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CA 2662827 C 2015/04/07

(11)(21) 2 662 827

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(86) Date de dépôt PCT/PCT Filing Date: 2007/09/05
(87) Date publication PCT/PCT Publication Date: 2008/03/13
(45) Date de délivrance/Issue Date: 2015/04/07
(85) Entrée phase nationale/National Entry: 2009/03/06
(86) N° demande PCT/PCT Application No.: US 2007/019357
(87) N° publication PCT/PCT Publication No.: 2008/030469
(30) Priorité/Priority: 2006/09/07 (US60/842,877)

(51) Cl.Int./Int.Cl. *A61K 9/20* (2006.01),
A61K 9/08 (2006.01)

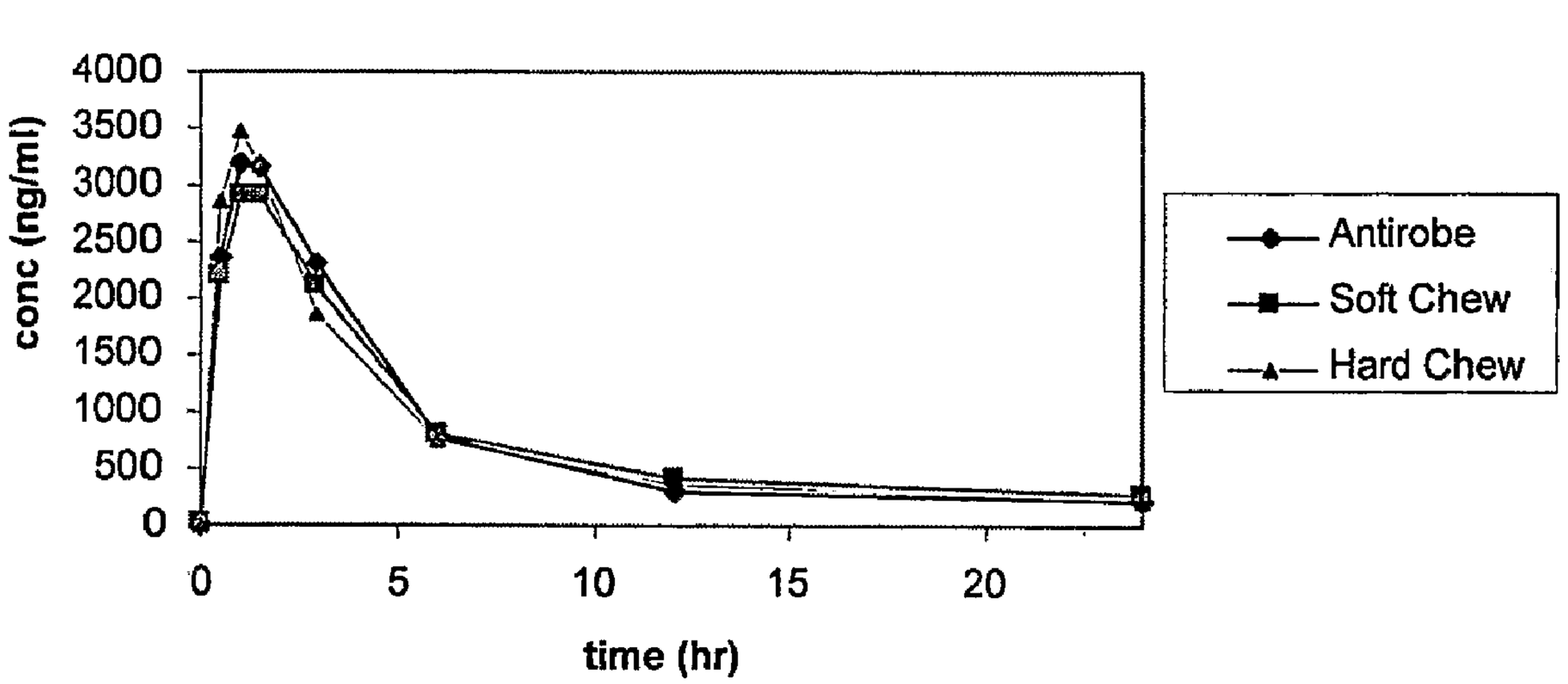
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(54) Titre : FORMULATIONS ANTIBIOTIQUES VETERINAIRES INNOVANTES EN COMPRIMES MACHABLES TENDRES OU INJECTABLES A LONGUE DUREE D'ACTION

(54) Title: SOFT CHEWABLE, TABLET, AND LONG-ACTING INJECTABLE VETERINARY ANTIBIOTIC FORMULATIONS



(57) Abrégé/Abstract:
This document relates to formulations for combating bacterial infections in animals which provide for improved long-acting oral and injectable formulations for systemic delivery of antibiotics, which are designed to achieve high bioavailability.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 March 2008 (13.03.2008)

PCT

(10) International Publication Number
WO 2008/030469 A3

(51) International Patent Classification:
A61K 9/20 (2006.01) *A61K 9/08* (2006.01)

(21) International Application Number:
PCT/US2007/019357

(22) International Filing Date:
5 September 2007 (05.09.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/842,877 7 September 2006 (07.09.2006) US

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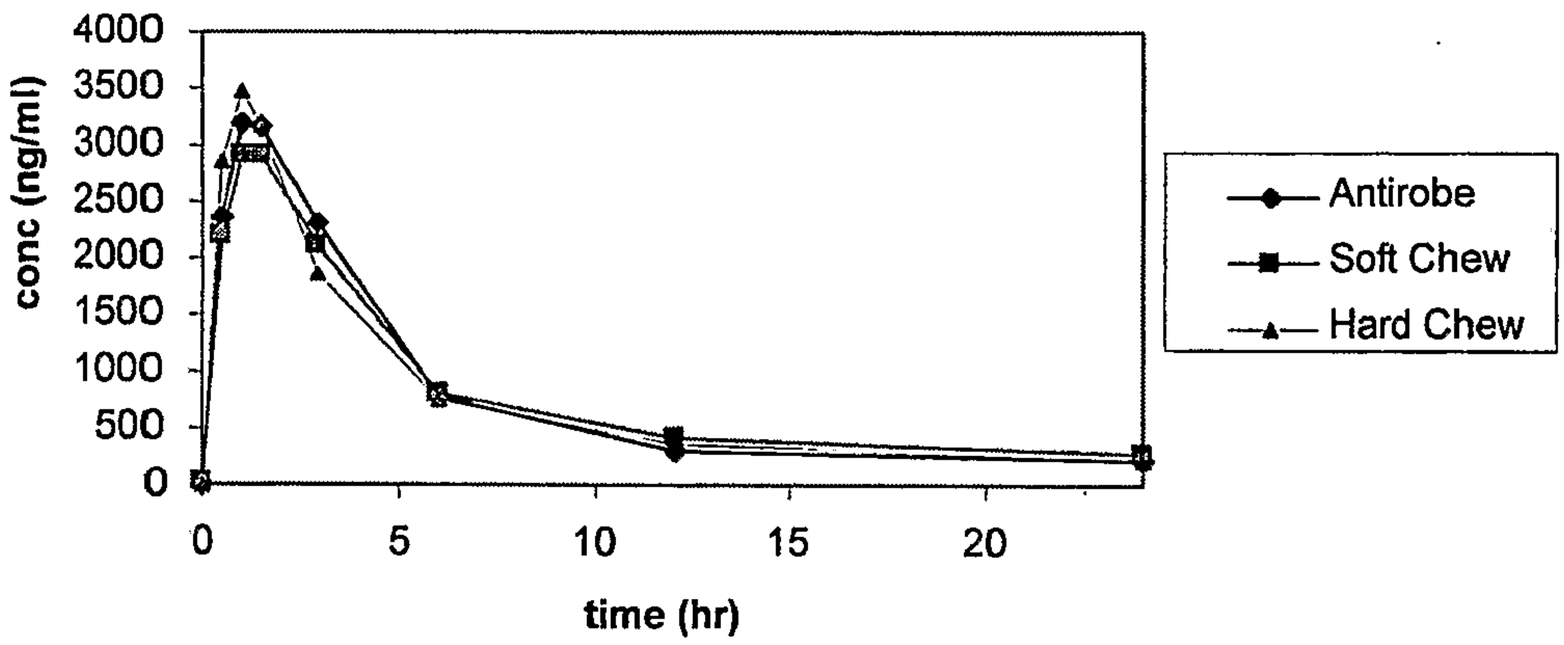
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
24 July 2008

(54) Title: SOFT CHEWABLE, TABLET, AND LONG-ACTING INJECTABLE VETERINARY ANTIBIOTIC FORMULATIONS



(57) Abstract: This document relates to formulations for combating bacterial infections in animals which provide for improved long-acting oral and injectable formulations for systemic delivery of antibiotics, which are designed to achieve high bioavailability.

WO 2008/030469 A3

51440-115

TITLE OF THE INVENTION

SOFT CHEWABLE, TABLET, AND LONG-ACTING INJECTABLE VETERINARY ANTIBIOTIC FORMULATIONS

FIELD OF THE INVENTION

This application relates to formulations for combating bacterial infections in animals. In particular, this invention provides for improved long-acting oral and injectable formulations for systemic delivery of antibiotics, which are designed to achieve high bioavailability.

BACKGROUND OF THE INVENTION

Antibiotics are a class of drugs that destroy or inhibit the growth of certain types of bacteria, and are commonly used to effectively control a variety of acute and chronic bacterial infectious diseases in birds and animals. Antibiotic therapy may result in killing the microorganism (bactericidal drugs) or inhibiting bacterial growth (bacteriostatic drugs). Antibiotics are classified as broad-spectrum or narrow-spectrum, depending on the types of bacteria they can kill or inhibit. The broad-spectrum antibiotics have antimicrobial effect on both the Gram-positive and Gram-negative bacteria, whereas the narrow-spectrum antibiotics only affect either the Gram-positive or the Gram-negative bacterial strains. There are five major groups of antibiotics that are classified by primary mechanism of action: cell wall synthesis inhibitors, cell membrane inhibitors, protein synthesis inhibitors, nucleic acid effectors, and folate inhibitors.

The kind of antibiotic, the time period for treatment, and the route of administration all vary based on the disease conditions and animal species. Therefore, it is generally helpful to discuss animals that are treated with antibiotics as members of one of three major groups: companion animals, food animals including poultry, and utility animals such as horses, which may also be considered companion animals, depending upon their use.

Antibiotic therapy for food animals usually does not extend beyond 5-10 days, while treatment of companion animals may extend for weeks or months for many chronic conditions. For example, some of the pathological conditions in dogs and cats, including chronic skin diseases, chronic otitis, chronic dermatitis, urinary tract infections, penetrating wounds and post-surgical treatment, may require prolonged or repeated systemic antibiotic administration. Long-term antibiotic therapy is also often required in cases of bacterial osteomyelitis.

