

Ease of oral administration and owner-perceived acceptability of triglyceride oil, dissolving thin film strip, and gelatin capsule formulations to healthy cats

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Objective—To compare owner-assessed ease of administration and overall acceptability of 3 chemically inactive formulations administered PO to cats.

Animals—90 healthy client-owned cats.

Procedures—Cats were randomly assigned to receive 1 of 3 formulations PO once daily for 14 days: medium chain triglyceride (MCT) oil, dissolving thin film strips (proprietary ingredients), or gelatin capsules filled with microcrystalline cellulose. Owners administered the formulations and rated ease of administration daily on a 10-cm visual analogue scale (VAS). At the end of the study, owners rated overall acceptability of formulations from their own perspective and their overall perception of acceptability to their cat.

Results—Mean VAS scores for daily ease of administration of MCT oil and film strips were significantly higher than scores for gelatin capsules at all time points, except on days 2, 4, and 7. There was no difference between MCT oil and film strip formulation scores. Mean VAS scores were 8.8 (MCT oil), 8.9 (film strips), and 7.4 (gelatin capsules) for overall acceptability to owners and 8.0 (MCT oil), 8.3 (film strips), and 6.7 (gelatin capsules) for overall owner-perceived acceptability to cats.

Conclusions and Clinical Relevance—Daily ease of administration on 11 of 14 days and overall owner-perceived acceptability to cats were scored significantly higher for film strips and MCT oil, compared with scores for gelatin capsules. Overall acceptability to owners followed a similar pattern; however, the differences were not significant. Dissolving thin film strip or MCT oil vehicles may allow for easier PO administration of medication to cats than does administration of gelatin capsules. (*Am J Vet Res* 2010;71:610–614)

Oral administration of medication to cats can be a challenge for many pet owners, and owner compliance is a concern for veterinarians when treatment for cats relies on orally administered drugs. Traditionally, medications intended for oral administration in cats are manufactured into tablets, capsules, or solutions in oil or water. There are many opinions regarding the formulation that is easiest to administer to cats, but to the authors' knowledge, no scientific studies have indicated the superiority of any vehicle formulation over any other.

In addition to anecdotal concerns about pill administration in cats, studies^{1–3} have revealed that pills and

ABBREVIATIONS

CI	Confidence interval
LSM	Least squares mean
MCT	Medium chain triglyceride
VAS	Visual analogue scale

capsules administered to cats can become trapped in the esophagus,^{1,2} where the medications can cause damage to the mucosa.³ Although it is compelling to consider alternative formulations for the delivery of oral medication in this species, increased difficulty of administration could result in reduced owner compliance, and this concern would have to be considered carefully against the decreased risk of esophageal injury.

In the few studies^{4,5} that have been published on the subject, owner compliance has been reported to range from 20% to 80%. The investigators of those studies reported frequent owner complaints that administration of pills to cats was physically challenging or caused cats to avoid interaction with the owners. Any formulation that would increase the ease of medication administration would be likely to increase owner compliance. An objective evaluation of owners' preferences for various formulations and their perceptions of formulation ac-

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ceptability to their cats would provide valuable information to veterinarians prescribing medications and to the pharmaceutical industry during development of new drugs.

A limited number of drugs for human use (eg, laxatives such as sennosides,^a antihistamines such as diphenhydramine HCl,^b topical anesthetics such as benzocaine,^c and antifoaming medications such as simethicone^d) have been made available for oral administration in the form of a dissolving thin film strip, similar to strips used as breath fresheners.^{6,7} These strips may be designed to facilitate absorption in the oral mucosa or gastrointestinal tract or to have topical effects, depending on the intended result.⁷ Use of the film strip formulation has not been reported in veterinary medicine, and therefore to the authors' knowledge, no information is available on the ease of administration to cats or how well it is tolerated in this species. The study reported here was designed to compare 3 formulations that could potentially improve client compliance in oral administration of medications to cats, which could enhance the development of future drugs. It was not designed to evaluate the formulation technology. We tested the hypothesis that no difference would be detected in ease of administration for owners or perceived acceptability to cats between MCT oil, film strip, and gelatin capsule formulations.

