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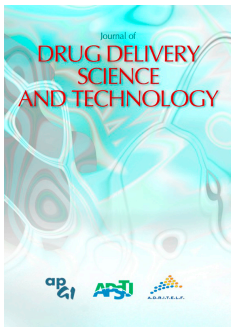

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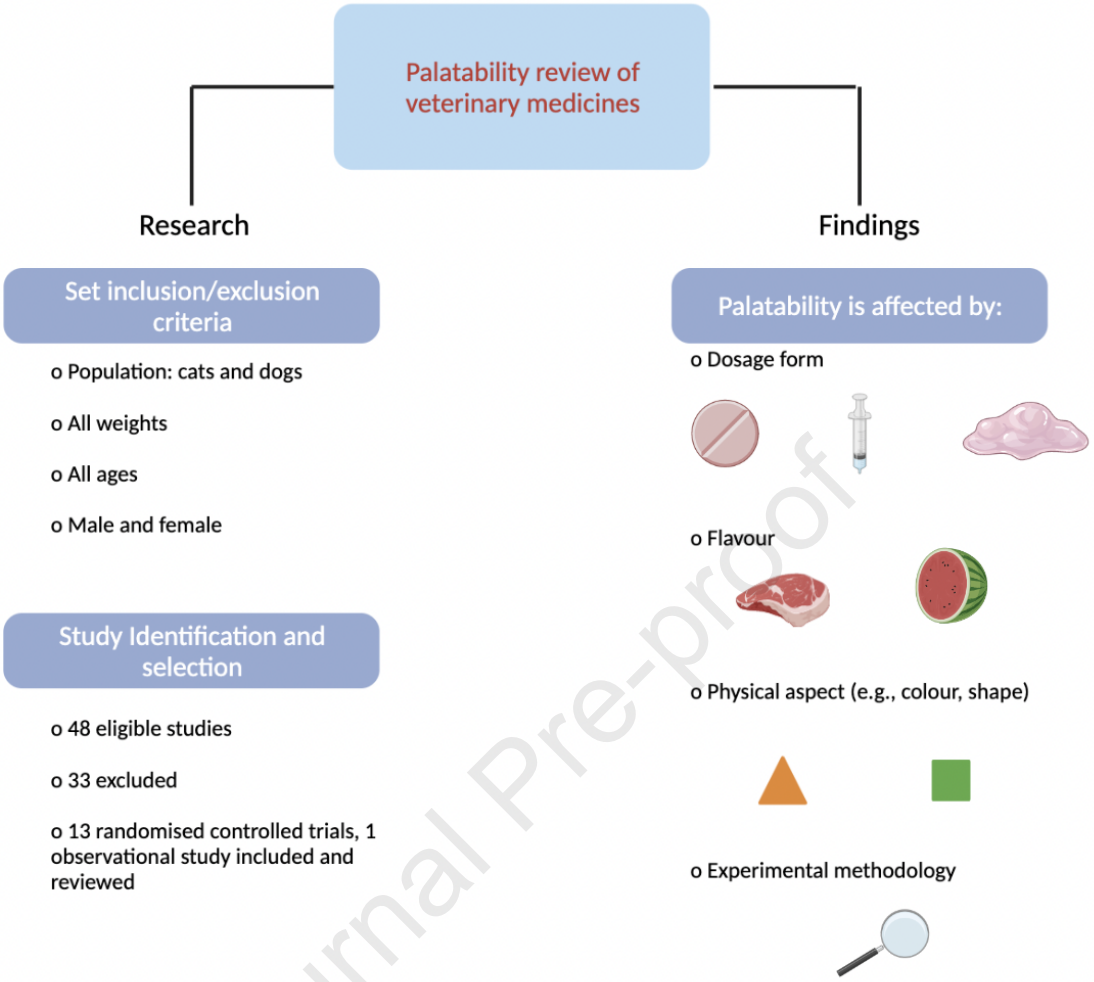

Palatability assessment of oral dosage forms for companion animals: a systematic review

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Abstract

The challenging administration of poorly palatable oral dosage forms to companion animals has fostered sub-optimal treatment outcomes for animals and thus a need for highly palatable treatments. Pharmaceutical companies are creating formulations to answer this need, but lack of a standardised procedure renders palatability assessment complicated and hinders comparison between studies. The gold standard in assessing voluntary acceptance is to utilise an acceptance test and/or preference test but slight variations as to how these are conducted can be observed between studies. This systematic review aims to examine palatability assessment methods and how palatability of oral dosage forms influences acceptability of medicines in companion animals. Solid oral dosage forms are well tolerated by dogs but very poorly by cats. Cats accept pastes more readily although this dosage form seems more suited for short-term forced administration and owner convenience. Liquid formulations seem to be well tolerated in cats but poorly in dogs. Meat-based flavours yield high palatability. The shape and colour of dosage forms also seem to impact palatability. Methodology can induce bias and must therefore be adapted to the animals and dosage forms tested. It seems there is a lack of evidence relating to formulation parameters that yield high palatability in companion animals. Additional studies and revised guidelines from the European Medicines Agency on palatability testing of veterinary medicinal products are therefore required. This review provides insight as to which dosage form, flavours and physical aspect generate increased palatability and which methodological parameters should be altered or monitored to avoid bias.

Keywords: Acceptance test, preference test, palatability, veterinary, companion animals, oral formulations

1. Introduction

Administration of oral drugs to companion animals (i.e., dogs and cats) is challenging, especially in felines, but can be achieved in one of two ways. The first is known as the 'poke-down' method. It consists of placing a medication at the base, or far back, of the animal's tongue, closing its mouth and repositioning the head and neck to their natural position while massaging the throat or diverting the animal until the dosage form is swallowed [1,2]. Massaging the throat may be preferable over distracting the animal as it encourages swallowing [1]. However, Thombre [3] remarks this is "easier said than done" as cats are independent animals that are less "accustomed to being restrained" [3, p.1400]. It is important to note that forcibly administering medication to cats can cause owner injuries and negatively impact cat-owner relationships which is especially problematic in the case of chronic illness treatments [4]. Ahmed and Kasraian [5] report that voluntary acceptance of flavoured tablets in cats is lower than 50%. The second method achieves consumption by dissimulating a tablet, either whole or crushed, within a highly palatable food item such as peanut butter and meat paste (e.g., beef) [6,1]. Like the 'poke-down' method, this technique has some limitations. Certain medications require fasted administration, while other drugs may be too bitter or odorous to successfully taste mask. Pet owners often report that pets eat the food around the tablet without consuming the drug [1,4]. Other methods include liquefying (crushing and dissolving) or crushing the tablet and sprinkling it over food; however, both may face taste-masking difficulties [2]. Cat medication may be dispersed onto their fur to allow ingestion during self-grooming [3]. While these methods yield some success, they are suboptimal and are complicated by taste and compliance issues. This translates to a clear need for voluntarily accepted highly palatable oral dosage forms for companion animals.