Generally, antibiotics are administered by a variety of routes including, for example, oral ingestion, topical application or parental administration. The particular route of administration selected by the practitioner depends upon factors such as the physiochemical properties of the pharmaceutical or therapeutic agent, the condition of the host, and economic factors.

For example, one method of formulating a therapeutic agent for oral, topical, dermal or subdermal administration is to formulate the therapeutic agent as a paste or as an injectable formulation and reference is made to U.S. application Ser. No. 09/504,741, filed Feb. 16, 2000, issued September 7, 2004 as U.S. Patent 6,787,342, entitled PASTE FORMULATIONS; Ser. No. 09/346,905, filed Jul. 2, 1999, issued May 29, 2001 as U.S. Patent 6,239,112, entitled WATER MISCIBLE MACROLIDE SOLUTIONS; Ser. No. 09/112,690, filed Jul. 9, 1999, issued September 28, 1999 as U.S. Patent No. 5,958,888, entitled WATER MISCIBLE MACROLIDE SOLUTIONS; Ser. No. 08/675,380, filed July 2, 1996, issued March 3, 1998 as U.S. Patent No. 5,723,447, entitled WATER MISCIBLE ERYTHROMYCIN SOLUTIONS; Ser. No. 09/152,775, filed Sep. 14, 1998, issued January 16, 2001 as U.S. Patent No. 6,174,540, entitled LONG ACTING INJECTIBLE FORMULATIONS CONTAINING HYDROGENATED CASTOR OIL; and Ser. No. 09/271,098, filed March 18, 1999, issued May 11, 2004 as U.S. Patent No. 6,733,767, entitled LIQUID POLYMERIC COMPOSITIONS FOR CONTROLLED RELEASE OF BIOACTIVE SUBSTANCES.

Other methods of formulating therapeutic agents include placing the therapeutic agent in a solid or liquid matrix for oral delivery. These methods include chewable drug-delivery formulations. One problem associated with oral formulations is that the therapeutic agent often provides an unpleasant taste, aroma, or mouth feel to the formulation, which cause, especially in the situation with animals, the oral formulation to be rejected by the patient. See,

e.g., U.S. Pat. No. 5,380,535 to Geyer et al., which provides for a lipid based, chewable formulations for oral delivery of therapeutic agents, such as aspirin, ibuprofen or erythromycin, which are unpalatable to humans; U.S. Pat. No. 5,894,029 to Brown et al., which provides for dried puff pet foods comprising farinaceious materials, proteinaceous materials, such as meats or vegetable protein sources, and optionally medicaments or vitamins; or U.S. Pat. No. 5,637,313 to Chau et al., which describes chewable dosage forms comprising a water soluble matrix comprising hydrogenated starch hydrolystate bulking agent and a water insoluble bulking agent. Reference is also made to Ser. No. 10/745,784, filed December 23, 2003, now pending, entitled NON-ANIMAL PRODUCT CONTAINING VETERINARY FORMULATIONS; and Ser. No. 10/222,559, filed August 16, 2002, now pending, entitled NON-ANIMAL PRODUCT CONTAINING VETERINARY FORMULATIONS.

Traditionally, in veterinary formulations, palatability had been achieved by the inclusion of animal byproducts or flavors derived from animal sources into the formulation. For example, it is customary to include attracts, such as chicken powder, liver powder, beef, ham, fish, or rawhide-derived products in dog chews to make the chew palatable to the dog. See, e.g., U.S. Patent 6,086,940; U.S. Patent 6,093,441; U.S. Patent 6,159,516; U.S. Patent 6,110,521; U.S. Patent 5,827,565; U.S. Patent 6,093,427, all to Axelrod *et al.* However, the use of animal products or byproducts or flavors derived from animal sources have recently fallen into disfavor because of the possibility of chemical or biological contamination, which lead to toxicity or diseases such as bovine spongiform encephalopathy. Hence, there is a need for oral veterinary formulations that do not contain animal products, byproducts, or flavors derived from animal sources while still exhibiting good organoleptic properties. While non-animal derived products such as valerian plants are know as scent attractants in food products or pet toys (U.S. Patent 5,785,382 to Childers-Zadah) or animal chews that contain fruit flavors as the attractant (see, U.S. Patents 6,274,182; 6,200,616 and 6,126,978 to Axelrod *et al.*), these patents do not describe using valerian plants or fruit flavors in oral formulations in which the pharmaceutical agents needs to be masked.

Another problem associated with oral formulations relates to "bioavailability", which indicates the percentage of a drug dose which reaches its site of action, or a biological fluid, from which the drug has access, to its site of action (Grant R. Wilkinson, Goodman & Gilman's The Pharmacological Basis of Therapeutics, Tenth Ed., 5 (Hardman, J.G., Limbird, L.E., and Gilman, A.G., eds., McGraw-Hill, 2001) (1941). The bioavailability of drugs is a

complex issue. For example, a drug given orally must be absorbed first from the stomach and intestine, but this may be limited by the characteristics of the dosage form and/or the drug's physicochemical properties. In addition drug then passes through the liver, where metabolism and/or biliary excretion may occur before it reaches the systemic circulation. Accordingly, a fraction of the administered and absorbed dose of drug will be inactivated or diverted before it can reach the general circulation and be distributed to its sites of action. If the metabolic or excretory capacity of the liver for the agent in question is large, bioavailability will be substantially reduced (the so-called first pass effect). This decrease in availability is a function of the anatomical site from which absorption takes place; other anatomical, physiological, and pathological factors can influence bioavailability and the choice of the route of administration must be based on an understanding of these conditions (Grant R. Wilkinson, Goodman & Gilman's The Pharmacological Basis of Therapeutics, Tenth Ed., 5 (Hardman, J.G., Limbird, L.E., and Gilman, A.G., eds., McGraw-Hill, 2001) (1941).

One obvious way to change the bioavailability of a therapeutic agent is to change the route of administration from, for example, oral to parenteral. However, the use of parenteral injection may not always be appropriate. For example, intravenous injection has an increased risk of adverse effects and is not suitable for oily solutions or insoluble substances. Subcutaneous injections are not suitable for large volumes and may present possible pain or necrosis from irritating substances. Other strategies include increasing drug potency, changing dosage regimens, or using combination therapies. Furthermore, the choice of pharmaceutical formulation plays a role in rendering the therapeutic agent effective upon administration.

Antibiotic usage in veterinary medicine presents other unique considerations. Animal patients vary from small companion animals and birds that live in intimate proximity to their owners to pastured food and fiber producing animals with little human contact. The animal species, their human contact, temperament, size, use, emotional and economic value, and pathological conditions are all important factors that must be considered in selecting an appropriate type of antibiotic and administration route for therapy.

The particular dosage form varies based upon the kind of antibiotic used, the animal species being treated, and on whether the type of infection being treated requires local or systemic delivery. The advantage of local antibiotic therapy compared with systemic therapy is that a high concentration of antibacterial is delivered locally, thus avoiding the adverse effects that are associated with systemic antibacterial therapy. In general, companion and

utility animals may be treated with a greater variety of therapeutic options than food animals, which are generally treated through systemic antibiotic administration. Local delivery of antibiotic is preferred or practical for some types of diseases in companion and utility animals. For example, doxycycline-loaded biodegradable polymer gel has been used to treat periodontal disease in beagles. On the other hand in horses, antibiotics are commonly used systemically for treatment of respiratory disease, wound infections, sinus infections, and neonatal sepsis. Because of the large size of the horses and susceptibility to antibiotic induced diarrhea and colitis, there exists a need to improve localized delivery of antibiotics in the equine patients.

The common approaches for systemic delivery of antibiotics are through oral and parenteral administration. The routes of parenteral injection could be intravenous, intramuscular or subcutaneous. However, intravenous administration may not be feasible or practical in species other than companion animals and utility animals such as horses, due to labor cost and management practices.

Antibiotics are used for three major purposes in farm animals: (a) to treat an individual or an outbreak of bacterial infection (treatment), (b) to prevent outbreaks of bacterial disease in animals at risk during certain phases of production (prophylaxis) and (c) to use the antibiotics in animal feed for growth promotion effects (growth promoter). Growth promoters and some prophylactic antibiotics are normally administered orally via feed or drinking water.

Drinking water and feed medication are preferred for poultry, mainly because of the large number of birds involved. However, therapeutic levels of antibiotics may not be achieved due to inadequate feed or water uptake by an individual sick bird, instability of the antibiotics in feed or water, or inappropriate feeding time and techniques. Therefore, in the case of serious disease, parenteral administration of the antibiotics for the sick birds can be a viable alternative; however, the therapy is rarely used. Parenteral administration of the antibiotics is time and labor consuming for the owner, and stressful for the sick birds, because multiple injections of a conventional injectable formulation are often required.

Parenteral administration of antibiotics is often preferred as a treatment mode for food animals. Therefore, antibiotic treatment of pastured animals or large companion animals generally requires confinement of these animals for the duration of therapy. However, repeated restraint and administration within a relatively short period of time add to the stress of illness and may complicate convalescence and recovery. Even docile animals tend to become fractious and uncooperative after multiple days of parenteral therapy.

It is therefore evident from the foregoing description that there are advantages of systemic or local delivery of long-acting antibiotic formulations to food producing and companion animals, and birds for the treatment of infectious diseases. Some of these advantages include improved patient compliance, convenience for the owner and veterinarians, and improved cost effectiveness of treating bacterial diseases. Long-acting antibiotic formulations can even reduce the amount of antibiotics used for therapy and/or prophylaxis in food animals, since the convenient and easily administered long-acting formulations make it possible to treat each affected animal in a more efficient and effective manner.

Several different approaches to develop long-acting antibiotic formulations have been explored. These include formulating oral dosage forms, injectable formulations such as suspensions, concentrated solutions, injectable gels and microparticles and implants. The selection of the development approach of long-acting antibiotic formulations is determined by the intended application criteria, such as type of disease, systemic or local therapy, short-term or long-term therapy and type of animals being treated.

Biodegradable polymers have been used in parenteral controlled release formulations of bioactive compounds. Gels prepared with biodegradable polymers such as poly(lactide-co-glycolide), poly(lactic acid) and polyoxyethylene polyoxypropylene block copolymers (poloxamers or, LUTROL® F) and biocompatible, non-toxic solvents, such as triethyl citrate and acetyl triethyl citrate or water have been used to develop long-acting antibiotics formulations. The reversible thermal gelation characteristics of the formulations allowed the liquid injection to gel at the injection site at body temperature.

In one approach the polymer is fabricated into microspheres that may be injected via syringe, and the bioative compound is entrapped within the microspheres. This approach has not proved to be practical in part due to the difficulty in the manufacturing procedure for producing sterile and reproducible products, and the high cost of manufacturing. In another approach the biodegradable polymer and the bioactive material are dissolved in a biocompatible water-miscible solvent to provide a liquid composition. When the liquid composition is injected into the body, the solvent dissipates into the surrounding aqueous environment, and the polymer forms a solid depot from which the bioactive material is released.

