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Formulation of Veterinary Dosage Forms

edited by
Jack Blodinger

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Merck Sharp & Dohme Research Laboratories
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Preface

Pharmaceutical science, as applied to the development of drug dosage forms, is invariably associated with the field of human health; however, the methodology and techniques used in developing human drug dosage forms are equally applicable to the formulation of veterinary dosage forms.

Until recently, the only drugs available for animal treatment were those developed for human use. *One for a Man, Two for a Horse*, the title of a book published in 1961 by Doubleday & Co., Inc., expresses well the thinking that was typical in the late 1950s. In the past several decades, animal science research has provided many new drugs with specific applications for animals . Considerable emphasis has been seen in the field of growth promotion and the treatment and prevention of disease in economic animals: those raised as a source of food or to produce foods such as milk and eggs. Economic animals are rarely treated individually, since the ailment of one animal in a flock or herd is readily transmitted to all other members.

The labor cost for treating these animals is becoming an increasingly important aspect of any food operation, and therefore, formulations are required that can be adapted to mass medication techniques using mechanical equipment. Many specialized dosage forms have been developed to meet this need for efficient administration of new drugs. The multiplicity of species differences has led to dosage forms specific to a single species. There are no counterparts in human medicine for some of the routes employed, such as intramammary infusion, gavage, or introduction through food or drinking water.

The formulator of a drug dosage form for animals enjoys the advanrage over the formulator of a human drug of being able to study the dosage form in the target animal at as early a time as he or she desires, subject only to the availability of the animal. The bioavailability and pharmacokinetic data obtainable from preliminary studies, coupled with preformulation data, permit the formulator to develop forms with maximum absorption and bioavailability.

This book describes the types of drug formulations administered to animals, the art and science used in their development, and the techniques needed to administer them so as to ensure optimum efficacy and maximum economy. Emphasis will be placed upon those forms which differ from those known in the human field and for which development techniques have not already been reported. This volume will not attempt to cover the activities relating to toxicity, metabolism, or efficacy and maximum economy. Emphasis will be placed upon those forms which differ from those known in the human field and for which development techniques have not already been reported. This volume will not attempt to cover the activities relating to toxicity, metabolism, or efficacy studies. We will show how the principles of pharmaceutical science can be applied to the development of animal dosage forms that are physically and chemically stable, biologically available, and practical to produce and administer.

While the primary audience for this book is the veterinary product formulator, other allied professionals will also profit from its use. The veterinarian will gain some insight into the selection of dosage forms for optimum effect, the government liaison administrator will have some help in determining data to be gathered for regulatory approval, and the pharmacy student seeking a career in industry will be made aware of the need for his or her talents in an exciting and worthy area of research.

I wish to thank Miss Elizabeth J. Krause for the many hours she spent typing, proofreading, and retyping the manuscripts in this publication.

Jack Blodinger

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The Basis for Selection of the Dosage Form

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I. INTRODUCTION

Each species of domestic animal has certain distinguishing features, some of which contribute to variations in its handling of a drug. Dietary habit now appears to provide the most satisfactory basis for grouping species in a general way. Herbivorous species consist of the horse and ruminant animals (cattle, sheep, and goats), omnivorous species (pig), and carnivorous species (dog and cat). In terms of physiological function, the digestive system is the principal distinguishing feature between herbivorous and carnivorous species. Other distinguishing features, which could be considered as allied to dietary habit, are the activity of the hepatic microsomal enzymes and the urinary pH reaction. In these respects, the pig resembles more closely the carnivorous species. Within each group the individual species are distinct, so that extrapolation of pharmacological data from one species to another may not be valid. However, with an understanding of comparative pharmacology, information derived from studies in one species can be applied for predictive purposes to another species. The confidence of such predictions is largely determined by a knowledge of the physicochemical properties of the drug substance which, in turn, determine its pharmacokinetic behavior and fate in the body.