The ideal formulation should be consumed voluntarily by the animal [1]. This is particularly important for chronic illnesses which require chronic drug administration [7]. In recent years, a market for high palatability products has appeared as pharmaceutical companies attempt to answer this need. In 2014, the European Medicines Agency (EMA) released the "Guideline on the demonstration of palatability of veterinary medicinal products" to regulate the field [8]. While a plethora of palatability studies is available for pet food, reports of veterinary drug palatability are scarce. Much of the work within the field of

palatability has been produced for pet food companies attempting to elucidate taste preferences in companion animals.

Acceptance refers to the voluntary choice of the animal to consume what is offered to it. When attempting to measure palatability, some studies factor in pet engagement or speed of acceptance – i.e., prehension rate (time taken for an animal to voluntarily consume food/tablet) [9,10]. However, these methods seem more appropriate for the pet food industry where it would be of interest to test how fast a pet is attracted to food or treats rather than simply accepting what is presented to it. Additionally, it is important to note that it is extremely hard to measure palatability in companion animals as response upon presentation is highly dependent on the individual animal and its preferences. For example, cats are known to seldom ingest medication in the form of tablets, especially if the drug is bitter or odorous [4]. Griffin [11] explains these difficulties in assessing palatability by the large gap within the literature regarding mechanisms and biochemical processes responsible for the perception of taste and olfaction, and the tests used to assess the acceptance of pet products [11].

Acceptance and preference tests are commonly used to quantify palatability (see Table 1). The acceptance test is a one-pan intake test that aims to determine whether the animal will ingest the formulation when offered. Generally, the formulation that is being tested for is crossed over with a control formulation or with multiple treatment groups [12]. Studies conducting a cross-over design test of multiple formulations must ensure that all subjects are ultimately presented with each medication [12]. The lack of an established experimental procedure to test for palatability has led to discrepancies in techniques used. Some studies will offer medication to a pet from a human hand while others place the medication in a bowl before presenting it to the pet. Variations of procedure can also be observed in the time allowed for consumption, ranging from 60 seconds to 30 minutes [13,14]. The general approach to record the data is to count how many animals either fully consumed the medication, did not ingest the dosage form at all, or did not consume the treatment fully but only partially within the time frame specified. Acceptance tests offer the advantage of directly measuring compliance [15]. The preference test is a two-pan test that allows the animal to express its preference between two formulations. It aims to determine whether the pet

prefers one dosage form over another [1]. A preference test can discriminate between a test formulation and a control formulation or between multiple test formulations. For example, one study could test two dosage forms of high palatability, low palatability, or differences in palatability [12]. Hence, the preference test is much more sensitive than the acceptance test. Like in the acceptance test, data is recorded by counting how many animals either fully consumed the medication, did not ingest the dosage form at all, or did not consume the treatment fully but only partially within the time frame specified. In the context of veterinary formulations, the second formulation must be removed, and consumption forbidden after preference for one product is expressed and it is ingested [12]. This is because consuming multiple pharmaceutical products may be unsafe.

Table 1: Summary and comparison of the acceptance and preference tests

	Acceptance test	**Preference test**
Type of test	One-pan	Two-pan
Optimal study design	Randomised cross-over	Randomised cross-over
Data obtained	Binary	Binary
Conventional procedure	- Present treatment to animal in a bowl or on the floor for predetermined amount of time - If no consumption, present treatment from the hand for predetermined amount of time - If no consumption, test terminated	- Two formulations presented at once in a test tray holding formulations in separate bowls for predetermined amount of time - If no consumption, treatments are presented from the hand according to tray position for predetermined amount of time - If no consumption, test terminated
Advantages	- Direct measure of compliance	- Allows pet to express preference - More sensitive than acceptance test
Disadvantages	- Does not determine preference between treatments	- Does not determine specifically what makes a formulation attractive

Dosing compliance is a renowned issue within the realm of oral veterinary formulations often resulting in sub-par treatment outcomes [16]. The palatability of a dosage form can significantly impact dosing compliance. It is therefore in the best interest of both pets and

their owners to develop palatable products. This is especially relevant in the case of chronic illnesses which require frequent treatment administration over extended periods [17]. Improved palatability can be achieved through various approaches such as taste-masking the active pharmaceutical ingredient or incorporating food-based excipients within a formulation. However, compliance issues are not always related to the palatability of a product, or even the dosage form itself. Instead, Siven et al. [2] report that compliance issues are often due to owners' failure to adhere to the treatment regimen. Additionally, palatability is influenced by many external factors such as single animal food preferences, which may result in difficulty interpreting results and bias [18].

This review aims to systematically analyse the palatability assessment of pharmaceutical formulations for canines and felines. This review may offer insights as to which assessment methods yield optimal results with limited bias. It may also provide indications on the formulation parameters (e.g., dosage form) inducing highest palatability.

2. Methods

This systematic literature review was conducted following the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) 2020 updated guidelines although no risk of bias tool was utilised [19]. The methodology utilised to identify and analyse the studies in this review was adapted from a published systematic review [20].

2.1 Search

Scientific databases including PubMed, ScienceDirect and Web of Science were used to perform a systematic literature search for relevant veterinary studies, including randomised controlled trials and observational studies published until August 2022. The search terms used were (oral) AND (palatability OR taste-masking OR taste-masked OR acceptance OR preference) AND (dogs or cats). References and bibliographies were manually analysed to identify and include studies and reviews that the databases may have omitted.

2.1.1 Inclusion criteria

- Dogs or cats of all breeds including mixed breeds
    - Weight range: all weights
    - Animals of all ages
    - Genders: both male and female
    - Minimum 10 animals included in study
- Cross-over design or observational study
- All offering regimens
- Time allowed for consumption ranging from 0 to 30 minutes
- Outcomes of the articles measured any of:
    - Acceptance (or consumption)
        - Assessed as: consumed fully, partially, or refused
    - Preference (or relative voluntary acceptance)
        - Measured as: consumed fully, partially, or refused
    - Product prehension (yes/no)

2.1.2 Exclusion criteria

- Studies related to the palatability of pet food industry products
- Studies not designed as cross-over or observational study
- Studies examining the efficacy of the various taste-masking approaches on humans
- Studies examining the palatability of drugs for humans
- Studies published in other languages than English
- Studies published before 2006

2.2 Data extraction

The articles identified by the databases were screened according to title and abstract to identify the most relevant studies. Those selected were then evaluated against the inclusion and exclusion criteria to assess suitability for this review. The inclusion of studies was decided

according to subject characteristics (i.e., dog or cat of all breeds etc.) and testing methods. The following data were extracted from the selected articles for inclusion in this study: study reference, place of conduct, study design, subject characteristics, duration, testing method, formulations tested, testing outcome and significant findings.

2.3 Study Selection

In total, 818 654 records were identified through database and register searches. After the screening process, 48 studies were assessed for eligibility. 33 of those articles were excluded based on the inclusion and exclusion criteria. 13 randomised controlled trials that satisfied the inclusion and exclusion criteria were included in this systematic review. One observational study was included. Study selection protocol is presented in Fig 1.