European Patent Application 0537559 concerns polymeric compositions having a thermoplastic polymer, rate modifying agent, water soluble bioactive material and water-miscible organic solvent. Upon exposure to an aqueous environment (e.g. body fluids) the

liquid composition is capable of forming a biodegradable microporous, solid polymer matrix for controlled release of water soluble or dispersible bioactive materials over about four weeks. The thermoplastic polymer may be, among many listed, polylactide, polyglycolide, polycaprolactone or copolymers thereof, and is used in high concentration (45 to 50%). The rate modifying agent may be, among many others listed, glycerol triacetate (triacetin); however, only ethyl heptanoate is exemplified; and the amount of the rate modifying agent is no more than 15%.

Indeed, with respect to the patent literature, reference is made to: U.S. PAT. NO. INVENTOR 4,150,108 Graham 4,329,332 Couvreur et al. 4,331,652 Ludwig et al. 4,333,919 Kleber et al. 4,389,330 Tice et al. 4,489,055 Couvreur et al. 4,526,938 Churchill et al. 4,530,840 Tice et al. 4,542,025 Tice et al. 4,563,489 Urist 4,675,189 Kent et al. 4,677,191 Tanaka et al. 4,683,288 Tanaka et al. 4,758,435 Schaaf 4,857,335 Bohm 4,931,287 Bae et al. 5,178,872 Ohtsubo et al. 5,252,701 Jarrett et al. 5,275,820 Chang 5,478,564 Wantier et al. 5,540,912 Roorda et al. 5,447,725 Damani et al. 5,599,852 Scopelianos et al. 5,607,686 Totakura et al. 5,609,886 Wantier et al. 5,631,015 Bezwada et al. 5,654,010 Herbert et al. 5,700,485 Johnson et al. 5,702,717 Berde et al. 5,711,968 Tracy et al. 5,733,566 Lewis 4,938,763 Dunn et al. 5,077,049 Dunn et al. 5,278,201 Dunn et al. 5,278,202 Dunn et al. 5,288,496 Lewis 5,324,519 Dunn et al. 5,324,520 Dunn et al. 5,340,849 Dunn et al. 5,368,859 Dunn et al. 5,401,507 Lewis 5,419,910 Lewis 5,427,796 Lewis 5,487,897 Polson et al. 5,599,552 Dunn et al. 5,632,727 Tipton et al. 5,643,595 Lewis 5,660,849 Polson et al. 5,686,092 Lewis et al. 5,702,716 Dunn et al. 5,707,647 Dunn et al. 5,717,030 Dunn et al. 5,725,491 Tipton et al. 5,733,950 Dunn et al. 5,736,152 Dunn et al. 5,744,153 Yewey et al. 5,759,563 Yewey et al. 5,780,044 Yewey et al.

These documents tend to provide compositions that form a solid, gel or coagulated mass; for instance, a significant amount of polymer is contemplated in these documents, akin to European Patent Application 0537559.

Mention is also made of: Shah et al (J. Controlled Release, 1993, 27:139-147), as relating to formulations for sustained release of bioactive compounds containing various concentrations of poly(lactic-co-glycolic) acid copolymer (PLGA) dissolved in vehicles such as triacetin; Lambert and Peck (J. Controlled Release, 1995, 33:189-195), as a study of the release of protein from a 20% PLGA solution in N-methylpyrrolidone exposed to aqueous fluid; and Shivley et al (J. Controlled Release, 1995, 33:237-243), as a study of the solubility parameter of poly(lactide-co-glycolide) copolymer in a variety of solvents, and the in vivo

release of naltrexone from two injectable implants (5% naltrexone in either 57% PLGA and 38% N-methylpyrrolidone or 35% PLGA and 60% N-methylpyrrolidone).

Various other gel-forming agents have been studied for usefulness as carriers for therapeutic agents, for example poloxamers. Poloxamers are a family of more than 30 different nontoxic nonionic surface active agents. Concentrated aqueous solutions of many of the poloxamers form gels, a property that reverses upon a decrease in temperature, whereupon the gel reverts to a liquid.

The use of poloxamers as delivery vehicles, such as controlled or sustained release systems, gels, microemulsionsand nanoparticles may provide enhanced solubility of therapeutic agents, enhanced bioavailability, lengthened contact at specifically selected sites in the body, combined with the reduction in quantity of applied drug. All of these aspects may be exploited in order to optimize systemic and minimize side effects of active drugs.

Chowdhury et al., U.S. Publication No. 20040087520, in part discusses the usefulness of poloxamers for *topical or ophthalmic delivery* of various therapeutic agents, including antibiotics. In this regard, this reference is primarily involved with studies of localized application of antibiotics at a surgical site to prevent surgical site infections.

Poloxamers have also been investigated for usefulness in controlled release injectable gel formulations. For example, when injected intramuscularly, the formulation forms a depot for the controlled release of drug by gelling at body temperature. Paavola, et al., investigated a method of delaying the action of a local anesthetic, lidocaine, in post-operative and chronic pain using a low-viscosity gel containing a poloxamer (Paavola, A. et al., Pharm. Res. Vol. 12, No. 12, 1995). The 2% lidocaine-containing gels were evaluated in rats. Based on the results, compared to other carriers, the poloxamer gel was held to be the most effective, providing release of lidocaine for up to 240 minutes. The reference did not discuss the feasibility of using gels as injectable sustained-release vehicles for antibiotics or any other therapeutic agents.

Another formulation approach of developing long acting injectable formulations is to prepare concentrated solutions of antibiotics for injection, using suitable pharmaceutically acceptable water-miscible solvents such as polyethylene glycol, propylene glycol, n-methyl pyrrolidone, and 2-pyrrolidone. After an intramuscular or subcutaneous injection of the concentrated antibiotic solution, the drug precipitates at the injection site since the water-miscible solvent is carried away or diluted by the biological fluids, or absorbed rapidly from the injection site. The precipitated drug particles are slowly dissolved in the biological fluid at the site of injection, and the dissolved drug is absorbed into the blood stream.

Although most of the antibiotics currently on the market can generally be used in any animal species, developing a long-acting formulation which is suitable requires consideration of the size of animal species, physiological features of the animal, diseases to be treated, and the economic and emotional interest of the animal owners.

With all of the above factors at play in the development of antibiotic formulations, it remains a challenge to develop long-acting injectable formulations that remain effective for a sufficiently long time in order that a single injection is all that is necessary. The present invention fulfills this long-felt need.

Citation or identification of any document in this application is not an admission that such document is available as prior art to the present invention.

SUMMARY OF THE INVENTION

The present invention relates to novel chewable and tablet veterinary formulations that provide bioavailability of antibiotics that is comparable to a conventional capsule product. This invention further provides for improved veterinary formulations or which possess good consistency and acceptability by the animal, as well as a process to prepare said veterinary formulations. The invention further relates to a long-acting injectable formulation that provides sustained concentrations of therapeutic agents for 7-10 days.

The present invention encompasses a chewable veterinary formulation which may comprise an antibiotic, a hydrophobic material, soy protein fines, a disintegrant, a solvent, and optionally a flavor, and optionally a preservative.

In one embodiment, the formulation comprises an antibiotic between 1 and 5% of the formulation, a hydrophobic material between 2 and 15%, soy protein fines between 20-60%, flavor between 5-30%, preservative between 0.2 to 1%, disintegrant between 2 and 10%, and solvent between 2 and 20%.

Advantageously, the antibiotic of the chewable formulation is selected from the group consisting of amikacin, aminosalicyclic acid, amoxicillin, amoxicillin and clavulanate potassium, ampicillin, azithromycin, bacampicillin, bacitracin, capreomycin, carbenicillin, carbenicillin indanyl sodium, cefaclor, cefadroxil, cefaloridine, cefamandole, cefazolin, cefazolin sodium, cefepime, cefinetazole, cefixime, cefmetazole, cefodizime, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotetan, cefoxitin, cefoxitin sodium, cefpirome, cefpodoxime, cefpodoxime proxetil, cefquinome, ceftaxidime, ceftibuten, ceftiofur, ceftizoxime, ceftriaxone, cefuroxime, cephacelor, cephadrine, cephalexin, cephalothin, cephamandole, cephapirin, cepharadine, cephprozil, chloramphenicol, chlortetracycline, ciprofloxacin, clarithromycin, clindamycin HCl, clindamycin or salts thereof, clindamycin

phosphate, clofazimine, cloxacillin, colistin, co-triamoxazole, cycloserine, dalfopristin, danofloxacin, demeclocycline, dicloxacillin, difloxacin, dihydro-streptomycin, dirithromycin, docycycline, efrotomycin, enoxacin, enrofloxacin, ertapenem, erythromycin and salts thereof, ethambutol HCl and other salts, ethionamide, florfenicol, flumequine, fosfomycin, fosfomycin, gamithromycin, gatifloxacin, gentamycin, imipenem, imipenem-cilastin, isoniazid, kanamycin, levofloxacin, lincomycin, linezolid, lomefloxacin, loracarbef mafenide, marbofloxacin, meropenem, methenamine, methicillin, metronidazole, mezlocillin, minocycline, moxifloxacin, nafcillin, nalidixic acid, neomycin, netilmicin, nitrofurantoin, norfloxacin, novobiocin, ofloxacin, orbifloxacin, ormetoprim, oxacillin, oxytetracycline, paromomycin, penicillin G, penicillin G aqueous, penicillin G benzatine, penicillin G procaine, penicillin V, penicillin V penicillin salts and complexes, pentamidine, piperacillin, piperacillin sodium, piperacillin-tazobactam, polymixin B, pyrazinamide, rifampin, roxithromycin, salts of carbenicillin, silver sulfadiazine, sparfloxacin, spectinomycin, spiramycin, streptomycin, streptozocin, sufadimethoxine-ormetoprim, sulfacetamide, sulfacytine, sulfadiazine, sulfadimethoxine, sulfadimethoxine-trimethoprim, sulfamerazine, sulfamethazine, sulfamethixole, sulfapyridine, sulfapyrizine, sulfasalazine, sulfinethoxazole, sulfisoxazole, tazobactam, teicoplanin, , tetracycline, tetracycline HCl, tiamulin, ticarcillin, ticarcillin and clavulanate potassium, tilmicosin, tobramycin, trimethoprim, trimetrexate and ketolides, troleanomycin, trovafloxacin, tulathromycin, tylosin, vancomycin and ketolides such as telithromycin and HMR 3004.

More advantageously, the chewable formulation comprises an antibiotic that is clindamycin or a pharmaceutically acceptable salt or hydrate thereof. Most advantageously, the antibiotic is clindamycin HCl.

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In a particular embodiment, the invention relates to a chewable antibiotic veterinary formulation comprising: an antibiotic between 1 and 5%, a hydrophobic material between 2 and 15%, soy protein fines between 20-60%, a flavor between 5-30%, a preservative between 0.2 to 1%, a disintegrant between 2 and 10%, and a humectant between 2 and 20% of the formulation; wherein the antibiotic is clindamycin or a pharmaceutically acceptable salt or hydrate thereof.

