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Review

Key Considerations in Designing Oral Drug Delivery Systems for Dogs

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ABSTRACT

The present review discusses the pharmaceutical impact of the anatomy and physiology of the canine gastrointestinal tract to provide a comprehensive guide to the theories and challenges associated with the development of oral drug delivery systems for dogs. Novel pharmaceutical technologies applied to veterinary drugs are discussed indicating the advantages and benefits for animals. There are currently immense research and development efforts being funneled into novel canine health products. Such products are being used to overcome limitations of drugs that display site-dependent absorption or possess poor biopharmaceutical properties. Techniques that are employed to increase bioavailability of the Biopharmaceutics Classification System class II drugs are discussed in this article. Furthermore, an overview of palatable oral formulations for dog care is provided as an approach to easy administration. *In vitro* and *in vivo* evaluation and correlation of oral drug formulations in dogs are also addressed. This article assesses the outlook of canine oral drug development recognizing substantial growth forecasts of the dog care market.

Introduction

Dogs, as traditional companion animals, are a crucial part of many families throughout the world. They provide the owner with a sense of responsibility, demand care, and also afford companionship. As the bond between dogs and their owners only seems to be strengthening, it is not surprising that canine health products in the global market are gaining much attention and have become more specialized over the last few decades. The dog care market will continue to be attractive in the near future. Ideal canine health products maximize dog/owner compliance, enhance efficacy, and match the owner's demands and expectations and thus will drive the global market. Increasing dog/owner compliance leads to an easier or more convenient treatment for owners. Oral drug delivery systems are by far the most popular dosage forms for dogs, as they are simple to administer and available in many therapeutic categories.

This article provides a comprehensive overview of the anatomy and physiology of the canine gastrointestinal tract (GIT). This information is not only essential when producing an oral delivery system for dogs, but also for human health product R&D, as dogs are one of the major animal models used in early investigations of products destined for human preclinical trials. A significant challenge faced by pharmaceutical scientists when developing novel oral dosage forms is the vast variation in the dimensions of the canine GIT observed between and within breeds. Novel pharmaceutical technologies applied to veterinary drugs are of great benefit to owners and animals and the major advantageous technologies are summarized in this article to provide guidance on applications, challenges, and opportunities in the development of canine pharmaceuticals. A palatable oral formulation is an ideal approach to enhance the voluntary uptake of the medicines by the canine (self-administration), thus improving compliance. Furthermore, the owner can readily control dosage and monitor compliance without undue stress. Thereby, the benefits of these products can be assured by adjusting the dosing regimen to allow for the size and breed of the dogs. In order to achieve these objectives, the oral health products for dogs must be suited to a multiplicity of factors. Such factors are described in detail in this article, some of which include flavor, aroma, texture, and appearance. *In vitro* and *in vivo* evaluation and correlation of oral drugs are also described and discussed, offering guidance in addressing the challenges associated with obtaining correlational evidence for the development of new products.

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The Anatomy and Physiology of Canine Gastrointestinal System

There is a widespread lack of awareness of the differences in GIT physiology and anatomy between breeds of dogs.[1] For example, large breed dogs (e.g., 60 kg) have a GIT which comprises 2.8% of their total body weight, whereas small breed dogs (e.g., 5 kg) have a GIT which comprises 7% of their total body weight.[2,3]

When administering oral pharmaceuticals to individual breeds of dogs, variations in drug pharmacokinetics and pharmacodynamics may be observed. Consequently, the veterinarian is required to have a good understanding of the anatomy and physiology of the canine GIT, and formulation scientists also need this knowledge for appropriate product development.

Dog Breeds

Worldwide there are more than 400 canine breeds documented, in which mature body weights vary from 1.8 kg for the smaller breeds to 90 kg for the larger ones.[2] The percentage of lean body mass observed between canine breeds may be an important source of variation contributing to changes in the dose-response relationship. The clinical testing of novel or generic veterinary pharmaceuticals in various canine breeds can reveal variation in efficacy and toxicity dependent or independent of dose. Although mass plays a major role in dose-response relationships, other variations between breeds including ADME (absorption, distribution, metabolism, and excretion) differences, environmental factors, disease states, feeding habits, and age are crucial and must be taken into consideration.[2] The greyhound, for example, is primarily comprised of lean mass, with a far lower percentage body fat in comparison to other common breeds. For this reason, when a lipophilic drug is administered, greater plasma concentrations may be experienced as a result of a decreased volume of distribution.[2] Sulfonamides are widely used veterinary antibacterial agents; however, toxicity can vary between breeds. Reports show that numerous larger breeds of dogs are at higher risk of sulfonamide polyarthropathy than smaller breeds. In the case of Doberman Pinschers, predisposition to sulfonamide toxicity may be related to the breed's decreased ability to detoxify the hydroxylamine metabolites.[2]