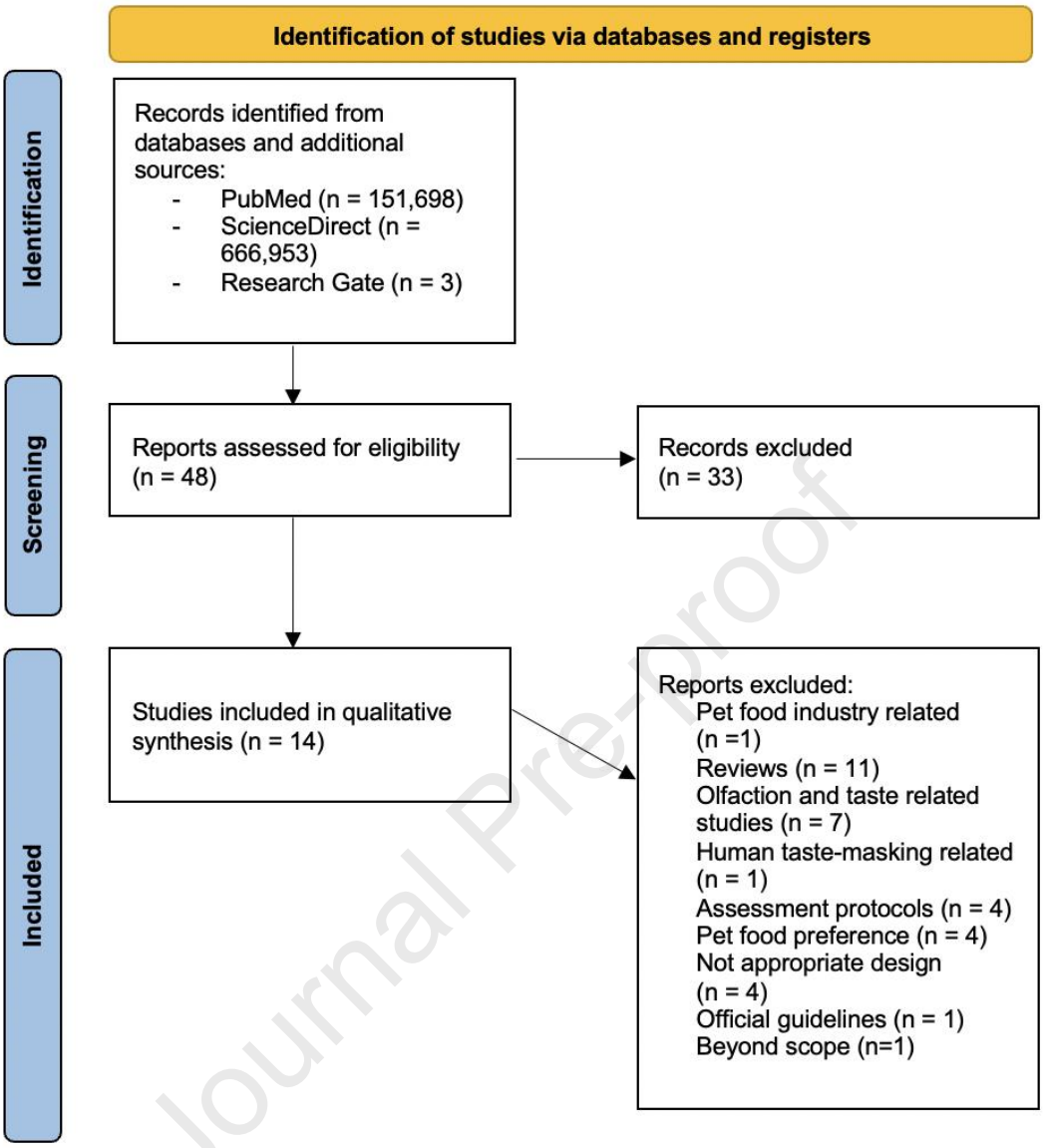

Figure 1: PRISMA flow diagram of the study selection process adapted from PRISMA 2020 flow diagram [19]

3. Results and Discussion

The tables in the following section (Table 2 and Table 3) regroup important characteristics and results obtained from the studies assessed for this review. Table 2 presents randomised-controlled trials that were designed as cross-over studies, Table 3 describes an observational study. The studies included in both tables were conducted worldwide, in countries including France, the USA, the Netherlands, South Africa, the United Kingdom, Australia, and Finland.

Table 2: Summary table of randomised controlled trials (cross-over design) identified for review

Reference	Sample size	Age range (in years)	Formulations tested	Physical aspect and flavour of formulation	Testing method	Time allowed for consumption	Offering regimen	Wash out period	Acceptance Outcome
[25]	37 dogs	1-3	**Rimadyl®** (20 mg carprofen; Zoetis) and **Carprieve®** (20 mg carprofen; Norbrook Laboratories) chewable tablets for treatment of osteoarthritis	- Rimadyl®: light brown square tablet with "R" engraved on one side and bisected on the other side flavoured with pig liver powder -Carprieve®: Light brown, round, flat, bevel-edged tablet flavoured with spray-dried pig liver powder	37 individual acceptability tests	2 minutes	Acceptance test (see Table 1)	Yes; 7 days	- Rimadyl® = 73% - Carprieve® = 70.3% N.S. (P = 0.65)
[14]	20 dogs	1-4	- **Nelio® 20** (18.42 mg benazepril; Sogeval), - **Fortekor® 20** (18.42 mg benazepril; Novartis) - **Benakor® 20** (18.42 mg benazepril; Virbac) tablets for treatment of heart failure	- Nelio®: Clover shaped scored beige tablet with pig liver flavour - Fortekor®: Beige to light brown, ovoid, divisible tablet flavoured with artificial special dry flavour - Benakor®: yellow, elongated, divisible tablet but does not contain any flavouring	60 individual acceptance tests and 120 individual preference tests	2 minutes	Acceptance test (see Table 1) - Preference test (see Table 1)	Yes; 4 days	Preference: - Nelio® 20 vs Fortekor® 20: Nelio = 58% Fortekor = 42% N.S. (P>0.05) - Nelio® 20 vs Benakor® 20: Nelio = 63% Benakor = 38% (P<0.02) Acceptance: - Nelio® = 90% - Fortekor®= 95% N.S. (P>0.05) - Benakor®= 50% (P<0.02)