In another embodiment, the invention relates to a process for preparing a chewable veterinary formulation according to any one of claims 1 to 12 which comprises the steps of: (a) blending the pharmaceutical agent, hydrophobic material, disintegrant, flavor; (b) adding the water, preservative, and the humectant to the mixture from step (a) and mixing the mixture; and (c) without drying, extruding the mixture.

In another embodiment, the invention relates to the formulation as described herein for use in treating a bacterial infection in an animal.

Advantageously, the chewable formulation comprises a hydrophobic material selected from the group consisting of glyceryl behenate, hydrogenated vegetable oil, stearic acid, glyceryl monostearate, glycerylpalmito stearate or cetyl alcohol. Most advantageously, the hydrophobic material is hydrogenated vegetable oil.

Advantageously, the chewable formulation comprises a filler selected from the group consisting of soy protein, corn cob, or corn gluten meal. More advantageously, the filler is soy protein.

Advantageously, the chewable formulation comprises a flavor wherein the flavor is a hickory smoke flavor or a beef flavor.

Advantageously, the chewable formulation comprises a preservative selected from the group consisting of parabens (methylparaben and/or propylparaben), benzalkonium chloride,

benzethonium chloride, benzoic acid, benzyl alcohol, bronopol, butylparaben, cetrimide, chlorhexidine, chlorobutanol, chlorocresol, cresol, ethylparaben, imidurea, methylparaben, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric acetate, phenylmercuric borate, phenylmercuric nitrate, potassium sorbate, sodium benzoate, sodium propionate, sorbic acid, thimerosal, propyl paraben, myristyl gama-picolinium chloride, paraben methyl, paraben propyl and quaternary ammonium compounds. More advantageously, the preservative is methylparaben and/or propylparaben.

Advantageously, the chewable formulation comprises a disintegrant selected from the group consisting of sodium starch glycolate, crospovidone, croscarmellose sodium, starch, micocrystalline cellulose, alginic acid, veegum, crospovidone, bentonite, and pregelatinized starch. More advantageously, the disintegrant is crospovidone.

Advantageously, the chewable formulation comprises a humectant is selected from the group consisting of propylene glycol, glycerin, polyethylene glycol 400 and polyethylene glycol 3350. More advantageously, the humectant is propylene glycol or purified water.

The chewable formulations are prepared according to methods conventional in the art, such as wet and dry granulation processes.

Advantageously, the process for preparing a chewable formulation comprises the steps of:

(a) blending the pharmaceutical agent, hydrophobic material, disintegrant, flavor;

(b) adding the water, preservative, and the humectant to the mixture from step (a) and mixing the mixture; and

(c) without drying, extruding the mixture.

Advantageously, administration of the chewable formulation of the present invention achieves bioavailability in an animal of a therapeutic agent that is comparable to commercially available products, and effectively treats bacterial infections in an animal.

The time course of treatment to be administered is easily determined by one skilled in the art. Advantageously, the animal receives treatment on days 0, 7, 14, 21, and 28.

The present invention further encompasses a tablet veterinary formulation comprising an antibiotic, a lactose carrier, mannitol, a binder and disintegrant, an aqueous solvent, and optionally a flavor, and optionally color.

In one embodiment, the tablet formulation comprises an antibiotic between 4 and 15%, a lactose carrier between 40 and 80%, mannitol between 5 and 15%, a binder and

disintegrant between 3 and 10%, flavor between 10 and 20%, color between 0.1 and 0.5%, and aqueous solvent is of a concentration sufficient to q.s. to 100%.

Advantageously, the antibiotic of the tablet formulation is selected from the group consisting of amikacin, aminosalicyclic acid, amoxicillin, amoxicillin and clavulanate potassium, ampicillin, azithromycin, bacampicillin, bacitracin, capreomycin, carbenicillin, carbenicillin indanyl sodium, cefaclor, cefadroxil, cefaloridine, cefamandole, cefazolin, cefazolin sodium, cefepime, cefinetazole, cefixime, cefmetazole, cefodizime, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotetan, cefoxitin, cefoxitin sodium, cefpirome, cefpodoxime, cefpodoxime proxetil, cefquinome, ceftaxidime, ceftibuten, ceftiofur, ceftizoxime, ceftriaxone, cefuroxime, cephacelor, cephadrine, cephalexin, cephalothin, cephamandole, cephapirin, cepharadine, cephprozil, chloramphenicol, chlortetracycline, ciprofloxacin, clarithromycin, clindamycin HCl, clindamycin or salts thereof, clindamycin phosphate, clofazimine, cloxacillin, colistin, co-triamoxazole, cycloserine, dalfopristin, danofloxacin, demeclocycline, dicloxacillin, difloxacin, dihydro-streptomycin, dirithromycin, docycycline, efrotomycin, enoxacin, enrofloxacin, ertapenem, erythromycin and salts thereof, ethambutol HCl and other salts, ethionamide, florfenicol, flumequine, fosfomycin, fosfomycin, gamithromycin, gatifloxacin, gentamycin, imipenem, imipenem-cilastin, isoniazid, kanamycin, levofloxacin, lincomycin, linezolid, lomefloxacin, loracarbef mafenide, marbofloxacin, meropenem, methenamine, methicillin, metronidazole, mezlocillin, minocycline, moxifloxacin, nafcillin, nalidixic acid, neomycin, netilmicin, nitrofurantoin, norfloxacin, novobiocin, ofloxacin, orbifloxacin, ormetoprim, oxacillin, oxytetracycline, paromomycin, penicillin G, penicillin G aqueous, penicillin G benzatine, penicillin G procaine, penicillin V, penicillin V penicillin salts and complexes, pentamidine, piperacillin, piperacillin sodium, piperacillin-tazobactam, polymixin B, pyrazinamide, rifampin, roxithromycin, salts of carbenicillin, silver sulfadiazine, sparfloxacin, spectinomycin, spiramycin, streptomycin, streptozocin, sufadimethoxine-ormetoprim, sulfacetamide, sulfacytine, sulfadiazine, sulfadimethoxine, sulfadimethoxine-trimethoprim, sulfamerazine, sulfamethazine, sulfamethixole, sulfapyridine, sulfapyrizine, sulfasalazine, sulfinethoxazole, sulfisoxazole, tazobactam, teicoplanin, , tetracycline, tetracycline HCl, tiamulin, ticarcillin, ticarcillin and clavulanate potassium, tilmicosin, tobramycin, trimethoprim, trimetrexate and ketolides, troleanomycin, trovafloxacin, tulathromycin, tylosin, vancomycin and ketolides such as telithromycin and HMR 3004.

More advantageously, the tablet formulation comprises an antibiotic that is clindamycin or a pharmaceutically acceptable salt or hydrate thereof. Most advantageously, the antibiotic is clindamycin HCl.

Advantageously, the tablet formulation comprises a filler selected from the group consisting of anhydrous lactose, hydrated lactose, sprayed dried lactose, crystalline maltose and maltodextrins. More advantageously, the filler is lactose.

Advantageously, the tablet formulation comprises a binder selected from the group consisting of polyvinyl pyrrolidone, povidone, starch, pregelatinized starch, gelatin, methylcellulose, hydroxypropyl cellulose, carboxymethyl cellulose sodium, ethylcellulose, sodium alginate, tragacanth, and acacia. More advantageously, the binder is polyvinyl pyrrolidone.

Advantageously, the tablet formulation comprises a disintegrant selected from the group consisting of sodium starch glycolate, crospovid one, croscarmellose sodium, starch, micocrystalline cellulose, alginic acid, veegum, crospovidone, bentonite, and pregelatinized starch. More advantageously, the disintegrant is crospovidone.

Advantageously, the tablet formulation comprises a flavor, wherein the flavor is a hickory smoke flavor or a beef flavor.

Advantageously, the tablet formulation comprises a colorant selected from the group consisting of dyes, an aluminum lake, caramel, colorant based upon iron oxide or a mixture of any of the foregoing. More advantageously, the colorant is selected from the group consisting of organic dyes and titanium dioxide.

Advantageously, the process for preparing a tablet formulation comprises the steps of mixing the ingredients intimately and pressing into single scored tablets.

Advantageously, administration of the tablet formulation of the present invention achieves bioavailability in an animal of a therapeutic agent that is comparable to commercially available products, and effectively treats bacterial infections in an animal.

The time course of treatment to be administered is easily determined by one skilled in the art. Advantageously, the animal receives treatment on days 0 ,7, 14, 21, and 28.

The present invention further encompasses novel long-acting injectable (LAI) formulations that provide slow release of therapeutic agent and which thereby provide sustained concentrations of therapeutic agent, lasting anywhere from 7-10 days. Such a dosage regimen allows for convenience in administration, increases in compliance, and decreases in error in treatment.

In one embodiment, the LAI formulation comprises an antibiotic, one or more poloxamers or other similar gelling agents, and sterile water for injection.

Advantageously, the LAI formulation comprises an antibiotic between 9 and 18%, a poloxamer between 5 and 30%, and sterile water for injection of a concentration sufficient to q.s. to 100%.

Advantageously, the antibiotic of the LAI formulation is selected from the group consisting of amikacin, aminosalicyclic acid, amoxicillin, amoxicillin and clavulanate potassium, ampicillin, azithromycin, bacampicillin, bacitracin, capreomycin, carbenicillin, carbenicillin indanyl sodium, cefaclor, cefadroxil, cefaloridine, cefamandole, cefazolin, cefazolin sodium, cefepime, cefinetazole, cefixime, cefmetazole, cefodizime, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotetan, cefoxitin, cefoxitin sodium, cefpirome, cefpodoxime, cefpodoxime proxetil, cefquinome, ceftaxidime, ceftibuten, ceftiofur, ceftizoxime, ceftriaxone, cefuroxime, cephacelor, cephadrine, cephalexin, cephalothin, cephamandole, cephapirin, cepharadine, cephprozil, chloramphenicol, chlortetracycline, ciprofloxacin, clarithromycin, clindamycin HCl, clindamycin or salts thereof, clindamycin phosphate, clofazimine, cloxacillin, colistin, co-triamoxazole, cycloserine, dalfopristin, danofloxacin, demeclocycline, dicloxacillin, difloxacin, dihydro-streptomycin, dirithromycin, docycycline, efrotomycin, enoxacin, enrofloxacin, ertapenem, erythromycin and salts thereof, ethambutol HCl and other salts, ethionamide, florfenicol, flumequine, fosfomycin, fosfomycin, gamithromycin, gatifloxacin, gentamycin, imipenem, imipenem-cilastin, isoniazid, kanamycin, levofloxacin, lincomycin, linezolid, lomefloxacin, loracarbef mafenide, marbofloxacin, meropenem, methenamine, methicillin, metronidazole, mezlocillin, minocycline, moxifloxacin, nafcillin, nalidixic acid, neomycin, netilmicin, nitrofurantoin, norfloxacin, novobiocin, ofloxacin, orbifloxacin, ormetoprim, oxacillin, oxytetracycline, paromomycin, penicillin G, penicillin G aqueous, penicillin G benzatine, penicillin G procaine, penicillin V, penicillin V penicillin salts and complexes, pentamidine, piperacillin, piperacillin sodium, piperacillin-tazobactam, polymixin B, pyrazinamide, rifampin, roxithromycin, salts of carbenicillin, silver sulfadiazine, sparfloxacin, spectinomycin, spiramycin, streptomycin, streptozocin, sufadimethoxine-ormetoprim, sulfacetamide, sulfacytine, sulfadiazine, sulfadimethoxine, sulfadimethoxine-trimethoprim, sulfamerazine, sulfamethazine, sulfamethixole, sulfapyridine, sulfapyrizine, sulfasalazine, sulfinethoxazole, sulfisoxazole, tazobactam, teicoplanin, , tetracycline, tetracycline HCl, tiamulin, ticarcillin, ticarcillin and clavulanate potassium, tilmicosin, tobramycin, trimethoprim, trimetrexate and

ketolides, troleanomycin, trovafloxacin, tulathromycin, tylosin, vancomycin and ketolides such as telithromycin and HMR 3004.