Materials and Methods

Animals—A total of 90 healthy client-owned neutered cats of both sexes were included in the study, which was designed as a multicenter trial and was performed at the University of Pennsylvania School of Veterinary Medicine and the University of Minnesota College of Veterinary Medicine. Body weight was measured at the time of enrollment in the study, and a physical examination of each cat was performed by the veterinarian who was the primary investigator at each university site. Predetermined inclusion criteria required that cats were between 1 and 15 years of age, healthy, and not receiving any orally administered medications or treatments. History of previous treatments given PO was not evaluated. Cats were excluded from participation in the study if they had vomited more than once in the previous 2 weeks, had periodontal disease with a severity rating > stage 1,⁸ or had a history of intolerance of orally administered treatments (eg, biting or scratching when treatments were attempted or evasiveness to the extent that the cat would elude the owner to avoid treatment).

The study protocol was approved by the institutional animal care and use committee at each site, and informed consent was obtained from all owners.

Study design—Each cat was assigned to a treatment group in the order of enrollment in accordance with a computer-generated blocked randomization scheme with a block size of 3. The randomization scheme was concealed from investigators and all other study personnel at each site so that individuals were not aware of the prospective group assignment prior to making the decision to enroll a cat into the study. Questionnaires, formulations, and study materials were distributed to

owners at the time of enrollment. Only 1 cat/household was included in the study, and caregivers were required to be at least 18 years of age, willing to participate, and able to give the medication and keep appropriate records (checklists, formulation administration records, and VASs).

Study personnel at each site were trained in administration techniques for the various formulations by Pfizer Animal Health employees. Study personnel then trained owners to restrain their cats and administer the assigned formulation. For demonstration purposes, each cat was administered the formulation at the time of enrollment, but the daily ease of administration form was not completed by owners until the study began in the home environment on the following day.

The assigned formulation was administered PO once daily for 14 consecutive days (days 0 to 13). Owners were advised to administer the formulation at approximately the same time each day, but the time of day was allowed to vary among cats. In households with > 1 caregiver, only 1 individual was permitted to administer the formulation to the cat.

Formulations and administration—Three chemically inactive formulations (MCT oil,^e dissolving thin film strip,^f and opaque gelatin capsules filled with microcrystalline cellulose^g) without added flavoring were obtained from each of 3 manufacturers. For the MCT oil, owners were provided with 25 mL of oil in a resealable glass bottle with 14 single-use, 1-mL tuberculin syringes and were instructed to administer 0.1 mL/kg to cats PO. For the film strips, owners were provided with 14 strips wrapped separately in plastic foil and instructed to apply a single strip to the cat's outer gingival surface, outer dental surfaces, or both. A pair of plastic forceps was supplied to facilitate handling of the film strips, and owners were permitted to roll the strips to form a scroll to facilitate placement. For the gelatin capsules, owners were provided with a pill-administration device^h and a vial containing 14 capsules. Use of the pill-administration device was encouraged but not required; owners were instructed to administer capsules by use of the single method with which they were most comfortable.

Rating of administration experiences—Owners evaluated ease of administration of the assigned formulation once daily for 14 days by use of a standardized form, which included a 10-cm VAS.⁹ Each experience was scored from 0 (left end of the scale; unable to administer formulation) to 10 cm (right end of the scale; no difficulty administering formulation). After day 14, owners marked 2 additional VASs to indicate overall acceptability of the assigned formulation from their own perspective and their overall perception of acceptability to their cat. The overall experiences were scored from 0 (left end of the scale; unacceptable) to 10 cm (right end of the scale; excellent acceptability). Owners were instructed to take into consideration issues such as ease of administration, convenience, and messiness in determining the score for overall acceptability from their own perspective. Owners were instructed to consider whether the cat was easy to catch prior to administration and whether it struggled during administration

when scoring their overall perception of acceptability to their cat.

Statistical analysis—Prior to initiating the study, sample size was calculated to provide 80% power with a significance level (α) of 0.1, assuming an SD of 3 and the ability to detect differences of at least 2 on a VAS. Sample size was calculated, and results were analyzed by use of a statistical software program.¹ The LSM was calculated for VASs at each time point. An *F* test was performed for the overall treatment effect from a mixed linear model. If significance was found, pairwise comparisons were performed via the Fisher protected least significant difference method. Values of $P < 0.05$ were considered significant in 2-tailed analysis.