The translocation processes for drugs are common to all mammalian species. Since passive diffusion is the mechanism by which drugs penetrate biological membranes, lipid solubility and degree of ionization are the main properties of a drug substance that govern its translocation, i.e., absorption, distribution, and mechanism of elimination. The blood plasma is the body fluid into which drugs are absorbed and by which they are conveyed throughout the body for distribution to other tissues. Drugs distribute nonselectively to tissues: only a small fraction of the dose administered ever reaches the site of action. The pattern of distribution is determined largely by the degree of perfusion of tissues, molecular structure, and, in a general way, lipid solubility of the drug substance. The liver and the kidneys, which are highly perfused and represent the principal organs of elimination for the majority of therapeutic agents, continually receive

a major fraction of the amount of drug in the plasma. Because of the central role of the plasma in translocation processes, the plasma concentration of a drug is usually directly related to the concentration in the immediate vicinity of the site of action, i.e., the biophasic concentration. Consequently, the plasma concentration versus time profile for a drug reflects the temporal course of its action.

Factors influencing the concentration of a drug in the plasma include: the size of the dose, formulation of the drug preparation, route of administration, extent of distribution and plasma protein binding, and rate of elimination. When a drug is given orally in solid form, it must first be released from the preparation, then traverse the gastrointestinal mucosal barrier to enter the portal venous blood in which it is conveyed to the liver, and finally, must pass through the liver before entering the systemic circulation (Fig. 1). Each of these events has the potential to decrease the amount of drug which reaches the systemic circulation intact (i.e., unchanged); the net effect is reflected in the bioavailability profile [1]. High hepatic clearance is a characteristic feature of drugs (such as lidocaine, propranolol, and diazepam) which exhibit the *first-pass* effect.

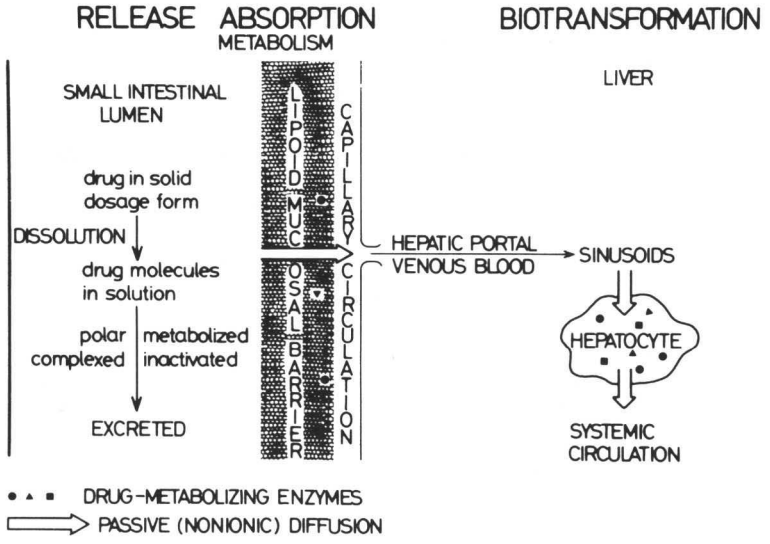

Figure 1 Events that may decrease the systemic availability of a drug given orally as a solid dosage form. (From J. D. Baggot, Chapter 18 in *Veterinary Gastroenterology*, ed. N. V. Anderson, Philadelphia, Lea & Feabiger, 1980).

The binding of drugs to plasma proteins (mainly albumin) restricts their distribution, thereby decreasing their accessibility to sites of action. This results in higher plasma concentrations if total rather than free drug is measured, and decreases the rate of excretion by glomerular filtration. The binding interaction is reversible, however, which implies that the drug-albumin complex serves as a circulating reservoir of potentially active drug. In mammals, the extent of binding of a drug is usually sufficiently narrow to permit it to be classified as extensive (>80%), moderately high (50 to 80%), or low (<50%). Species variations in binding do not relate to the total protein concentration in the plasma but may be attributed, at least tentatively, to differences in the composition and conformation of plasma albumin. Although an examination of the binding data for a variety of drugs in a number of species does not permit ranking of the species, humans appear to bind acidic drugs more extensively than domestic animals.