More advantageously, the LAI formulation comprises an antibiotic that is clindamycin or a pharmaceutically acceptable salt or hydrate thereof. Most advantageously, the antibiotic is clindamycin phosphate.

Advantageously, the poloxamer of the LAI formulation is selected from any available poloxamer. More advantageously, the poloxamer is selected from the group consisting of any LUTROL®. More advantageously, the poloxamer is LUTROL® F 127 or LUTROL® F 68.

Advantageously, the process for preparing the LAI veterinary formulation comprises the steps of:

(a) stirring the poloxamer into purified water at 5°C;

(b) optionally adding a second poloxamer to the mixture from step (a) and mixing the mixture; and

(c) optionally adding a polyacrylic acid into an aliquot of water, and completely hydrating the polyacrylic acid before mixing it into the poloxamer solution at 5°C;

(d) neutralizing the Carbopol using triethanolamine.

(e) dissolving the drug in ethanol/propylene glycol and adding it to the above solution.

Advantageously, administration of the LAI formulation of the present invention provides slow release of antibiotic and sustained concentrations of therapeutic agent, lasting anywhere from 7-10 days, and thereby effectively treats bacterial infections in an animal with a single injection. The time course of treatment to be administered is easily determined by one skilled in the art. Advantageously, a single injection is necessary for therapeutic agents, the effectiveness of which is desired for between 7 and 10 days. Wherein a prolonged effect is desired, subsequent injections may be required every 7-10 days.

These and other embodiments are disclosed or are obvious from and encompassed by, the following Detailed Description.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates the mean concentrations of clindamycin in dog serum after treatment with soft chewable or hard chewable formulations as compared to the commercial product, ANTIROBE®.

DETAILED DESCRIPTION

As used herein, the following terms have the meanings ascribed to them unless specified otherwise. In this disclosure, "comprises," "comprising," "containing" and "having" and the like can have the meaning ascribed to them in U.S. Patent law and can mean "includes," "including," and the like; "consisting essentially of" or "consists essentially" likewise has the meaning ascribed in U.S. Patent law and the term is open-ended, allowing for the presence of more than that which is recited so long as basic or novel characteristics of that which is recited is not changed by the presence of more than that which is recited, but excludes prior art embodiments.

The phrases "oral bioavailability" and "bioavailability upon oral administration" as used herein refer to the systemic availability (i.e., blood/plasma levels) of a given amount of antibiotic administered to a patient.

The term "clearance" as used herein refers to the removal of a substance from the blood, e.g., by renal excretion, expressed in terms of the volume flow of blood or plasma that would contain the amount of substance removed per unit time.

The term "half-life" as used herein refers to the period of time required for one-half of an amount of a substance to be lost through biological processes.

The term "bioavailability" as used herein refers to the physiological availability of a given amount of a drug, as distinct from its chemical potency. The term may also refer to the proportion of the administered dose which is absorbed into the bloodstream.

The term "animal" is used herein to include all vertebrate animals, including humans. It also includes an individual animal in all stages of development, including embryonic and fetal stages. As used herein, the term "production animals" is used interchangeably with "livestock animals" and refers generally to animals raised primarily for food. For example, such animals include, but are not limited to, cattle (bovine), sheep (ovine), pigs (porcine or swine), poultry (avian), and the like. As used herein, the term "cow" or "cattle" is used generally to refer to an animal of bovine origin of any age. Interchangeable terms include "bovine", "calf", "steer", "bull", "heifer", "cow" and the like. As used herein, the term "pig" is used generally to refer to an animal of porcine origin of any age. Interchangeable terms include "piglet", "sow" and the like.

In a first embodiment, the present invention provides for a soft chewable veterinary formulation, which comprises an effective amount of therapeutic agent which comprises at

least one antibiotic, a hydrophobic material, at least one filler, at least one disintegrant, at least one product containing flavor, at least one preservative, and at least one humectant.

For soft chewable formulations, the antibiotic may be selected from the following, which is to be considered non-limiting: beta lactam, semisynthetic penicillins, bacitracin, cephalosporins, quinolones, fluorinated quinolones, polymyxin, tetracyclines, chloramphenicol, macrolides, aminoglycosides, nalidixic acid, rifamycins, and sulfonamides. Some examples include Amikacin, aminosalicyclic acid, amoxicillin, amoxicillin and clavulanate potassium, ampicillin, azithromycin, bacampicillin, bacitracin, capreomycin, carbenicillin, carbenicillin indanyl sodium, cefaclor, cefadroxil, cefaloridine, cefamandole, cefazolin, cefazolin sodium, cefepime, cefinetazole, cefixime, cefmetazole, cefodizime, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotetan, cefoxitin, cefoxitin sodium, cefpirome, cefpodoxime, cefpodoxime proxetil, cefquinome, ceftaxidime, ceftibuten, ceftiofur, ceftizoxime, ceftriaxone, cefuroxime, cephacelor, cephadrine, cephalexin, cephalothin, cephamandole, cephapirin, cepharadine, cephprozil, chloramphenicol, chlortetracycline, ciprofloxacin, clarithromycin, clindamycin HCl, clindamycin or salts thereof, clindamycin phosphate, clofazimine, cloxacillin, colistin, co-triamoxazole, cycloserine, dalfopristin, danofloxacin, demeclocycline, dicloxacillin, difloxacin, dihydro-streptomycin, dirithromycin, docycycline, efrotomycin, enoxacin, enrofloxacin, ertapenem, erythromycin and salts thereof, ethambutol HCl and other salts, ethionamide, florfenicol, flumequine, fosfomycin, fosfomycin, gamithromycin, gatifloxacin, gentamycin, imipenem, imipenem-cilastin, isoniazid, kanamycin, levofloxacin, lincomycin, linezolid, lomefloxacin, loracarbef mafenide, marbofloxacin, meropenem, methenamine, methicillin, metronidazole, mezlocillin, minocycline, moxifloxacin, nafcillin, nalidixic acid, neomycin, netilmicin, nitrofurantoin, norfloxacin, novobiocin, ofloxacin, orbifloxacin, ormetoprim, oxacillin, oxytetracycline, paromomycin, penicillin G, penicillin G aqueous, penicillin G benzatine, penicillin G procaine, penicillin V, penicillin V penicillin salts and complexes, pentamidine, piperacillin, piperacillin sodium, piperacillin-tazobactam, polymixin B, pyrazinamide, rifampin, roxithromycin, salts of carbenicillin, silver sulfadiazine, sparfloxacin, spectinomycin, spiramycin, streptomycin, streptozocin, sufadimethoxine-ormetoprim, sulfacetamide, sulfacytine, sulfadiazine, sulfadimethoxine, sulfadimethoxine-trimethoprim, sulfamerazine, sulfamethazine, sulfamethixole, sulfapyridine, sulfapyrizine, sulfasalazine, sulfinethoxazole, sulfisoxazole, tazobactam, teicoplanin, , tetracycline, tetracycline HCl, tiamulin, ticarcillin, ticarcillin and clavulanate potassium, tilmicosin, tobramycin,

trimethoprim, trimetrexate and ketolides, troleanomycin, trovafloxacin, tulathromycin, tylosin, vancomycin and ketolides such as telithromycin and HMR 3004.

The amount of therapeutic agent depends on the individual therapeutic agent, the animal being treated, the disease state, and the severity of the disease state. The determination of those factors is well within the skill level of the practitioner.

Preferred formulations are those containing about 0.01 to 50% w/w of therapeutic agent and especially preferred formulations are those containing about 2.5 to about 5% w/w of therapeutic agent.

Advantageously, the soft chewable formulation contains as an antibiotic, clindamycin, or salts thereof. Most preferred is clindamycin HCl in a range of 1-5% w/w.

For soft chewable formulations, the hydrophobic material may include surfactants of different degrees of hydrophobicity or hydrophilicity which can be prepared by reaction of alcohols or polyalcohols with a variety of natural and/or hydrogenated oils. Most commonly, the oils used are castor oil or hydrogenated castor oil, or an edible vegetable oil such as corn oil, olive oil, peanut oil, palm kernel oil, apricot kernel oil, soybean oil, or almond oil. Preferred alcohols include glycerol, propylene glycol, ethylene glycol, polyethylene glycol, sorbitol, and pentaerythritol. Among these alcohol-oil transesterified surfactants, preferred hydrophilic surfactants are PEG-35 castor oil (Incrocas*-35), PEG-40 hydrogenated castor oil (Cremophor* RH 40), PEG-25 trioleate (TAGAT® TO), PEG-60 corn glycerides (Crovol M70), PEG-60 almond oil (Crovol* A70), PEG-40 palm kernel oil (Crovol PK70), PEG-50 castor oil (Emalex C-50), PEG-50 hydrogenated castor oil (Emalex* HC-50), PEG-8 caprylic/capric glycerides (Labrasol*), and PEG-6 caprylic/capric glycerides (Softigen* 767). Preferred hydrophobic surfactants in this class include PEG-5 hydrogenated castor oil, PEG-7 hydrogenated castor oil, PEG-9 hydrogenated castor oil, PEG-6 corn oil (Labrafil® M 2125 CS), PEG-6 almond oil (Labrafil® M 1966 CS), PEG-6 apricot kernel oil (Labrafil® M 1944 CS), PEG-6 olive oil (Labrafil® M 1980 CS), PEG-6 peanut oil (Labrafil® M 1969 CS), PEG-6 hydrogenated palm kernel oil (Labrafil® M 2130 BS), PEG-6 palm kernel oil (Labrafil® M 2130 CS), PEG-6 triolein (Labrafil® M 2735 CS), PEG-8 corn oil (Labrafil® WL 2609 BS), PEG-20 corn glycerides (Crovol* M40), and PEG-20 almond glycerides (Crovol* A40).