[13]	33 dogs	1-9	**Drontal® P meat taste** (praziquantel 50 mg, pyrantel 50 mg, febantel 150 mg; Bayer) and **Dolpac® 10** (praziquantel 50 mg, 49.94 mg pyrantel, 200.28 mg oxantel; Vetoquinol); broad-spectrum anthelmintics for the treatment of endoparasites	- Drontal P®: Light brown to brown, round, flat tablet, cross scored on one side with artificial beef flavour irradiated - Dolpac®: Light yellow to yellow, scored, oblong tablet with bacon flavouring	62 individual acceptance tests	30 minutes	- Each dog is offered one tablet in a bowl - If product not ingested after 30 minutes, test terminated	Yes; 7 days	- Drontal® P = 97% - Dolpac® = 40% (*P*<0.01)
[1]	150 dogs	1-12	**Drontal® Plus** (praziquantel 50 mg, pyrantel 50 mg, febantel 150 mg; Bayer) and **Milbemax® Chewable Tablets** (milbemycin oxime 12.5 mg, 125 mg praziquantel; Novartis) for the treatment of endoparasites	- Drontal P®: Light brown to brown, round, flat tablet, cross scored on one side with artificial beef flavour irradiated - Milbemax® Chewable tablet: Oval-shaped, dark brown, with natural chicken flavour	300 individual acceptance tests	4 minutes	- Product was offered from owner's hand for 2 minutes - If tablet was not taken after 2 minutes, it was placed on the floor and dog was encouraged to ingest tablet - If no consumption after another 2 minutes, test was terminated	Yes; 4-21 days	- Drontal® P = 88% - Milbemax® = 86.7% N.S. (*P*=0.6698)
[16]	46 dogs (42 dogs for preference tests)	1-11	**Metacam® Chewable Tablets** (meloxicam 1 mg; Boehringer Ingelheim Ltd.) and **Rimadyl® Palatable Tablets** (carprofen 50 mg; Pfizer) NSAIDs for the treatment of osteoarthritis	Metacam®: Round mottled beige biconvex chewable tablets, scored on the upper side, flavoured with pig liver powder - Rimadyl®: Light brown square tablet with "R" engraved on one side and bisected on the other side flavoured with pig liver powder	91 individual acceptance tests and 124 individual preference tests	1 minute	- Acceptance test (see Table 1) - Preference test (see Table 1)	None	- Metacam® = 13% of dogs - Rimadyl® = 97.8% (*P*<0.0001) - 40 dogs preferred Rimadyl® while one dog preferred Metacam® (*P*<0.0001)
[15]	Acceptance study 1: 45 dogs Acceptance study 2: 43 dogs	Acceptance study 1: 1-11 Acceptance	Study 1 and 4: **Rimadyl® Palatable Tablets** (carprofen 50mg; Pfizer) vs **Carprodyl® Tablets** (carprofen 50mg; Ceva) Study 2 and 5: **Rimadyl® Palatable Tablets** (carprofen 50mg; Pfizer) vs	- Rimadyl®: Light brown square tablet with "R" engraved on one side and bisected on the other side flavoured with pig liver powder - Carprodyl®:	273 individual acceptance tests and 385 individual preference tests	1 minute	- Acceptance test (see Table 1) - Preference test (see Table 1)	None	Acceptance study 1: - Rimadyl® = 93.2% - Carprodyl® = 25% (*P*<0.001) Acceptance study 2: - Rimadyl® = 90.7% - Norocarp® = 48.8% (*P*<0.005)

	Acceptance study 3: 49 dogs Preference study 4: 44 dogs Preference study 5: 42 dogs Preference study 6: 44 dogs	study 2: 1-10 Acceptance study 3: 1-11 Preference study 4: 1-11 Preference study 5: 1-10 Preference study 6 1-10	**Norocarp® Tablets** (carprofen 50mg; Norbrook) Study 3 and 6: **Rimadyl® Palatable Tablets** (carprofen 50mg; Pfizer) vs **Previcox® Chewable Tablets** (firocoxib 57mg; Merial)	Clover-shaped scored beige tablet with pig liver flavour - Norocarp®: Light brown, round, flat, bevel-edged tablet flavoured with spray-dried pig liver powder - Previcox® Tan-brown, round, convex, tablets with a cross-shaped break line on one side flavoured with Charter Hickory smoke flavour					Acceptance study 3: - Rimadyl® = 98% - Previcox® = 47.9% (P<0.001) Preference study 4: - Rimadyl® = 94.7% - Carprodyl® = 3.8% (*P*<0.0001) Preference study 5: - Rimadyl® = 79.0% Norocarp® = 16.9% (*P*<0.0001) Preference study 6: Rimadyl® = 76.9% - Previcox® = 16.9% (*P*<0.0001)
[7]	60 dogs	1-13	**Dolagis®** (carprofen 50mg; SOGEVAL) and **Rimadyl®** (carprofen 50mg; Pfizer)	- Dolagis®: Clover-shaped scored beige tablet containing pig liver flavouring - Rimadyl®: Light brown square tablet with "R" engraved on one side and bisected on the other side flavoured with pig liver powder	177 individual preference tests	1 minute	Preference test (see Table 1)	Not mentioned	- Rimadyl® = 65% - Dolagis® = 35% (*P*=0.0201)
[26]	13 privately-owned cats	1-9	**Noten®** (atenolol 50mg; Alphapharm) (human tablet, used off-license for animals), **Compounded atenolol paste** (25 mg/mL; prepared extemporaneously) and **atenolol suspension** (3.75g for 150 mL; prepared	Noten®: White to off white, circular, flat-faced bevelled edge, uncoated tablets with inscription "AA" on one side and break line on the other side, no flavouring	- Survey of owners before study, after each treatment protocol, and at end of experiment - Owners to keep diary and record time of treatment,	None, forced administration	- For the tablet and suspension, poke down method - For the paste, head of animal tilted to back or side so that a side of the gum is exposed. Paste smeared on gums or	Yes; 8 days	Difficulty of administration: - easy (n=3) - intermediate (n=8) - difficult (n=2) - Owners complied better to dose, rate, and frequency of

			extemporaneously) for the treatment of hypertrophic cardiomyopathy (HCM)	Compounded atenolol paste: Light brown paste flavoured with crushed and dried Purrfect liver treats (Love'em) Atenolol suspension: no physical description included, flavoured with crushed and dried Purrfect liver treats	ease of administration etc		premolars or upper palate (also poke-down method)		compounded suspension (P<0.05) - No difference in number of treatments successfully administered between all types of formulations - Owners' preference for paste and suspension decreased after study, starting from 69.2% to 46.2% preference. - N.S. (P>0.05)
[23]	24 cats	2-7	**EFEX® Chewable Tablets** (marbofloxacin 10mg; Sogeval), **Marbocyl® P Tablets** (marbofloxacin 20mg; Vetoquinol), and **Marbocyl® Vet Tablets** (Product now deregistered (Swedish Medical Products Agency, 2012)) (20mg marbofloxacin; Vetoquinol); fluoroquinolone antibiotics for bacterial infections	- EFEX® Chewable tablets: Oblong scored beige tablet flavoured with pig liver powder - Marbocyl® P: Beige brown spotted round tablet with pig liver powder - Marbocyl® Vet: Anhydrous lactose and API, no additional information found	72 individual acceptance tests	1.5 minutes	- Tablet presented to cat on floor allowing 30s for prehension* without encouragement - If not consumed, tablet presented again in clean saucer - If still no consumption, presented from hand of investigator - If no consumption after the 3 attempts, test terminated	Not mentioned	- EFEX = 70.8% - Marbocyl P = 62.5% N.S. (0.50<P<0.90) - 12.5% for Marbocyl Vet (0.001<P<0.01)
[22]	40 cats and kittens	Kittens - 15-25 weeks Adults - 7-52 months	**Milpro® flavour-coated tablets** (16 mg milbemycin oxime and 40 mg praziquantel; Virbac) and **Milbemax® flavour-coated tablets (**16 mg milbemycin oxime and 40 mg praziquantel; Novartis)	- Milpro® Oval shaped, red to pink tablets with a score on both sides flavoured with natural poultry liver flavour - Milbemax® Oblong shaped, reddish to reddish-brown, artificial beef flavoured tablet with a score on both sides. One side bears the imprint "KK", the other side "NA"	80 individual acceptance tests	2.5 minutes	Acceptance test (see Table 1)	Not mentioned	Adults: - Milpro® = 40% - Milbemax® = 35% - N.S. (P=1) Kittens: - Milpro® = 45% - Milbemax® = 20% N.S. (P=0.09)