Most drugs are eliminated by a combination of biotransformation, mainly hepatic metabolism, and renal excretion processes. A particular mechanism of elimination usually predominates, however, for a compound and is determined by the nature of the substance. A certain degree of lipid solubility, for example, appears to be a prerequisite for the metabolism of a drug by the hepatic microsomal enzyme system. The herbivorous species appear to be most efficient in metabolizing drugs by hepatic microsomal oxidative reactions. An appropriate functional group is required for a drug to undergo a conjugation reaction with, for example, glucuronic acid. Based on a knowledge of the functional group in a compound, the probable metabolic pathway(s) can be predicted (Table 1). Compounds with an ester linkage are likely to undergo hydrolysis mediated by plasma pseudocholinesterase. Since the activity of this enzyme varies among the species of domestic animals, compounds inactivated by the enzyme can be expected to vary in response according to the species. The predominant metabolic pathways leading to inactivation of a compound might be similar in different species, but the rate at which they will proceed is highly unpredictable. There are a few certain exceptions, however, the most notable being the slow formation of glucuronide conjugates in the cat (Table 2). The immediate significance is that compounds (such as aspirin and phenols) which undergo glucuronide formation appear to be relatively more toxic in cats, but this may be a manifestation of overdosage, giving rise to excessively high plasma concentrations of the drugs. The products of biotransformation reactions generally have decreased activity, are less lipid-soluble, and are polar in nature. The latter renders metabolites suitable as substrates for carrier-mediated excretion processes.

Polar drugs and compounds with limited solubility in lipid are eliminated mainly by renal excretion. The excretion mechanisms are complex and involve: (a) glomerular filtration of molecules that are free,

Table 1 Probable Biotransformation Pathways for Drugs

Functional group	Biotransformation pathways
Aromatic ring	Hydroxylation
Hydroxyl	
aliphatic	Chain oxidation; glucuronic acid conjugation; sulfate conjugation (to a lesser extent)
aromatic	Ring hydroxylation; glucuronic acid conjugation; sulfate conjugation; methylation
Carboxyl	
aliphatic	Glucuronic acid conjugation
aromatic	Ring hydroxylation; glucuronic acid conjugation; glycine conjugation
Primary amines	
aliphatic	Deamination
aromatic	Ring hydroxylation; acetylation; glucuronic acid conjugation; methylation; sulfate conjugation
Sulfhydryl	Glucuronic acid conjugation; methylation; oxidation
Ester linkage Amide bond }	Hydrolysis

Source: Ref. 58.

Table 2 Domestic Animal Species with Defects in Certain Conjugation Reactions

Species	Conjugation reaction	Major target groups	State of synthetic reaction
Cat	Glucuronide synthesis	-OH, -COOH $-NH_2$, >NH, -SH	Present, slow rate
Dog	Acetylation	Ar-NH_2	Absent
Pig	Sulfate conjugation	Ar-OH, Ar-NH_2	Present, low extent

Source: Ref. 58.

unbound in the plasma; (b) carrier-mediated excretion of certain polar organic compounds by the proximal tubular cells; and (c) pH-dependent passive reabsorption, by nonionic diffusion, of lipid-soluble substances (weak organic electrolytes) in the distal portion of the nephron. The usual urinary reaction of herbivorous species is alkaline (pH 7.0 to 8.0), while that of carnivores is acidic (pH 5.5 to 7.0). In any species, however, urinary pH is dependent mainly on diet. Suckling and milkfed animals generally excrete an acid urine, even if they excrete alkaline urine when mature. Polar compounds of molecular weight greater than 300, which may be glucuronide conjugates of drugs or endogenous substances, are excreted mainly in the bile. Species may be grouped together as "good" (rats, dogs, and chickens), "moderate" (cats, sheep), or "poor" (guinea pigs, rabbits, and rhesus monkeys) biliary excretors [2]. This grouping of species is based on the minimum molecular weight for the extensive excretion in the bile of polar compounds. The *enterohepatic circulation* of a drug implies that, after its biliary excretion into the intestine, it is reabsorbed and returned to the hepatic sinusoids where it reenters both the cycle and the systemic circulation. Glucuronide conjugates are susceptible to hydrolysis by β-glucuronidase, which is present in the intestinal microorganisms, thereby making the lipid-soluble parent compound available for reabsorption. The influence of the urinary pH reaction or the enterohepatic circulation on the excretion rate of a drug is very much dependent on the contribution of that mechanism to the overall excretion process of the drug. There is minimal variation among species in the manner by which polar compounds are handled by the excretion mechanisms. This is in contrast with the wide interspecies variation and unpredictability associated with the biotransformation of extensively metabolized drugs.