Preferred formulations are those containing about 0.01 to 50% w/w of hydrophobic material and especially preferred formulations are those containing about 1 to about 20% w/w of hydrophobic material.

*Trade-mark

Advantageously, the soft chewable formulation contains as a hydrophobic material, hydrogenated vegetable oil. Advantageously, the hydrogenated vegetable oil is present in the amounts of about 2-15% based upon total weight of formulation.

For soft chewable formulations, all fillers (or diluents) known in the soft chewable formulation art are contemplated. Non-limiting examples of fillers include soy protein, corn cob, or corn gluten meal.

Preferred formulations are those containing about 5 to 80% w/w of filler and especially preferred formulations are those containing about 10 to 70% w/w of filler.

Advantageously, the soft chewable formulation contains as a filler, soy protein fines. Advantageously, soy protein fines may be present in amounts of about 20% to 60% based upon total weight of formulation.

For soft chewable formulations, flavors include those known in pet foods which are artificial and include, for example:

DRY GARLIC-ADE OS	Formulated to provide a pungent garlic aroma.
LIQUID GARLIC-ADE OS	Same as dry garlic-ade in an oil miscible liquid form.
LIQUID GARLIC-ADE CONCENTRATE OM	Same as Dry Garlic-Ade but in a concentrated, oil miscible liquid form.
DRY ONION-ADE	Formulated to deliver an aroma and taste of cooked onions.
DRY GARLIC ONION-ADE	A dry blend of Garlic-Ade and Onion-Ade.
DRY CHEESE-ADE	A strong cheddar cheese flavor and aroma.
LIQUID CHEESE-ADE OM	An oil miscible, liquid version of Dry Cheese-Ade.
DRY CHICKEN-ADE	Formulated to provide the aroma of baked chicken.
LIQUID CHICKEN-ADE OS	An oil soluble liquid version of Dry Chicken-Ade.
LIQUID CHICKEN-ADE OS CONCENTRATE FFA	A concentrated form of Liquid Chicken-Ade OS.
DRY LIVER-ADE	Formulated to provide the aroma and flavor of cooked liver.
LIQUID LIVER-ADE CONCENTRATE	A concentrated liquid version of Dry Liver-Ade.
DRY PET-ADE BEEF STEW	A blend of many flavor components which provide of beef stew.
LIQUID PET-ADE BEEF STEW OS	An oil soluble, liquid version of Dry Pet-Ade Beef Stew.
PET-ADE BEEF STEW CONCENTRATE	A concentrated liquid version of Dry Pet-Ade Beef Stew.
DRY BEEF-ADE	A dry flavor formulated to provide the appeal of a baking roast.
DRY FISH MEAL FLAVOR CONCENTRATE	A dry flavor formulated to provide the odor of fish meal.
LIQUID FISH MEAL FLAVOR CONCENTRATE	A liquid version of Dry Fish Meal Flavor.
DRY KANIN-KRAVE	A spicy bone marrow flavor.
DRY BACON-ADE	A dry flavor which provides the aroma of frying bacon.

Sources for these flavors are well-know to a practitioner in this art. For example, Kermine Petfood Nutrisurance is a vegetarian flavor for pet food is sold by Kemine industries, Inc., Des Moines, IW. A discussion of commercial smoke flavorings is provided by Guillen *et al.* in J. Agr. and Food Chemistry vol. 4.

Preferred are the GRILLIN' line of grill flavors and blends marketed by the Red Arrow Products Company, LLC, Manitowoc, WI for human and pet food. These include GRILLIN' TYPE CB-200, GRILLIN' TYPE SD, GRILLIN' TYPE WS-50, GRILLIN' TYPE CN, GRILLIN'TYPE CB, GRILLIN' TYPE GS and GRILLIN' TYPE NBF.

Especially preferred are hickory smoked flavoring produced by combining torula yeast and an aqueous hickory smoke solution, sold by Red Arrow Products Co. as CHARTOR HICKORY or a hickory smoke flavoring produced by combining maltodextin with an aqueous hickory smoke solution, sold by Red Arrow Products Co. as CHARDEX HICKORY. Other flavors contemplated by the invention include those which impart a natural dry smoke flavor. These include CHARZYME (a smoke flavor produced by combining barley malt flour with an aqueous smoke flavor), CHARMAIZE (a smoke flavor produced by combining yellow flower and an aqueous smoke flavor) and CHARSALT (a blend of dendritic salt, aqueous smoke flavor, and hydrated silicon dioxide. All of these flavors may be obtained by Red Arrow Products Co. The determination of the amounts of flavor for a particular product is easily determined by a practitioner of this art.

Advantageously, the soft chewable formulation contains those flavors which provide a savory flavor. These flavors are well known to a practitioner of this art. Typical ranges are from 5-30% w/w. Advantageously, the flavor is a hickory smoke flavor or a beef flavor.

For soft chewable formulations, all preservatives known in the soft chewable formulation art are contemplated. Non-limiting examples include the parabens (methylparaben and/or propylparaben), benzalkonium chloride, benzethonium chloride, benzoic acid, benzyl alcohol, bronopol, butylparaben, cetrimide, chlorhexidine, chlorobutanol, chlorocresol, cresol, ethylparaben, imidurea, methylparaben, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric acetate, phenylmercuric borate, phenylmercuric nitrate, potassium sorbate, sodium benzoate, sodium propionate, sorbic acid, thimerosal, propyl paraben, myristyl gama-picolinium chloride, paraben methyl, paraben propyl and quaternary ammonium compounds and the like.

Preferred formulations are those containing about 0.05 to 5% w/w of preservative and especially preferred formulations are those containing about 0.1 to 2.5% w/w of preservative.

Advantageously, the preservative is methylparaben and/or propylparaben. Advantageously, the preservative is suitably used in the formulation in amounts ranging from about 0.01 to about 2.0% w/w, with about 0.2 to about 1.0% w/w being especially preferred.

For soft chewable formulations, all disintegrants known in the soft chewable formulation art are contemplated. Non-limiting examples include sodium starch glycolate, crospovidone, croscarmellose sodium, starch, micocrystalline cellulose, alginic acid, veegum, crospovidone, bentonite, and pregelatinized starch.

Preferred formulations are those containing about 0.05 to 20% w/w of disintegrant and especially preferred formulations are those containing about 1 to 12% w/w of disintegrant. Advantageously, the disintegrant is crospovidone.

Advantageously, the disintegrant is suitably used in the formulation in the amounts ranging from about 2-10% w/w.

For soft chewable formulations, all humectants known in the soft chewable formulation art are contemplated. Non-limiting examples include propylene glycol, glycerin, polyethylene glycol 400 and polyethylene glycol 3350.

Preferred formulations are those containing about 0.01% to 20% w/w.

Advantageously, the humectant is propylene glycol or purified water. Advantageously, these humectants may be present in amounts of about 2% to 20% based upon total weight of formulation.

The following chewable veterinary formulation is most preferred: clindamycin HCl between 1 and 10%, hydrogenated vegetable oil is between 2 and 15%, soy protein fines between 20-60%, flavor between 5-30%, preservative between 0.2 to 1%, disintegrant between 2 and 10%, and propylene glycol, purified water, and other ingredients between 2 and 20%.

Optionally, the chewable veterinary formulations may also include lubricants, such as polyethylene glycols (PEG's or CARBOWAX*), corn oil, mineral oil, hydrogenated vegetable oils (STEROTEX* OR LUBRITAB*), peanut oil, magnesium stearate, soybean oil and/or castor oil. The inclusion and identity of a lubricant is readily determined by a practitioner of this art are present in amounts, for example, of about 0.01 to about 20%, based upon total weight in the composition.

Absorbents may also be added to the chewable veterinary formulations. Such compounds are well known in the art to the practitioner as well as their use in pastes. These compounds effectively prevent or alleviate the phase separation of the product during storage. Preferred absorbents include magnesium carbonate, calcium carbonate, potassium

*Trade-mark

bicarbonate, sodium bicarbonate, starch, cellulose and its derivatives, or mixtures of absorbents, with magnesium carbonate being especially preferred. The inclusion of these compounds is optional with amounts of 0% to about 30%, 0 to about 15% or about 1% to about 15% or about 1% to about 10%, based on total weight of the formulation being especially preferred.

Antioxidants such as an alpha tocopheral, ascorbic acid, ascrobyl palmitate, fumeric acid, malic acid, sodium ascorbate, sodium metabisulfate, n-propyl gallate, BHA (butylated hydroxy anisole), BHT (butylated hydroxy toluene) monothioglycerol and the like, may be added to the present formulation. The antioxidants are generally added to the formulation in amounts of from about 0.01 to about 2.0%, based upon total weight of the formulation, with about 0.1 to about 1.0% being especially preferred.

Granulating solvents are well known to those skilled in this art. Non-limiting examples of such solvents are water, aqueous sorbitol solution, etc. Other compounds which can act as solvents include polyethylene glycol 3350, glycerol caprylate/caprate and polyglycolized glycerides (GELUCIRE*).

Compounds which stabilize the pH of the formulation (pH modifiers) are also contemplated. Again, such compounds are well known to a practitioner in the art as well as how to use these compounds. Buffering systems include, for example, systems selected from the group consisting of acetic acid/acetate, malic acid/malate, citric acid/citrate, tataric acid/tartrate, lactic acid/lactate, phosphoric acid/phosphate, glycine/glycimate, tris, glutamic acid/glutamates and sodium carbonate. Preferred ranges for pH include from about 4 to about 6.5.

Other compounds contemplated by the inventive formulations include complexing agents, such as cyclodextrins, PVP, PEG, ethyl lactate and niacinamide. Amounts of such compounds to be included in the inventive formulation are well known to a practitioner of the art. Also contemplated are therapeutic agents to be in the form of emulsions, liposomes or micelles.

Flow aids or glidants are also well known in the art and include, for example, silicon dioxide (CARBOSIL*) or silica gel (SYLOID*), talc, starch, calcium, stearate, magnesium stearate, and aluminum magnesium silicate (NEUSILIN*). Amounts of flow aids are readily determined by a practitioner in this art and include for using about 0.01 to about 25%, based upon weight of total composition. Non-limiting examples of lubricants for the tablets include magnesium and calcium stearate and stearic acid. Again, the various lubricants are well

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known to a practitioner of this art as well as the amounts of these compounds. Ranges include from about 0.01 to about 20% based upon the total weight of formulation.

Further, the present invention provides for a method for enhancing the palatability of an oral veterinary formulation, which comprises including in the formulation a flavor that is 'liked' by dogs.

This invention further provides for a process for preparing a chewable veterinary formulation, which comprises the steps of:

(a) blending the pharmaceutical agent, hydrophobic material, disintegrant, flavor;

(b) adding the water, preservative, and the humectant to the mixture from step (a) and mixing the mixture; and

(c) without drying, extruding the mixture.