[6]	23 cats	1—15	- **Synthetically flavoured mini-tablets** consisting of tested flavours and tablet excipients (listed in next column with microcrystalline cellulose making up the rest of m/m) - **Non-flavoured mini-tablet** (placebo) consisting of microcrystalline cellulose, mannitol, hydroxypropyl cellulose and sodium stearyl fumarate inside food item (chosen by owner based on animal preferences) - Positive controls: **organic yeast-flavoured mini-tablet** (Yeast Extract, AppliChem) and a **commercial vitamin mini-tablet** (Kitzyme, Bob Martin)	Synthetically flavoured mini-tablets (round, biconvex, 3mm diameter): - L-glutamic acid and monosodium salt hydrate 50% m/m - L-leucine 50% m/m - L-methionine 50%m/m - L-phenylalanine 50% m/m - L-proline 50% m/m - Thiamine hydrochloride 50% m/m - Thiamine hydrochloride and L-cysteine 50% m/m of flavour 1:1 mixture - Thiamine hydrochloride and L-leucine 50% m/m of flavour 1:1 mixture - Thiamine hydrochloride and L-methionine 50% m/m of flavour 1:1 mixture - Thiamine hydrochloride L-proline 50% m/m of flavour 1:1 mixture - L-carnitine 50% m/m - Taurine 50% m/m - D-(+)-Maltose monohydrate 50% m/m - 2-acetylthiazole 2% m/m - 2-acetylpyridine 2% m/m - 4-hydroxy-5-methyl-3(*2H*)-furanone 2% m/m - 2-pentylpyridine 2% m/m Yeast flavoured mini-tablet: - pale yellow powder, yeast flavour Kitzyme®: - beige biconvex mini-tablet, cross scored, with fish flavouring	79 individual acceptance tests	Not mentioned	- Mini-tablet offered to cat on table - If no consumption, it was offered by hand, holding it between two fingers, so that cat could sniff the mini-tablet - If still no consumption, the tablet was hidden inside a palatable food (relative to individual animal preferences)	Not mentioned	- No synthetically flavoured mini-tablet was significantly more acceptable than the placebo mini-tablets when concealed within a palatable food item - No statistically significant difference was found between synthetically flavoured mini-tablets and yeast-flavoured mini-tablet - Commercial vitamin mini-tablet was more palatable than most synthetically flavoured mini-tablets (*P* = 0.0625) - Most cats did not voluntarily accept synthetically flavoured mini-tablets without being concealed in food

[9]	25 dogs	> 6 months	**Atopica® oral solution** (100mg/mL; Elanco Animal Health) and **Cyclavance® Oral Solution** (100 mg/mL; Virbac); both cyclosporin solutions to treat canine atopic dermatitis	- Atopica® Clear, yellow to brownish liquid, no flavour - Cyclavance® Clear to slightly yellow solution, no flavour	Phase 1: - Intake classified as Score 1 (syringe easily inserted in mouth) or 2 (forced administration) Phase 2: - Acceptance was measured by prehension and consumption. Score 1 (immediate prehension 2s or less), Score 2 (delayed prehension 2s-1min), Score 3 (complete dosing ingesting within 5 minutes), Score 4 (no consumption within 5 minutes)	Phase 1: - both products administered directly into animal's mouth Phase 2: - 5 minutes	Phase I: - 5 mg/kg administered via syringe in mouth Phase 2: - 5 mg/kg mixed with 25g of food offered to dogs for 5 minutes	Phase 1: 5 days total; 3 days between formulations and 2 days after phase 1completion Phase 2: 2 days between formulations	Phase 1: - Atopica® = 100% - Cyclavance® = 98.9% of occasions - N.S. (*P* = 0.5) Phase 2: - Atopica® = 61.1% Cyclavance® = 56.4% - Atopica® showed 16.7% complete dosing - Cyclavance® showed 12.8% complete dosing - N.S. (*P* = 1.0000)
[12]	Study 1 Acceptance study: - 24 dogs Study 2 Acceptance study: - 48 dogs Study 3 Preference study: - 48 dogs	Study 1: 1-6 Study 2: 1-18 Study 3: 2-17	Study 1: - **3 chewable placebos** Study 2: - **3 different chewable** tablets of 3 different aromas Study 3: - **4 different aroma placebos**	Study 1: - one containing a palatant of animal origin - one containing a palatant of non-animal origin - the third was a control placebo that did not have excipients that give chewiness, taste, and smell to dosage - unspecified aspect Study 2: T01: aroma 1, T02: aroma 2, T03: aroma 3 – combination of aroma 2 and a different aroma)	Study 1: - Percentage acceptance was calculated Study 2: - Prehension recorded as yes or no and full, partial or no consumption. Percentage prehension and tablet consumption were calculated for each treatment Study 3:	Study 1: - 2 minutes Study 2: - 60 secs Study 3: - 1 minute	Study 1: - Product placed in bowl and offered to dog by an individual it was familiar with - If no/partial consumption after 2 min, test terminated Study 2: - Single tablet of test material offered in a bowl - If product not taken within 60s, test terminated	Study 1: Not mentioned Study 2: 4 days Study 3: Not mentioned	Study 1: - Chewable with non-animal origin = 22.6% - Animal-origin palatant = 73.3% Study 2: - Control = 69.9% - aroma 1 = 75.9% - aroma 2 = 75.2% - aroma 3 = 75.4% Study 3 (preference over placebo): - T01 = 72.0% - T02 = 66.7% - T03 = 63.6% - T04 = 40.0%

	(aromas and aspect not specified) Study 3: T01: Aroma 1, T02: aroma 2, T03: aroma 3, T04: aroma 4) with single control placebo – aromas and aspect not specified	- 48 preference tests - Number and percentage of dogs preferring each product were calculated for each tablet separately from control placebo	Study 3: - Dogs were offered a single tablet of aroma placebos in right or left bowl with control placebo in opposite bowl - 1 minute allowed for consumption - As soon as animal prehended, tray was removed

N.S: not statistically significant
**Prehension is described as the animal's action of taking a treatment into the mouth*