The Anatomy and Physiology of Canine Stomach

The stomach can be considered both as a container for grinding/storing food and as a part of the digestive tract. However, little to no absorption of nutrients or medicines occurs from the stomach.[4] The stomach grinds food particles physically and chemically. The rigorous movements in the stomach grinds, churns, and propels partially digested food through the pylorus.[4,5] Beagle dogs with weights between 10.2 and 11.6 kg were reported to have a maximum destructive force of 3.2 N in the stomach, regardless of diet condition.[6] Any food particles larger than 2 mm will be pushed back into the stomach through the wave of contractions, until reduced to a more digestible size, which is within the range of 0.1-0.63 mm.[4,5,7]

Ellenberger and Baum[8] demonstrated that the stomach capacity of dogs is between 100 and 250 mL/kg, ranging from 0.5 to 8 L per dog. However, a more recent study has shown the volume of the dog stomach to be similar to that of humans, which is roughly 1 L.[4,9] The similarity in size means that the basal volume of water is probably similar in both species. The amount of basal water volume is about 24 mL.[10] Gupta and Robinson[11] reported that when fasted, the mean resting volume of fluid in the stomach was estimated to be around 25 mL.

pH Value of Canine Stomach

In dogs, mucus- and acid-secreting cells line the single chamber of the stomach.[12] During the basal or resting state, the secretion rate of gastric acid is noted to be extremely low.[9] The basal gastric acid secretion rate has been reported to be roughly 0.1 μmol/min per kg.[9,13,14] This explains why the gastrointestinal pH of the dog is usually observed to be one pH unit higher than the gastrointestinal pH of humans.[15,16]

Published pH values for dogs are variable, resulting in contrasting results.[15] In the fasted state, gastric pH in humans is reported at approximately 1-2, whereas for dogs there is higher variations and can be as high as 6.8.[15] In the fasted state, a mean gastric pH of 1.4-3.4 was reported when a Bravo® pH capsule (6 × 5.5 × 25 mm) was used for measurement of gastric pH in beagle dogs.[17] Sagawa et al.[15] using the same pH capsule observed a mean gastric pH of 2.03 ± 0.59 and an average gastric emptying time (GET) of 1.4 h. In the fed state (after consuming a standard meal of 300 g of dry dog food wetted with 20-30 mL of tap water), when using the same Bravo pH capsule, a mean gastric pH of 1.2-2.5 was reported.[17] Sagawa et al.[15] found a mean gastric pH of 1.08 in fed dogs when 10 g of dry food (high density canine diet) was given and a mean gastric pH of 1.26 when 200 g of dry food was given. Akimoto et al.[18] reported pH values of the gastric fluids in 8 fasting beagle dogs ranging from 2.7 to 8.3, with a mean basal pH value of 7. The mean gastric pH was 6.8 ± 0.2.[18] When using a wireless motility capsule (WMC), a median gastric pH of 1.6 was found, ranging from 0.9 to 2.7.[19] Akimoto et al.[18] measured gastric pH levels of 8 fasted beagle dogs using samples of gastric aspirates and pH value was 2.7-8.3.

Generally, the fasted state gastric pH of dogs was reported to be 1.5 ± 0.04, with a range of 0.9-2.5, whereas fed state gastric fluids were higher with a mean of pH 2.1 with a range of 0.5-5.[9,13] A summary of pH value of canine stomach (Table 1) demonstrates the large variations in canine gastric pH and the limited data in this area. As mentioned earlier, there are many factors that can affect the dog's gastric pH.

Gastric Emptying Time

Gastric emptying is a complex activity influenced by several factors including particle size, shape and density, body size, meal composition, and stress.[4,5,13,20]

Generally speaking, liquids clear the stomach exponentially, while solids exit in a linear fashion.[13,20] It was shown that in the fasting state, granules and tablets have a slower gastric emptying rate than solutions in beagle dogs.[21] Data also showed that when fed, emptying rates of granules and tablets were delayed longer in beagle dogs than in humans.[21]

Table 1
pH Value of Beagle Dogs Stomach

No.	pH Value of Canine Stomach (Fasted)	pH Value of Canine Stomach (Fed)	Method of pH Value Measurement
1[17]	1.6-3.4	1.2-2.1	A Bravo pH capsule (home cage)
2[17]	1.4-2.1	1.4-2.5	A Bravo pH capsule (study cage)
3[15]	2.05	1.08-1.26	A Bravo pH capsule
4[17]	0.9-2.5	1.5	Heidelberg capsule
5[17]	0.5-3.9	–	Heidelberg capsule
6[17]	0.7-7.0	2.0-3.7	Ion-selective field effect transistor pH sensor
7[18]	2.7-8.3	–	Gastric fluid aspirates
8[19]	–	0.9-2.7	Wireless motility capsule