples grouped on the basis of owner-predicted preference (not predicted to prefer vs predicted to prefer) for oil-based flavors (A) and water-based flavors (B).

Figure 2). This effect disappears with evaluation of weight differences.

Owners overall reported that their cats would be very to extremely likely (3 to 5 on a 5-point Likert scale) to accept new flavors if offered them. There was no statistical differentiation between overall flavor acceptance based on owner-suspected acceptance of new flavors. Composite averages were taken of survey answers regarding likeliness to eat certain foods (dry, canned, scraps, treats, other pet food, hunted food, raw, and home cooked) and used as a metric of owner-perceived “pickiness” of cats. Composite averages were not significantly correlated to the likelihood that cats would be more or less likely to accept flavors. Owners also reported which flavor class they felt that their cats would prefer most from “poultry or chicken,” “seafood or fish,” “liver or red meat,” “sweet,” and “other.” Overall, when flavors that owners predicted their cats would prefer and flavors that owners predicted their cats would not prefer were evaluated, there was no difference. In water-based flavors, these ratios were nearly identical. For oil-based flavors, cats more commonly preferred flavors their owners did not predict would be well-accepted (median, 2; IQR, 1 to 5) over those they did predict to be accepted (median, 1.5; IQR, 1 to 3; **Figure 3**), though this was not statistically different.

Discussion

We found that oil-based compounding flavors had a significantly higher level of acceptance than water-based compounding flavors. However, while oil was significantly more accepted than water, study cats still did not accept 60% (124/211) of oil-based samples offered to them (compared to not accepting 85% [267/311] of water-based samples offered; Figure 2). While oil-based compounds should be chosen when possible, it is important to realize that cats still have low acceptance even with the preferred compounding options. These results were below a 70% voluntary acceptance level⁶ for a palatability claim of a veterinary-approved drug in the European Union. However, a common reason for compounding medications is to enhance palatability^{3,4} when palatable drug formulations are not available. It is possible that even modest improvements in palatability could have clinical utility. Additional research is needed to clarify whether adding compounding flavor enhances acceptance of individual medications and whether a generalized preference for oil-based flavoring agents is maintained under these conditions. It is possible that there may be interactions between medications themselves and compounding flavors that may make a universal “best” compounding flavor for cats unlikely.

Results of the present study indicated that owner perception of feline acceptance directly correlated with the amount of a compounding flavor consumed as measured by residual sample weight. It was also found that volume and sample weight were correlated. These findings indicated that residual volumes and owner perception are both valid metrics for de-

termination of flavor acceptance and could be used in further studies determining flavor acceptance. Measuring residual weights had many challenges including accounting for leakage, bulky kit returns, storage space, and scale access. Having alternative methods to reliably assess acceptance would be useful for future studies.

There was no significant difference between flavor acceptance at an individual flavor level; however, oil-based chicken and oil-based fish were the most accepted flavors overall, and the least accepted flavors were water-based vanilla butternut and water-based marshmallow. Of only the water-based flavors, the sweet flavors were still significantly less accepted than the other water-based compounds, including the control. This difference was significant when measured by owner perception but lost distinction when using weight changes. This may have been because the variability was too subtle and the sample size too small to detect the greater variability that weights provided over owner perception. Cats lack a sweet receptor gene⁹ and are unable to taste sweet flavors, so it might be expected that other flavors are more accepted compared to sweet. However, it was interesting that cats accepted sweet flavors significantly less than the control. This suggested that cats, despite not having a gene to taste sweetness, actively disliked the sweet compounding flavors included in this study. Despite previous studies suggesting acceptance of sucrose⁸ and glucose,¹¹ almost no cats in the present study voluntarily accepted the sweet flavors. The cause of this was unclear but could indicate that another component of the compounding negatively affected palatability. Additionally, our water-based flavorings were produced using a standard compounding vehicle containing a sweetening excipient. This could have contributed to the generally reduced acceptance of the water-based flavors compared to the oil-based flavors. On the basis of results of the present study, sweet flavors should be avoided when possible.

When trying to predict which cats would accept a flavoring compound, we found no difference between cats that had previously been given liquid medications and those that had not. We also found no difference in flavor acceptance based on owner-perceived pickiness, meaning cats that were rated more likely to accept flavors on owner survey were not actually more likely to accept flavors during the trial than those cats rated less likely to accept flavors by their owners.

Interestingly, we found that owners were not good at predicting which compounding flavor their cats would accept. While not statistically significant, cats less commonly accepted flavors that their owners predicted they would prefer, and they more commonly accepted flavors that their owners thought they would not prefer. The cause of this was unclear but may reflect a novelty factor or another factor affecting palatability. If an owner predicts that their cat will not like a flavor, they might be less likely to offer that flavor of treats or food. Therefore, when cats of the present study were offered such flavors, the

cats might have been more likely to accept it as a novel flavor. If flavor novelty enhances acceptance, it is possible that acceptance would decrease with continued exposure. This could be clinically important because many medications need to be given continuously for several days or weeks. Results of the present study suggested that owner perception might not correlate with their cat's preferred flavoring; however, future studies are needed to determine why this is the case and whether feline acceptance of more novel flavors wanes with repeated exposure.

The present study had several limitations. Our study population mostly consisted of cats owned by UW-Madison veterinary school employees and students, which could have created a population bias. In addition, flavors were selected on the basis of previous research and commercially available flavorings. When possible, an oil and a water variety of each flavor was selected. However, depending on availability, these flavors were not always identical (ie, chicken vs chicken pot pie), which could influence acceptance. Likewise, certain flavors, notably the sweet flavors, did not have similar flavorings in the oil formulations. Additionally, we used 3 different compounding suppliers based on availability; therefore, differences between manufacturing details could influence results. While the flavors were randomized and blinded to the owners, they did have unique colors and odors. Black feeding trays were used to reduce color variations to the cat. However, this could have created some bias in the owner interpretation of preference. The kits were kept in the refrigerator prior to administration of the compounding flavors to best mimic the storage of most medicated compounding flavors. However, offering a cold liquid could have affected acceptance, as cats generally prefer warm food.¹⁴ Because the purpose of this study was to pick commercially available and commonly used compounding flavors, the specific characteristics of the flavors were not specifically evaluated. Future research could be performed to look specifically at these characteristics, such as osmolality, viscosity, and the presence or absence of common ingredients to assess their individual roles in acceptance.

This study provided valuable information to help guide compounding flavor selection in our feline patients. We found that voluntary acceptance of liquid compounding flavors was low. When possible, oil-based flavorings should be selected based on their higher acceptance rates and sweet flavorings should be avoided. We also discovered that owners might not be a reliable source when selecting which compounding flavor their cat will accept. Future research should be conducted to determine whether adding various medications to the flavors affects acceptance or preferences. Similar studies could also be performed with nonliquid compounding vehicles such as chewables to determine whether palatability changes on the basis of formulation type. Additionally, future research is needed to evaluate whether standard additive compounding vehicles should avoid the use of sweetening excipients to enhance acceptance in cats.

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Supplementary Materials

Supplementary materials are posted online at the journal website: avmajournals.avma.org