Table 3: Summary table of the observational study identified for review

Reference	Sample size	Mean Age range (in years)	Formulations tested	Physical aspect and flavour of formulation	Testing method	Time allowed for consumption	Offering regimen	Wash-out period	Outcome
[24]	172 cats	3.5-4	**Ipakitine® powder** (IPB + N-binder, Vetoquinol) (to spread on food), **Azodyl® powder in single-dose capsules** (N-binder, Vetoquinol), **Renalzin® paste** (IPB, Bayer), **Rubenal® tablet** (Vetoquinol), **Pronefra ® liquid suspension** (IPB + N-binder; Virbac). All are supplements used in the treatment of chronic kidney disease (CKD)	- Ipakitine® Fine white unflavoured powder - Azodyl® White unflavoured capsule - Renalzin® Neutral taste and odourless paste, no colour description found - Rubenal® No physical description found other than 'tablet', no flavouring - Pronefra® Brown suspension flavoured with poultry	172 individual acceptance tests	10 mins	- Each cat was offered its allocated formulation in its box and observed by video to not interfere with its behaviour	None	Useful consumption (more than 50% of tablet consumed): - Azodyl = 47% - Ipakitine = 0% - Pronefra = 70% - Renalzin = 23% - Rubenal = 13% (0.0001≤P≥0.046)

The palatability of oral veterinary pharmaceutical products is impacted by three major factors: first, the dosage form used; second, the flavour and the physical aspect such as colour [14,21]; third, experimental methodology where factors such as population selection can impact the outcome.

3.1 Effect of dosage form on palatability

3.1.1 Solid oral dosage forms

Solid dosage forms include formulations such as tablets, capsules, and powders. Study results varied greatly depending on the animals used (i.e., cats or dogs). The acceptance of tablets was generally lower in cats than in dogs. This is most likely because, for cats, tablets are more adapted to forced administration unless highly palatable [22]. Savolainen et al. [6] found that cats did not voluntarily accept mini-tablets unless concealed in food. However, Cron et al. [23] investigated the recently developed Efex® tablets designed for high palatability in cats and found an acceptability of 71%. According to the EMA guidelines, this result would qualify this formulation as palatable in cats (acceptance > 70.0%). Ipakitine® (IPB + N-binder) powder and Azodyl® (N-binder) capsules, supplements used in the treatment of chronic kidney disease (CKD), resulted in poor palatability with acceptance levels in cats reaching 47% and 0% respectively [24]. Since acceptability is below 70%, these dosage forms could not be considered palatable [21].

On the other hand, dogs readily accept palatable solid dosage forms. Zemirline et al. [14] found that the acceptance of Nelio® and Fortekor®, two benazepril formulations (see Table 2), yielded 90% and 95% voluntary full consumption. Payne-Johnson et al. [16] found that Rimadyl® palatable tablets, a non-steroidal anti-inflammatory drug, was fully accepted by 98% of dogs. An earlier study conducted by the same lead author found that the same tablet resulted in acceptance rates >90% (see Table 2) [15]. Nonetheless, dogs, like cats, are reluctant to ingest formulations that are not specifically designed to achieve high palatability. For example, Dewsbury et al. [25] concluded that Carprieve® tablets, a carprofen generic (see Table 2), was only accepted by 70% of dogs, which according to EMA guidelines, does not

qualify as palatable in dogs (acceptance < 80%). Similarly, Zemirline et al. [14] found that Benakor® benazepril tablets were only accepted by 38% of animals and Courbet et al. [13] found that Dolpac® tablets, a broad-spectrum anthelmintic, was fully ingested by 40% of test subjects.

While solid formulations designed to achieve high palatability are well accepted in dogs, only a few are well tolerated by felines. Formulations that do not aim to achieve high palatability resulted in low acceptance rates in both cats and dogs. Capsules and powder seem to be the least optimal solid dosage forms in cats since their acceptance was the lowest of solid dosage forms. Tablets were not palatable to cats either indicating a need to develop highly palatable solid oral formulations for companion animals.

3.1.2 Semisolid dosage form

Semisolid dosage forms are a diverse class of formulations including ointments, pastes, gels, and creams. Two studies included in this review investigated the acceptance of pastes in felines. Bernachon et al. [24] assessed the palatability of Renalzin®, a paste used in the treatment of CKD, by administering it alongside 5g of kibble, 3 hours after the animal's morning meal. The authors found that the formulation was accepted by 23% of test subjects. This does not qualify the formulation as palatable since its acceptance is considerably below the 70% threshold prescribed by the EMA. Khor et al. [26] examined the palatability of an extemporaneously prepared atenolol paste against that of an atenolol tablet for humans, Noten® and an atenolol suspension used in the treatment of hypertrophic cardiomyopathy, through an owner surveying system. The paste was administered by tilting the animal's head either to the side or to the back allowing for a part of the gum to be exposed. The formulation was then spread either over the gums, premolars, or upper palate [26]. The cat owners reported no difference in successful administration or palatability between dosage forms. The authors asked the owners to report whether their pet "like[d] the taste of the oral formulation" [26]. 69% of the time, cats seemed to enjoy the compounded paste which potentially indicates this dosage form is palatable. 69% of owners expressed a preference for the paste and the suspension at the beginning of the study, while only 46% did at the end,

suggesting preference for tablets in the long term. The authors noticed the major cause of non-compliance was owner-related (34% doses not given at the right time; 42% doses not given within optimum time for efficacy). Hence, results from this study may be biased since owners carried out the experiment and thus true palatability of pastes may not be accurately reflected. Additionally, animals were not given free choice but were forcibly administered the treatments also providing bias in palatability results. Hence, it seems while pastes may be a good alternative for short term forced administration treatments they must be designed to be easily administered (e.g., via syringe) to ensure owner compliance. Increasing owner compliance would allow animals to benefit from optimal treatment regimens, in turn increasing treatment outcome.

3.1.3 Liquid formulations

Liquid formulations exist in various dosage forms such as suspensions, solutions, and emulsions. Three studies included in this review investigated the effect of liquid formulations on palatability in companion animals. Kammanadiminti et al. [9] examined the acceptance of Atopica® and Cyclavance®, two cyclosporin solutions used to treat canine atopic dermatitis. Both formulations generated similar levels of acceptance with 61% for Atopica® and 56% for Cyclavance®. Nonetheless, full ingestion of these treatments was markedly low, reaching 17% and 13% for Atopica® and Cyclavance® respectively (Phase 1 excluded as treatments were forcibly administered). These formulations cannot be considered as palatable as they do not reach the 80% threshold determined by the EMA. Nonetheless, the acceptance of these products was much higher than that of Atopica® capsules and may be a good alternative in the treatment of canine atopic dermatitis [10,9]. However, according to the results of this study, tablets remain more accepted in dogs.

Liquid formulations may be the most optimal dosage form for cats. Although no difference in palatability was observed between treatments, a survey by Khor et al. [26] reported 77% owner perception of animal enjoyment for the atenolol suspension tested in cats. Moreover, Bernachon et al. [24] observed 70% acceptance for Pronefra®, a liquid suspension used in the treatment of CKD. The results of both studies comply with the 70% threshold to classify

formulations as palatable and present the highest acceptance rates of all studies examining the palatability of formulations in felines. Hence, liquid dosage forms, specifically liquid suspensions, may be optimal for cats which might be explained by their preference for moist foods [3].