In a second embodiment, the present invention provides for a tablet veterinary formulation, which comprises an effective amount of therapeutic agent which comprises at least one antibiotic, at least one filler, at least one disintegrant, at least one binder, at least one product containing flavor, at least one colorant, and at least one granulating solvent.

For tablet formulations, the antibiotic may be selected from the following, which is to be considered non-limiting: beta lactam, semisynthetic penicillins, bacitracin, cephalosporins, quinolones, fluorinated quinolones, polymyxin, tetracyclines, chloramphenicol, macrolides, aminoglycosides, nalidixic acid, rifamycins, and sulfonamides. Some examples include amikacin, aminosalicyclic acid, amoxicillin, amoxicillin and clavulanate potassium, ampicillin, azithromycin, bacampicillin, bacitracin, capreomycin, carbenicillin, carbenicillin indanyl sodium, cefaclor, cefadroxil, cefaloridine, cefamandole, cefazolin, cefazolin sodium, cefepime, cefinetazole, cefixime, cefmetazole, cefodizime, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotetan, cefoxitin, cefoxitin sodium, cefpirome, cefpodoxime, cefpodoxime proxetil, cefquinome, ceftaxidime, ceftibuten, ceftiofur, ceftizoxime, ceftriaxone, cefuroxime, cephacelor, cephadrine, cephalexin, cephalothin, cephamandole, cephapirin, cepharadine, cephprozil, chloramphenicol, chlortetracycline, ciprofloxacin, clarithromycin, clindamycin HCl, clindamycin or salts thereof, clindamycin phosphate, clofazimine, cloxacillin, colistin, co-triamoxazole, cycloserine, dalfopristin, danofloxacin, demeclocycline, dicloxacillin, difloxacin, dihydro-streptomycin, dirithromycin, docycycline, efrotomycin, enoxacin, enrofloxacin, ertapenem, erythromycin and salts thereof, ethambutol HCl and other salts, ethionamide, florfenicol, flumequine, fosfomycin, fosfomycin, gamithromycin, gatifloxacin, gentamycin, imipenem, imipenem-cilastin, isoniazid,

kanamycin, levofloxacin, lincomycin, linezolid, lomefloxacin, loracarbef mafenide, marbofloxacin, meropenem, methenamine, methicillin, metronidazole, mezlocillin, minocycline, moxifloxacin, nafcillin, nalidixic acid, neomycin, netilmicin, nitrofurantoin, norfloxacin, novobiocin, ofloxacin, orbifloxacin, ormetoprim, oxacillin, oxytetracycline, paromomycin, penicillin G, penicillin G aqueous, penicillin G benzatine, penicillin G procaine, penicillin V, penicillin V penicillin salts and complexes, pentamidine, piperacillin, piperacillin sodium, piperacillin-tazobactam, polymixin B, pyrazinamide, rifampin, roxithromycin, salts of carbenicillin, silver sulfadiazine, sparfloxacin, spectinomycin, spiramycin, streptomycin, streptozocin, sufadimethoxine-ormetoprim, sulfacetamide, sulfacytine, sulfadiazine, sulfadimethoxine, sulfadimethoxine-trimethoprim, sulfamerazine, sulfamethazine, sulfamethixole, sulfapyridine, sulfapyrizine, sulfasalazine, sulfinethoxazole, sulfisoxazole, tazobactam, teicoplanin, , tetracycline, tetracycline HCl, tiamulin, ticarcillin, ticarcillin and clavulanate potassium, tilmicosin, tobramycin, trimethoprim, trimetrexate and ketolides, troleanomycin, trovafloxacin, tulathromycin, tylosin, vancomycin and ketolides such as telithromycin and HMR 3004.

Preferred formulations are those containing about 0.01 to 50% w/w of therapeutic agent and especially preferred formulations are those containing about 2 to about 20% w/w of therapeutic agent.

Advantageously, the tablet formulation contains clindamycin, or salts thereof. Most preferred is clindamycin HCl in a range of 4-15% w/w.

For tablet formulations, all fillers (or diluents) known in the tablet art are contemplated. Non-limiting examples of fillers include anhydrous lactose, hydrated lactose, sprayed dried lactose, crystalline maltose and maltodextrins.

Advantageously, the tablet formulation contains as a filler, lactose. Advantageously, the lactose may be present in amounts of about 40% to 80% based upon total weight of formulation.

Advantageously, the tablet formulation contains as a diluent, binder, carrier, filler, or as a flow enhancer, mannitol in a range of 5-15% w/w.

For tablet formulations, all binders known in the tablet art are contemplated. Non-limiting examples of binders include polyvinyl pyrrolidone, povidone, starch, pregelatinized starch, gelatin, methylcellulose, hydroxypropyl cellulose, carboxymethyl cellulose sodium, ethylcellulose, sodium alginate, tragacanth, and acacia.

Preferred formulations are those containing about 1 to 20% w/w of binder and especially preferred formulations are those containing about 2-12% w/w of binder.

Advantageously, the tablet formulation contains, as a binder, polyvinyl pyrrolidone.

Advantageously, the binder may be present in amounts of about 3-10% w/w, depending on the selection, and the amount, of disintegrant.

For tablet formulations, all disintegrants known in the tablet art are contemplated. Non-limiting examples of disintegrants include sodium starch glycolate, crospovidone, croscarmellose sodium, starch, micocrystalline cellulose, alginic acid, veegum, crospovidone, bentonite, and pregelatinized starch.

Preferred formulations are those containing about 1 to 20% w/w of disintegrant and especially preferred formulations are those containing about 2-12% w/w of disintegrant.

Advantageously, the tablet formulation contains as a disintegrant, crospovidone.

Advantageously, the disintegrant may be present in amounts of about 3-10% w/w, depending on the selection, and therefore the amount, of binder.

For tablet formulations, all flavors known in pet foods, which are artificial, are contemplated and include, for example:

DRY GARLIC-ADE OS	Formulated to provide a pungent garlic aroma.
LIQUID GARLIC-ADE OS	Same as dry garlic-ade in an oil miscible liquid form.
LIQUID GARLIC-ADE CONCENTRATE OM	Same as Dry Garlic-Ade but in a concentrated, oil miscible liquid form.
DRY ONION-ADE	Formulated to deliver an aroma and taste of cooked onions.
DRY GARLIC ONION-ADE	A dry blend of Garlic-Ade and Onion-Ade.
DRY CHEESE-ADE	A strong cheddar cheese flavor and aroma.
LIQUID CHEESE-ADE OM	An oil miscible, liquid version of Dry Cheese-Ade.
DRY CHICKEN-ADE	Formulated to provide the aroma of baked chicken.
LIQUID CHICKEN-ADE OS	An oil soluble liquid version of Dry Chicken-Ade.
LIQUID CHICKEN-ADE OS CONCENTRATE FFA	A concentrated form of Liquid Chicken-Ade OS.
DRY LIVER-ADE	Formulated to provide the aroma and flavor of cooked liver.
LIQUID LIVER-ADE CONCENTRATE	A concentrated liquid version of Dry Liver-Ade.
DRY PET-ADE BEEF STEW	A blend of many flavor components which provide of beef stew.
LIQUID PET-ADE BEEF STEW OS	An oil soluble, liquid version of Dry Pet-Ade Beef Stew.
PET-ADE BEEF STEW CONCENTRATE	A concentrated liquid version of Dry Pet-Ade Beef Stew.
DRY BEEF-ADE	A dry flavor formulated to provide the appeal of a baking roast.
DRY FISH MEAL FLAVOR CONCENTRATE	A dry flavor formulated to provide the odor of fish meal.
LIQUID FISH MEAL FLAVOR CONCENTRATE	A liquid version of Dry Fish Meal Flavor.

DRY KANIN-KRAVE	A spicy bone marrow flavor.
DRY BACON-ADE	A dry flavor which provides the aroma of frying bacon.

Sources for these flavors are well-know to a practitioner in this art. For example, Kermine Petfood Nutrisurance is a vegetarian flavor for pet food is sold by Kemine industries, Inc., Des Moines, IW. A discussion of commercial smoke flavorings is provided by Guillen *et al.* in J. Agr. and Food Chemistry vol. 4.

Preferred are the GRILLIN' line of grill flavors and blends marketed by the Red Arrow Products Company, LLC, Manitowoc, WI for human and pet food. These include GRILLIN' TYPE CB-200, GRILLIN' TYPE SD, GRILLIN' TYPE WS-50, GRILLIN' TYPE CN, GRILLIN'TYPE CB, GRILLIN' TYPE GS and GRILLIN' TYPE NBF.

Especially preferred are hickory smoked flavoring produced by combining torula yeast and an aqueous hickory smoke solution, sold by Red Arrow Products Co. as CHARTOR HICKORY or a hickory smoke flavoring produced by combining maltodextin with an aqueous hickory smoke solution, sold by Red Arrow Products Co. as CHARDEX HICKORY. Other flavors contemplated by the invention include those which impart a natural dry smoke flavor. These include CHARZYME (a smoke flavor produced by combining barley malt flour with an aqueous smoke flavor), CHARMAIZE (a smoke flavor produced by combining yellow flower and an aqueous smoke flavor) and CHARSALT (a blend of dendritic salt, aqueous smoke flavor, and hydrated silicon dioxide. All of these flavors may be obtained by Red Arrow Products Co.

The determination of the amounts of flavor for a particular product is easily determined by a practitioner of this art. Preferred are those flavors which provide a savory flavor. These flavors are well known to a practitioner of this art.

Advantageously, the tablet formulation contains those flavors which provide a savory flavor. These flavors are well known to a practitioner of this art. Typical ranges are from 5-30% w/w. Advantageously, the tablet formulation contains a hickory smoke flavor or a beef flavor. Advantageously, flavor is added between 10 and 20% based upon total weight of formulation.

For tablet formulations, all colorants known in the tablet art are contemplated. Non-limiting examples include, but are not limited to, dyes, an aluminum lake, caramel (which may also function as a flavor), colorant based upon iron oxide or a mixture of any of the foregoing. Especially preferred are organic dyes and titanium dioxide. Preferred ranges include from about 0.5% to about 25% based upon total weight of formulation.

For tablet formulations, water is added, q.s. to 100%.

The following tablet formulation is most preferred: clindamycin HCl between 4 and 15%, lactose carrier between 40 and 80%, mannitol between 5 and 15%, binder and disintegrant between 3 and 10%, flavor between 10 and 20%, color between 0.1 and 0.5%, and purified water and other ingredients q.s. 100%.

Optionally, the tablet formulations of the present invention may further contain other inert ingredients such as absorbents, antioxidants, granulating solvents, stabilizers or surfactants. These compounds are well known in the formulation art.