To ensure selection of the most efficient dosage form and that reasonable predictions can be made as to the performance of formulations and drugs, the physicochemical, pharmacological, and physiological influences on drug response are discussed here.

II. BETWEEN-SPECIES DIFFERENCES

It is most important that the drug preparation selected be administered at a dosage appropriate for the particular species of animal. Species variations in response to a fixed dosage can be attributed either to differences in disposition factors which determine the concentration of the drug in the biophase, i.e., immediate vicinity of the site of action, or to inherent differences in the sensitivity of tissue receptor sites.

Clinical pharmacologic studies mainly support the view that species variations in response are attributable to differences in one or more of the following processes: systemic availability, accessibility to site of action, and rate of elimination. The term elimination refers to biotransformation and excretion: the processes responsible for removal

of the drug per se from the body. It has been shown, for example, that the duration of pentobarbital anesthesia in dogs and goats is related to the rate of hepatic metabolism of the drug [3]. For years, morphine was believed to invariably produce "maniacal" excitement in cats and consequently was considered contraindicated for use in this species. It is now known that when given by subcutaneous injection in proper dosage, which is 1 mg/kg in dogs and 0.1 mg/kg in cats, for the relief of intense pain, morphine will produce a sedative and marked analgesic effect in both species. Xylazine, a nonnarcotic sedative analgesic, has been found clinically to be the most useful drug for alleviating moderate pain in ruminant animals (cattle, sheep, and goats). These species appear to be 10 times more "sensitive" to this drug (Table 3), based on dosage level (mg/kg of body weight), than are the companion animals (horses, dogs, and cats). The varying susceptibility of different species to neuromuscular blockade with succinylcholine can be attributed to variations in activity of plasma pseudochlinesterase, which inactivates the drug by hydrolytic action.

A species comparison of oral dosage regimens for aspirin (Table 4) when the drug is used to produce a continuous analgesic effect is informative. The dose (25 mg/kg) is the same for dogs and cats, but the interval is three times longer in cats; attributable to slow elimination of the drug, due mainly to the relative deficiency in microsomal glucuronyl transferase activity [7]. Both components of the dosage regimen for aspirin in cows hinge on slow absorption of the drug from the reticulorumen, as the half-life of salicylate is less than 1 hr [6].

A. Comparative Physiology of the Digestive System

Domestic animals may be divided, according to their dietary habit as stated previously, into herbivorous (horse, cow, sheep, and goat), omnivorous (pig), and carnivorous (dog and cat) species.

A distinguishing feature of the herbivorous species is their nutritional dependence on bacterial fermentation processes. Another way of classifying the domestic animals is based on the anatomical arrangements of the gastrointestinal tract. The ruminant species (cow, sheep,

Table 3 Species Variations in Drug Dosage

Drug substance (route of injection)	Dose (mg/kg)			
	Ruminant	Horse	Dog	Cat
Xylazine (intramuscular)	0.2	2.0	2.0	2.0
Succinylcholine (intravenous)	0.02	0.1	0.3	1.0

Table 4 Dosage Regimens for Aspirin in Different Species

Species	Dose* (mg/kg)	Dosage Interval (hr)	Steady-state serum salicylate concentration (μg/ml)	Reference
Dog	25	8	125 - 200	4
Cat	25	24	100 - 250	5
Cow	100	12	40 - 60	6

*Usual dose of aspirin is 10 mg/kg for dogs and cats.

and goat) and the monogastric or simple-stomached species (pig, dog, and cat) are distinctly different, while the horse, although simple-stomached, occupies a somewhat intermediate position. The volume and composition of the gastrointestinal contents and, in a particular way, the pH gradients between plasma and gastrointestinal fluids play an important role in determining absorption of orally administered drug products, as well as distribution or excretion into the tract of parenterally administered preparations.