3.2 Effect of flavour and physical aspect on palatability

While dosage form impacts the voluntary acceptance of oral formulations, other factors such as taste, smell, form, size, texture, hardness, and colour also contribute to the palatability of a treatment [14,21]. The selection of excipients and physical appearance is therefore crucial to ensure good palatability levels.

3.2.1 Flavour excipients

In most formulations tested in the studies found in Table 2 and Table 3, animal-based natural or artificial flavours seem to be the gold standard in achieving high palatability. Cats are known to be attracted by meat-based flavours such as fish and liver [3]. Dogs also respond well to meat-based products such as beef and pork [3]. Accordingly, formulations with the highest palatability included flavours like pig liver, beef, natural chicken, and fish. Conversely, formulations that showed the lowest rates of voluntary consumption contained no flavouring. In the studies examined, Drontal® P flavoured with irradiated artificial beef flavouring achieved the highest acceptance rate of 97% in dogs [13]. Natural chicken flavour also led to high palatability formulations such as Milbemax® Chewable tablets which were accepted by 87% of canines and Pronefra®, accepted by 70% of felines [1,24]. In cats, Kitzyme®, containing fish flavouring, showed the highest palatability of all the treatments tested [6]. Contrarily, Benakor® and Marbocyl® Vet did not include any flavouring and were voluntarily consumed by 50% and 13% of test subjects [14,23]. The inclusion of flavouring is therefore useful in increasing a formulation's palatability, but high levels of voluntary consumption cannot solely be attributed such excipients.

3.2.2 Physical aspect

The physical appearance of a treatment also impacts the palatability of veterinary medicinal products [21]. The pet food industry established that companion animals show preference for interestingly shaped and large treats [3]. Studies found in the tables above indicate that treatments shaped as clovers (Nelio®), squares (Rimadyl®), ovals (Milbemax®) and round tablets (Drontal® P) generally show increased palatability over other shapes such as elongated tablets (Benakor®). The clover shape and round tablets present mixed results with Carprieve® (clover) yielding 70% acceptance and Metacam® (round) yielding 13% full consumption [25,16].

Formulations ranging from beige to brown also presented higher palatability regardless of dosage form. Drontal® P is a light brown tablet and demonstrated 97% spontaneous full consumption in dogs. Pronefra® is a brown suspension and demonstrated 70% acceptance in cats. Conversely, Cyclavance® oral solution is clear to yellow in colour and only resulted in 56% consumption. Similarly, Benakor® a yellow tablet resulted in only 50% acceptance.

Canned moist and semi-moist foods are also considered to be highly palatable [3], potentially explaining why cats preferred liquid formulations, such as the atenolol suspension (Table 2 and Table 3).

3.2.3 Formulation composition

The acceptance of a medication is also dependent upon its composition. Most active pharmaceutical ingredients (API) are bitter which induces poor palatability and an unpleasant odour [27]. Additionally, poor selection and improper quantities of excipients can lead to undesirable taste (e.g., bitterness) and thus lower palatability [28]. It is therefore crucial for formulators to ensure that novel dosage forms contain appropriate concentrations of APIs and excipients. For example, tablets containing higher drug loading compaction levels will inevitably be less palatable due to the presence of bitter compounds in large quantities. Common taste-masking methods include the synthesis of fast dissolving platforms (i.e. orally disintegrating tablets and chewable tablets), physical barriers (i.e. fluidised bed coating, microencapsulation, vapor dispersion, granulation-spheronisation and supercritical fluids),

chemical and solubility modifications (i.e. reducing solubility of drug, chemical derivatisation and complexation via cyclodextrins or resins), and solid dispersions (i.e. melt granulation, spray congealing, melt extrusion, and precipitation and drying) [29]. Alternatively, higher palatability can also be achieved by incorporating amino acids, sweeteners, and flavourings [28]. Many of the formulations in Table 2 and 3 are made up of the same excipients. For example, lactose monohydrate is found in Efex®, Nelio®, Rimadyl® and Carprieve®. It is a common excipient used in the formulation of solid medications [30]. Utilised as a binder, lactose monohydrate, generates hard tablets with acceptable disintegration properties [30]. The widespread use of lactose can be explained by its bland taste, low hygroscopicity, desirable compatibility with other components, and superior stability and water solubility [31]. Because of its bland taste, lactose is used in the coating of bitter pharmaceutical granules as it allows to decrease bitterness upon administration [32]. Other formulations found in Table 2 and 3 contain varying derivatives of lactose such as lactose anhydrous found in Benakor®. Croscarmellose sodium, found in Efex®, Nelio®, Fortekor®, and Carprieve®, is another excipient commonly found in oral formulations. It is used as a disintegrant for accelerated dissolution allowing for increased bioavailability [33]. Like lactose, it used as polymer coating because it results in decreased bitterness on administration [32]. Other formulations found in Table 2 and 3 contain varying derivatives of cellulose such as hypromellose found in Azodyl® or various polymers such as povidone K30 found in Dolpac® to achieve similar bitter inhibiting effects. Hence, formulation composition must be carefully crafted to achieve taste-masked readily accepted oral dosage forms.

3.3 Impact of methodology on palatability

While palatability is affected by factors such as physical aspect, taste and dosage form, other factors such as the experimental methodology can significantly alter results and induce study bias [34].

3.3.1 Study population

Although breed selection does not matter for palatability testing, animal selection is crucial in limiting bias [35,13]. Animal selection is pivotal because purpose-bred animals and home pets are different [1]. Laboratory-obtained results may therefore not reflect that of home pets. This is because some animals present different feeding behaviour than others, some eat everything they are given while some systematically reject what is offered, some animals even show side preference [13,14]. For example, small dogs can be "pickier" than larger ones, Petry et al. [1] observed that the >5-15 kg group yielded the most treatment failures (total refusal of tablets) with seven refusals for 13 tests per formulation.

While the EMA guidelines advocate testing the target population under field conditions, this is most often not possible. Indeed, Bernachon et al. [24] conducted an observational study in cats to assess the palatability of five different supplements that aid in the management of chronic kidney disease and concluded that while testing healthy cats may not accurately represent sick cats' palatability preferences, it avoids interference with treatment of sick animals. Study population selection is, therefore, necessary to ensure limited bias within studies. Inclusion of varied of dog species, sizes and weights is more representative of field conditions and may be the better approach to follow for studies carried out in labs [1]. Although assessing treatments in the target population may not always be possible, testing under both experimental and field conditions, is ideal to obtain the most accurate results [23].