Results

Ninety-one cats were screened for enrollment in the study, and 1 cat was excluded because of periodontal disease. Ninety cats (43 spayed females and 47 neutered males) of various breeds were enrolled in the study (15 in each treatment group at each of the 2 sites). Only 1 brachycephalic cat (a Persian) was enrolled in the study; it was randomly assigned to receive the gelatin capsule formulation. One cat enrolled in the oil group was withdrawn from the study because of lack of owner compliance with the study protocol (daily VAS scores were not completed as required). Daily ease of administration VAS scores for this cat were included on days 0, 1, and 3, but all other data were excluded. Mean \pm SD weight for all cats was 4.91 ± 0.98 kg (range, 2.70 to 6.81 kg). Mean \pm SD weights were 4.81 ± 0.96 kg, 4.91 ± 1.06 kg, and 5.03 ± 0.95 kg for cats that received the MCT oil, film strips, and gelatin capsules, respectively. There was no significant difference in mean weights among treatment groups.

Cat owners were clients, veterinary school students, and veterinary school employees. Most of the owners that were veterinary school employees were not medically trained personnel; in some cases, if the owner was a member of the medical staff, another individual in the household administered the formulation and performed evaluations, but the occupation of each owner was not tracked or recorded, and cats with medically trained owners were not specifically excluded.

Least square means for the daily ease of administration VAS scores were calculated for each time point. The LSMs of scores for MCT oil and film strips were significantly different, compared with the LSMs of scores for gelatin capsules at all time points, except for day 2 (no significant differences among any of the groups), day 4 (gelatin capsules vs MCT oil, $P = 0.072$), and day 7 (gelatin capsules vs film strips, $P = 0.089$). The daily LSMs of VAS scores for MCT oil and film strips were not significantly different from each other at any time points (Figure 1).

The VAS scores for overall acceptability of formulations to owners were not significantly different among any treatment groups (Figure 2). The LSM VAS score for overall acceptability to owners was 8.8 for MCT oil (SE, 0.38; 95% CI, 8.06 to 9.54), 8.9 for film strips (SE, 0.33; 95% CI, 8.25 to 9.55), and 7.4 (SE, 0.55; 95% CI, 6.32 to 8.48) for gelatin capsules.

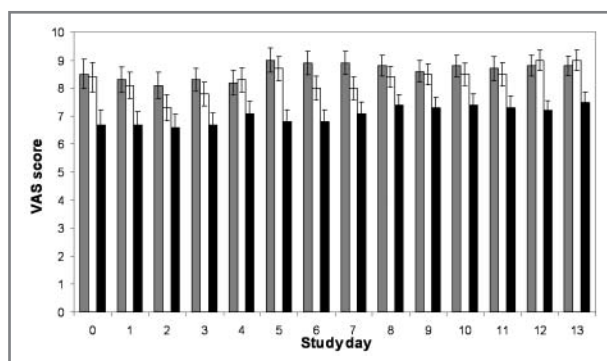


Figure 1—The LSM \pm SE of daily VAS scores for owner-evaluated ease of administration of 3 chemically inactive formulations (MCT oil [gray bars], dissolving thin film strip composed of proprietary ingredients [white bars], or gelatin capsule filled with microcrystalline cellulose [black bars]) given to healthy adult cats PO once daily for 14 days ($n = 30$ cats [days 0, 1, and 3] and 29 cats [all other time points] for the MCT oil group; 30 cats for film strip and gelatin capsule treatment groups). Owners rated ease of administration daily on a VAS of 0 (unable to administer formulation) to 10 cm (no difficulty administering formulation). Differences were not significant ($P \geq 0.05$) between MCT oil and film strip formulations at any time point. The VAS scores for gelatin capsule administration were significantly ($P < 0.05$) lower than scores for MCT oil and film strip administration at all times, except on days 2 (scores were not significantly [$P = 0.276$] different among any treatment groups), 4 (scores for gelatin capsules were not significantly [$P = 0.072$] different from scores for MCT oil), and 7 (scores for gelatin capsules were not significantly [$P = 0.089$] different from scores for film strips).