The physiology of digestion and drug absorption processes are, in general, similar in the pig, dog, and cat, and are not unlike those in the human. The simple stomachs of humans and dogs are lined with three main types of mucosal tissue: cardiac, gastric (oxyntic), and pyloric. The pig stomach is lined with the same mucosal types, but differs in that cardiac mucosa, the glands of which secrete mucus and bicarbonate ion [8], constitutes a much larger relative area of the stomach lining. The gastic mucosa proper contains the compound tubular glands which secrete hydrochloric acid (parietal or oxyntic cells) and pepsinogen (neck chief cells). The strongly acidic reaction of the gastic contents (usual pH range is 3 to 4) can inactivate certain drugs, such as penicillin G and erythromycin. This type of inactivation can usually be overcome by modifying the dosage form.

Gastric emptying is perhaps the most important physiological factor controlling the rate of drug absorption since, in monogastric species, the small intestine is the principal site of absorption. A drug in solution can be expected to be well-absorbed if it is stable (i.e., neither chemically or enzymatically inactivated) in the stomach, lipid-soluble, and not completely ionized in the upper portion of the small intestine. An effective pH of 5.3 in the microenvironment of the mucosal surface of the upper small intestine, rather than the reaction of the intestinal contents (pH 6.6), is consistent with observations on the absorption of drugs which are organic electrolytes. In the normal intestine, weak acids with pK_a values above 3 and bases with pK_a less than 7.8 have been shown to be very well absorbed [9]. Changes in the intestinal blood flow can alter the rate of absorption of lipid-soluble drugs [10,11].

Unlike other herbivorous species, the horse has a simple stomach but a major portion of its mucosal lining is composed of stratified squamous epithelium. The horse is a continuous feeder so that the stomach, which has a relatively small capacity, is almost never empty. Although the mean pH of gastric contents (pH 5.5) is higher than that in the dog and pig, the pH reaction in the equine stomach has been shown to vary widely from 1.13 to 6.8 [12]. The metabolic, digestive, and secretory functions of the digestive tract of the horse have been reviewed by Alexander [13]. Although microbial digestion of carbohydrate takes place in the stomach and large intestine of carnivores and omnivores, as well as herbivores, this fermentation process is of greater nutritional significance in herbivores [14]. Among the herbivorous species, there appears to be an inverse relationship between the volume of the stomach and that of the large intestine. The horse represents an extreme in colonic capacity and disturbance of the microorganisms indigenous to this region of the digestive tract, resulting from either a disease or antimicrobial therapy, can have serious consequences.

The principal feature of digestive physiology in the ruminant animal is that fermentation takes place continuously in the reticulorumen, which is a voluminous organ lined with stratified squamous epithelium. The approximate capacities of the adult reticulorumen are 100 to 225 liters in cattle and 6 to 20 liters in sheep and goats. Microbial digestion in the ruminant forestomach converts carbohydrate into volatile fatty acids (acetate, propionate, and butyrate), carbon dioxide, and methane. Only small quantities of other organic acids, including lactate, are normally produced. The forestomach contents vary from fluid to semisolid consistency and the pH reaction is normally maintained within a relatively narrow range (pH 5.5 to 6.5), in spite of the high concentration of volatile fatty acid produced. This is accomplished by buffers secreted in the alkaline saliva (pH 8.0 to 8.4) and also, apparently, directly by the forestomach epithelium. Despite the stratified squamous nature of its epithelial lining, the rumen has been shown to have considerable absorptive capacity [15,16]. After comminution by both microbial digestion and rechewing, the liquid portion of reticuloruminal contents, in which small particles of feed are suspended, is pumped by the omasum into the abomasum, or true stomach. Based on average values of salivary flow and volume of the rumen liquid pool (60 liters in cattle and 4.5 liters in sheep), the turnover rate for reticuloruminal fluid was estimated to be 2.0 liters/day for cattle and 1.1 to 2.2 liters/day for sheep [17]. The abomasum is the only part of the ruminant stomach that secretes digestive juices. The reaction of abomasal contents does not vary greatly and usually remains close to pH 3 [18].

Due to the large volume of ruminal fluid, a drug can attain a low concentration in this organ whether given in solution or in solid form.