Including a widely varied population of test subjects may not only help reflect true palatability but also contribute to reducing bias. Petry et al. [1] investigated the acceptance of Drontal® Plus tablets and Milbemax® chewable tablets in privately owned dogs. Drontal® Plus is a praziquantel-based oral tablet used to treat endoparasites in animals. It is formulated to treat 10 kg per tablet (i.e., dogs weighing 20 kg should ingest 2 tablets, dogs weighing 35 kg should consume 3.5 tablets, etc.) and contains irradiated artificial beef flavouring. Due to the dosing of each tablet, heavier dogs had to be included in this study to reflect palatability in large canines. Study bias would have occurred if only small dogs had been included because it can be assumed that one less palatable tablet is consumed with greater ease than multiple

[1]. Drontal® P was accepted by 88% of dogs with 48 dogs consuming three and more tablets (≥30kg). Animals receiving between 0.5 and 1.5 tablets (>5-15 kg) refused the treatment on 54% of occasions. This study complied with the EMA guidelines by testing a variety of client-owned dogs, representing field conditions and yielded results that would classify the formulation as palatable (acceptance > 80%) for most weight classes. Hence, including a wide variety of test subjects may allow to determine the true palatability of the formulation and reduce study bias [36].

3.3.2 Offering regimen and protocol

The slightly varying procedures observed in papers published before 2014 were adapted from the pet food industry due to their capacity of producing reproducible results. For example, Payne-Johnson et al. [16] initiated acceptance tests by offering a treatment in a bowl and if no consumption had occurred in the allocated time, the dosage form was offered from an investigator's hand. If no ingestion occurred again, the tests were terminated. This procedure is common to multiple papers (see Table 2). However, some articles such as Courbet et al. (canine study) [13] did not include the second step and others such as Khor et al. [26] administered solid, semisolid, and liquid dosage forms to cats using the traditional "poke-down" method which does not truly reflect acceptance as the animal is forced into ingesting a treatment. In 2014, the EMA guidelines on the demonstration of palatability of veterinary medicinal products were published to homogenise the experimental protocol found in animal palatability studies. However, the efficacy of these is rather limited as interstudy variations can still be observed. For example, an observational study carried out by Bernachon et al. [24] offered the formulations in cats' boxes and observed reaction by video to avoid interfering with the animal's behaviour – a procedure that completely differs from the standard acceptance or preference tests methodology observed in most other studies (see Table 2). Another study assessed palatability via questionnaires and surveys of cat owners [23]. This may be more representative of field situations but is limited due to subjectivity and may generate additional errors in protocol since owners might not strictly follow the guidelines provided. Moreover, certain studies advocate that encouragement of the animal should be allowed to replicate the animal's habitual setting and limit false

negatives [1]. The field could therefore benefit from revised guidelines to truly standardise the methodology although the EMA guidelines already offer a protocol for the assessment of voluntary acceptance.

In studies assessing palatability by preference testing, the experiments were carried out similarly (see Table 2). However, it is important to consider that some animals show side preference. One dog may consistently eat the treatment found in the right bowl while another may only consume the treatment from the left bowl. This behavioural laterality may be due to cerebral functional asymmetry and thus animal personality [37]. To address this, one study conducted by Zemirline et al. [14] randomly rotated the bowls daily in the preference tests. This slight modification may be beneficial when preference testing to reduce bias. Another method to prevent bias in preference testing is to measure individual preference rather than average preference as certain dogs show different preferences than the majority [14]. This may reveal differences in preference between certain weight classes or breeds that may have different feeding behaviours and thus impact the results of preference tests.

Nonetheless, studies such as Cron et al. [23] recognise that a fair assessment of palatability can be achieved by utilising bias reducing approaches. These include investigator training, acclimatisation of animals, fixed test time if every day, and using a cross-over design and should be included in the EMA guidelines to reduce interstudy differences and aid in the standardisation of an experimental protocol to test for palatability.

3.3.3 Wash-out period

Although EMA guidelines on palatability testing of veterinary formulations do not express the need for wash-out periods, they may be especially useful in canine studies. Some studies included a wash-out period (e.g., [25]), intended to prevent animals from habituating to the tested treatments. 6 canine studies included a wash-out period, ranging from 4 to 21 days. Only one cat study included a wash-out period of 8 days in its experimental protocol [26]. Neophobia may induce bias in results obtained because cats may reject formulations offered to them simply because they have never encountered it. This can lead to low acceptability

and preference rates, skewing results obtained. Conversely, wash-out periods may be necessary to include in canine studies to prevent conditioning and prevent animal confusion – the tablet given may be mistaken as a treat, especially by lab animals who are not used to receiving anything other than daily ratios of pet food [1].

4. Future perspective

There is a clear need to standardise the experimental methodology. This could be addressed by updating and revising the EMA guidelines on palatability testing. For example, these could include more precise indications on wash-out periods as well as study population selection as there is currently no clear indication for the latter. This would also allow for easier comparison of results which is hindered by interstudy variations. For example, one study included pet encouragement in the offering regimen which could have altered results. Other studies only assessed solid formulations while others assessed multiple dosage forms, impeding comparison. It is also important to note that animal breed may impact the acceptance of a drug. There are over 400 indexed canine breeds that display adult body weights ranging from 1.8kg to 90kg [38]. However, there are no studies to date assessing the difference in palatability between individual dog breeds. While current literature includes a variety of dog breeds in its study population, there is a need to address whether dog breeds lead to variations in acceptance. For example, a Beagle may have different food preferences than a Great Dane thereby affecting palatability, and thus acceptance

Additionally, while some studies qualified the formulations tested as palatable, most dosage forms do not reach the threshold prescribed by the EMA of 80% voluntary consumption in dogs and 70% in other species such as cats, thus more studies are required to truly establish which shapes, tastes and dosage forms yield the highest palatability. This would allow increasing treatment compliance for both owners and animals, in turn heightening treatment outcomes. To achieve this, pharmaceutical companies could collaborate with pet food companies to determine a standard panel of formulation considerations such as flavour and physical aspect that result in high palatability in companion animals.

The creation of databases that identify palatable characteristics such as excipients, flavors, or shapes, may lead to the formulation of highly palatable oral dosage forms capable

of heightening acceptance and hence disease outcome. These could resemble the Safety and Toxicity of Excipients for Paediatrics database (STEP) or Bitter DB (database of bitter compounds) which list compound characteristics such as toxicity and bitterness to aid in optimised drug formulation [39,40].

5. Conclusion

In conclusion, this systematic review aimed to summarise the current state of the art in the palatability assessment of oral veterinary medical products for companion animals. However, there is a limited number of studies available on the topic and the variety of formulations assessed is restrained. Nonetheless, this study provides a comprehensive evaluation of the effect of dosage form, flavour and physical aspect, composition, and experimental methodology on the palatability of veterinary formulations. The lack of a standardised procedure was apparent even though the European Medicines Agency published a set of guidelines on testing the palatability of veterinary treatments. This study found that canines generally accept solid dosage forms better than felines and that semisolid and liquid formulations are more adapted to felines than canines. Apart from dosage form, palatability was affected by flavour, physical aspect and formulation composition. Meat-based flavours such as beef, poultry and liver were palatable to both cats and dogs. Clover, square, and round-shaped tablets were more palatable than other elongated dosage forms. The field would benefit from a standardised methodology to limit bias and interstudy variation. Study population selection, offering regimens and whether to include a wash-out period are instrumental to accurately determine the true palatability of veterinary formulations.

6. Competing Interests

The authors of this paper have no competing interests to declare.

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