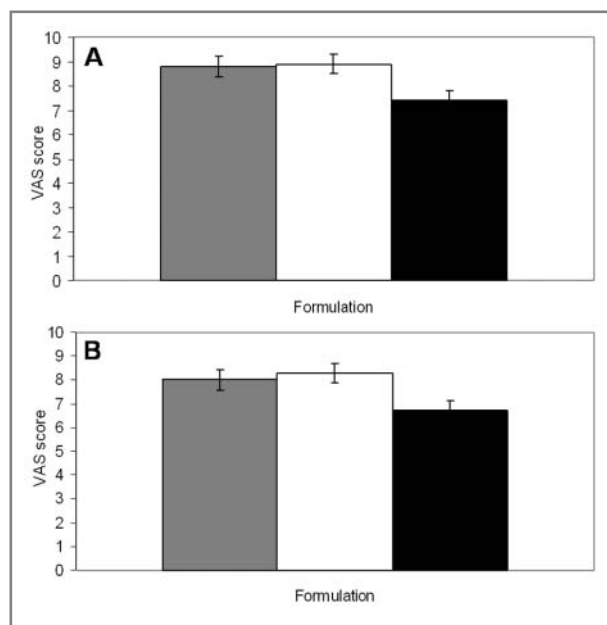


Figure 2—The LSM \pm SE of VAS scores for owner-evaluated overall acceptability of 3 chemically inactive formulations administered to cats PO once daily for 14 days ($n = 29$ cats for the MCT oil group [gray bars]; 30 cats for film strip [white bars] and gelatin capsule [black bars] groups). At the end of the study period, owners were instructed to indicate overall acceptability of the assigned formulation from their own perspective (A) and to indicate their overall perception of acceptability to their cat (B). Acceptability ratings were scored on a VAS of 0 (unacceptable) to 10 cm (excellent acceptability). In panel A, the VAS scores for overall acceptability from the owners' perspective were not significantly ($P \geq 0.05$) different among formulations. In panel B, the VAS scores for owners' overall perception of acceptability to cats were significantly ($P = 0.026$ and $P = 0.006$, respectively) higher for MCT oil and film strips than for capsules.

The LSM VAS score for owners' overall perception of formulation acceptability to cats was 8.0 (SE, 0.42; 95% CI, 7.2 to 8.8) for MCT oil, 8.3 (SE, 0.41; 95% CI, 7.5 to 9.1) for film strips, and 6.7 (SE, 0.41; 95% CI, 5.9 to 7.5) for gelatin capsules. Scores for overall perceived acceptability to cats for MCT oil and film strips were significantly ($P = 0.026$ and $P = 0.006$, respectively) higher than for gelatin capsules; however, no significant ($P = 0.593$) difference was detected between scores for MCT oil and film strips (Figure 2).

Ten adverse events were recorded during the study. Single incidents of vomiting were reported for 8 cats (5 in the MCT oil treatment group, 1 in the film strip treatment group, and 2 in the gelatin capsule treatment group). One owner reported that a cat in the MCT oil treatment group had diarrhea on day 11 that resolved without intervention to semiformal feces on day 12, and another owner reported an undefined skin condition in a cat in the gelatin capsule treatment group (this was observed on day 10 and resolved the same day). None of the recorded adverse events immediately followed administration of any of the formulations. The proportion of cats that vomited was not significantly ($P = 0.263$) different among groups.

Discussion

Analysis of the results for daily ease of administration and owners' overall perception of acceptability to cats suggest that the oral administration of medications to cats may be more readily accomplished by use of a dissolving thin film strip or MCT oil formulation, compared with use of the more traditional method of gelatin capsule administration. No difference in overall acceptability to owners (evaluated at the end of the study period) was detected; however, a larger sample size may have increased the power to detect a difference.

Interestingly, cat owners in this study rated the ease of administration for each formulation and their perceptions of the acceptability of each formulation to cats as moderate to high; no LSM was < 6.7 on the 10-point VAS. This may indicate that none of the formulations were particularly objectionable.

Healthy cats were used in this study; it is not known whether acceptability ratings would be different for owners if the cats had various medical conditions that required treatment. Depending on the disease process, it may be more or less difficult to administer medications PO to an ill cat. Additionally, fractious cats were not enrolled in this study and may represent a population that would yield different results. The number of cats in each household was not included in the analysis; owners with multiple cats could potentially be more adept at handling and medicating cats than owners that have only 1 cat. Finally, because of the participants' association with the veterinary schools as clients, faculty, staff, or students, they may have been more experienced or more dedicated to giving the assigned formulation and less likely to report difficulties. These circumstances could account for the relatively high scores across all treatment groups. The authors believed that the randomness of these factors across group assignments would minimize the effects on the study results; these factors may have resulted in higher overall acceptability

scores, but the differences among groups were still relevant. In addition, many of the participants were clients or nonmedical staff and similar to the general population of owners that would be expected to medicate their cats. These issues could be addressed in future studies via the inclusion of cats that are naïve to orally administered medication and owners that have not previously attempted to medicate their cats; however, these may be difficult populations to recruit.

No dissolving thin film strip medications are currently on the veterinary market, but this technology is being explored for use in new drug formulations. The film strip formulation has an advantage of adhering to the gingiva on application, which may make it difficult for pets to dislodge. In contrast to the veterinary market, dissolving thin film strips for oral delivery of several medications, such as analgesics, antitussives, cold symptom relief products, and antifoaming agents,⁷ are available for use in humans. The focus of the present study was to compare subjective owner assessments of ease of administration for each formulation and their perceptions of the acceptability of those formulations to their cats. More studies are needed to determine the effects that a dissolving film strip formulation would have on the delivery and absorption of active ingredients in medications that may be administered to cats by use of this vehicle.

All of the formulations tested in this study have potential disadvantages. Liquid medications can be aimed and dispensed in the wrong direction or have an undesirable spray effect if a cat shakes its head following administration. If the dissolving film strip is moistened prior to administration, it quickly becomes sticky and unusable. In addition, some medications could potentially cause mucosal irritation or ulcers if delivered in a film strip. Capsules can be administered and subsequently ejected from the mouth or regurgitated by cats.

In the study reported here, owners were instructed to give gelatin capsules in the manner that was most comfortable to them, and not all chose to use the pill-administration device. This option was offered to approximate the way a capsule formulation prescribed in a practice setting would be administered in the home environment, but the variation in methods may have influenced the study results. In addition, head shape could influence the difficulty of using different formulations of medication. In the present study, only 1 cat was brachycephalic, so no conclusions could be made about the influence of head shape on acceptability of formulations.

Taste of the formulations should not have affected acceptability ratings for cats because none of the formulations contained an active ingredient or added flavoring. However, some cats may have found the oil to be more palatable because of the fat content. If the medication being formulated has a bitter or foul taste, the authors speculate that cats may be more aversive to oil or film strip formulations, compared with their response to the same medication delivered in gelatin capsules. The opposite effect may be observed if an appetizing flavoring (eg, tuna or chicken) is added to the formulation. Future studies should evaluate the effect of both appetizing and aversive flavors on acceptability of the various formulations. It is unlikely that there will

be a universally accepted formulation for all medications because of inherent differences in the chemical properties and taste of each medication.

Because all formulations in the present study were chemically inactive, none of the adverse events reported were likely to have been related to the formulations. Vomiting was observed in a slightly higher number of cats in the oil group, although the difference was not significant among treatment groups. It is possible that oil may have caused gastrointestinal tract signs in some cats, even though the total volume of oil was small (0.1 mL/kg) and the vomiting events did not immediately follow administration of the oil. However, because vomiting was seen in all groups, it is also possible that this may have been related to stress.

Oil and dissolving thin film strip formulations were subjectively rated on a daily basis by owners as easier to administer and more acceptable to cats than was the gelatin capsule formulation in this study of healthy tractable cats. It is recommended that this information be considered when prescribing treatments or formulating new medications for cats. Although it is believed that this study will be applicable to all populations of domestic cats, ill or intractable cats and cats from non-veterinary school practices may represent populations that will yield different results. In addition, the taste of medications or added flavorings may make one formulation more or less favorable than another.

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- a. Pedia-lax quick dissolve strips, CB Fleet Co Inc, Lynchburg, Va.
 - b. Benadryl allergy quick dissolve strips, McNeil-PPC Inc, Parsippany, NJ.

- c. Ora film, Apothecus Pharmaceutical Corp, Oyster Bay, NY.
- d. Gas-X thin strips, Novartis Consumer Health, Parsippany, NJ.
- e. Captex 355 MCT oil, Abitec Corp, Janesville, Wis.
- f. 20 × 10-mm dissolving thin film strip, provided by Dennis Huczek, Pharmaceutical Sciences, Pfizer Animal Health, Kalamazoo, Mich.
- g. No. 4 capsule, 14.3 mm, Capsugel, Greenville, SC.
- h. Pet Piller, H-BAR-S Manufacturing, Boerne, Tex.
- i. SAS, version 9, SAS Institute Inc, Cary, NC.

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