Absorbents may also be added to the inventive formulations. Such compounds are well known in the art to the practitioner as well as their use in pastes. These compounds effectively prevent or alleviate the phase separation of the product during storage. Preferred absorbents include magnesium carbonate, calcium carbonate, potassium bicarbonate, sodium bicarbonate, starch, cellulose and its derivatives, or mixtures of absorbents, with magnesium carbonate being especially preferred. The inclusion of these compounds is optional with amounts of 0% to about 30%, 0 to about 15% or about 1% to about 15% or about 1% to about 10%, based on total weight of the formulation being especially preferred.

Antioxidants such as an alpha tocopheral, ascorbic acid, ascrobyl palmitate, fumeric acid, malic acid, sodium ascorbate, sodium metabisulfate, n-propyl gallate, BHA (butylated hydroxy anisole), BHT (butylated hydroxy toluene) monothioglycerol and the like, may be added to the present formulation. The antioxidants are generally added to the formulation in amounts of from about 0.01 to about 2.0% w/w, with about 0.1 to about 1.0% w/w being especially preferred.

Granulating solvents are well known to those skilled in this art. Non-limiting examples of such solvents are water, aqueous sorbitol solution, etc. Other compounds which can act as solvents include polyethylene glycol 3350, glycerol caprylate/caprate and polyglycolized glycerides (GELUCIRE).

Compounds which stabilize the pH of the formulation (pH modifiers) are also contemplated. Again, such compounds are well known to a practitioner in the art as well as how to use these compounds. Buffering systems include, for example, systems selected from the group consisting of acetic acid/acetate, malic acid/malate, citric acid/citrate, tataric acid/tartrate, lactic acid/lactate, phosphoric acid/phosphate, glycine/glycimate, tris, glutamic acid/glutamates and sodium carbonate. Preferred ranges for pH include from about 4 to about 6.5.

Other compounds contemplated by the inventive formulations include complexing agents, such as cyclodextrins, PVP, PEG, ethyl lactate and niacinamide. Amounts of such compounds to be included in the inventive formulation are well known to a practitioner of the art. Also contemplated are therapeutic agents to be in the form of emulsions, liposomes or micelles.

Flow aids or glidants are also well known in the art and include, for example, silicon dioxide (CARBOSIL) or silica gel (SYLOID), talc, starch, calcium, stearate, magnesium stearate, and aluminum magnesium silicate (NEUSILIN). Amounts of flow aids are readily determined by a practitioner in this art and include for using about 0.01 to about 25%, based upon weight of total composition. Non-limiting examples of lubricants for the tablets include magnesium and calcium stearate and stearic acid. Again, the various lubricants are well known to a practitioner of this art as well as the amounts of these compounds. Ranges include from about 0.01 to about 20% based upon total weight of formulation.

Moreover, in an alternative embodiment this invention provides for tablets which are coated. The inventive tablets are prepared according to methods conventional in the art, such as wet and dry granulation processes. The chewable formulations and tablets provided for by this invention may be coated using techniques conventional in the art. Coatings for chewables veterinary formulations include gelatin, glyceryl behenate, coca butter, and beeswax. Other coatings would be known to a practitioner in this art. Coatings for tablets include sugar coatings, such as seal coatings, subcoatings, and syrup coatings, as well as film coatings, such as pan-pour coatings and pan spray coatings. As well known to a practitioner of this art, the coatings contain additional components such as solvents, plasticizers, colorants, opaquant-extenders and film formers.

Often it is beneficial to administer a formulation that contains a combination of two or more antibiotics, which possess different activity, in order to obtain a composition with a broad spectrum of activity. The inventive oral formulations herein described may be used to co-administer more than one antibiotic.

The inventive tablet formulations are prepared according to methods conventional in the art, such as wet and dry granulation processes.

In a third embodiment, the present invention provides for a long-acting injectable (LAI) formulation, which comprises at least one therapeutic agent which comprises at least one antibiotic, at least one polxamer, and at least one aqueous solvent.

The antibiotic may be selected from the following, which is to be considered non-limiting: beta lactam, semisynthetic penicillins, bacitracin, cephalosporins, quinolones,

fluorinated quinolones, polymyxin, tetracyclines, chloramphenicol, macrolides, aminoglycosides, nalidixic acid, rifamycins, and sulfonamides. Some examples include Amikacin, aminosalicyclic acid, amoxicillin, amoxicillin and clavulanate potassium, ampicillin, azithromycin, bacampicillin, bacitracin, capreomycin, carbenicillin, carbenicillin indanyl sodium, cefaclor, cefadroxil, cefaloridine, cefamandole, cefazolin, cefazolin sodium, cefepime, cefinetazole, cefixime, cefmetazole, cefodizime, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotetan, cefoxitin, cefoxitin sodium, cefpirome, cefpodoxime, cefpodoxime proxetil, cefquinome, ceftaxidime, ceftibuten, ceftiofur, ceftizoxime, ceftriaxone, cefuroxime, cephacelor, cephadrine, cephalexin, cephalothin, cephamandole, cephapirin, cepharadine, cephprozil, chloramphenicol, chlortetracycline, ciprofloxacin, clarithromycin, clindamycin HCl, clindamycin or salts thereof, clindamycin phosphate, clofazimine, cloxacillin, colistin, co-triamoxazole, cycloserine, dalfopristin, danofloxacin, demeclocycline, dicloxacillin, difloxacin, dihydro-streptomycin, dirithromycin, docycycline, efrotomycin, enoxacin, enrofloxacin, ertapenem, erythromycin and salts thereof, ethambutol HCl and other salts, ethionamide, florfenicol, flumequine, fosfomycin, fosfomycin, gamithromycin, gatifloxacin, gentamycin, imipenem, imipenem-cilastin, isoniazid, kanamycin, levofloxacin, lincomycin, linezolid, lomefloxacin, loracarbef mafenide, marbofloxacin, meropenem, methenamine, methicillin, metronidazole, mezlocillin, minocycline, moxifloxacin, nafcillin, nalidixic acid, neomycin, netilmicin, nitrofurantoin, norfloxacin, novobiocin, ofloxacin, orbifloxacin, ormetoprim, oxacillin, oxytetracycline, paromomycin, penicillin G, penicillin G aqueous, penicillin G benzatine, penicillin G procaine, penicillin V, penicillin V penicillin salts and complexes, pentamidine, piperacillin, piperacillin sodium, piperacillin-tazobactam, polymixin B, pyrazinamide, rifampin, roxithromycin, salts of carbenicillin, silver sulfadiazine, sparfloxacin, spectinomycin, spiramycin, streptomycin, streptozocin, sufadimethoxine-ormetoprim, sulfacetamide, sulfacytine, sulfadiazine, sulfadimethoxine, sulfadimethoxine-trimethoprim, sulfamerazine, sulfamethazine, sulfamethixole, sulfapyridine, sulfapyrizine, sulfasalazine, sulfinethoxazole, sulfisoxazole, tazobactam, teicoplanin, , tetracycline, tetracycline HCl, tiamulin, ticarcillin, ticarcillin and clavulanate potassium, tilmicosin, tobramycin, trimethoprim, trimetrexate and ketolides, troleanomycin, trovafloxacin, tulathromycin, tylosin, vancomycin and ketolides such as telithromycin and HMR 3004.

Preferred formulations are those containing about 1 to 50% w/v of therapeutic agent and especially preferred formulations are those containing about 8 to about 20% w/v of therapeutic agent.

Advantageously, the tablet formulation contains clindamycin, or salts thereof. Most preferred is clindamycin HCl in a range of 9-18% w/v.

The poloxamer may be selected from the following: .alpha.-Hydro-.omega.-hydroxypoly(oxyethylene)poly(oxypropylene)poly(oxyethylene) block copolymer, 1,2-Propyleneglycol, ethoxylated and propoxylated, 106392-12-5, 11104-97-5, 53637-25-5, 60407-69-4, 65187-10-2, 69070-95-7, 75-H-1400, 75H90000, 9003-11-6, Adeka 25R1, Adeka 25R2, Adeka L 61, Adeka Pluronic* F 108, AIDS-162017, AIDS162017, alpha-Hydro-omega-hydroxypoly(oxyethylene)(sub a)-poly(oxopropylene)(sub b)-poly(oxyethylene)(sub a) block copolymer, alpha-Hydro-omega-hydroxypoly(oxyethylene)a-poly(oxopropylene)b-poly(oxyethylene)a block copolymer, Antarox* 17R4, Antarox 25R2, Antarox B 25, Antarox F 108, Antarox F 68, Antarox F 88, Antarox F 88FL, Antarox L 61, Antarox L 72, Antarox P 104, Antarox P 84, Antarox SC 138, Arco* Polyol R 2633, Arcol* E 351, B 053, BASF-L 101, Berol* TVM 370, Bloat guard, Block polyethylene-polypropylene glycol, Block polyoxyethylene-polyoxypropylene, Breox* BL 19-10, BSP 5000, C13430, Cirrasol* ALN-WS, component of Casakol, component of Epitrate, Crisvon Assistor SD 14, CRL 1005, CRL 1605, CRL 8131, CRL 8142, D 500 (polyglycol), Daltocel F 460, Dehypon KE 3557, Detalan, Eban 710, Emkalyx EP 64, Emkalyx L 101, Emkalyx L101, Empilan* P 7068, Emulgen PP 230, Epan 450, Epan 485, Epan 710, Epan 750, Epan 785, Epan U 108, Epon* 420, Ethylene glycol-propylene glycol block copolymer, Ethylene glycol-propylene glycol polymer, ETHYLENE OXIDE, PROPYLENE OXIDE BLOCK POLYMER, Ethylene oxide-propylene oxide block copolymer dipropylene glycol ether, Ethylene oxide-propylene oxide block copolymer ether with ethylene glycol, Ethylene oxide-propylene oxide block polymer, Ethylene oxide-propylene oxide copolymer, F 108, F 127, F 77, F 87, F 88, F-108, Genapol* PF 10, Glycols, polyethylene-polypropylene, Glycols, polyethylenepolypropylene, HSDB 7222, Hydrowet, Laprol 1502, LG 56, Lutrol* F, Lutrol F (TN), M 90/20, Magcyl, Meroxapol 105, Methyloxirane polymer with oxirane block, Methyloxirane-oxirane copolymer, Methyloxirane-oxirane polymer, Monolan 8000E80, Monolan* PB, N 480, Newpol PE-88, Niax* 16-46, Niax* LG 56, Nissan* Pronon 201, Nixolen SL 19, NSC 63908, NSC63908, Oligoether L-1502-2-30, Oxirane, methyl-, polymer with oxirane, Oxirane, methyl-, polymer with oxirane, block, Oxirane, methyl-, polymer with oxirane, ether with 1,2-propanediol (2:1), Oxirane, polymer with methyloxirane, Oxirane-methyloxirane polymer, P 103, P 104, P 105, P 123, P 65, P 84, P 85, PEG/PPG-125/30 Copolymer, Plonon 201, Plonon 204, Pluracare*,

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Pluracol* V, Pluriol* PE, Pluriol PE 6810, Pluronic*, Pluronic 10R8, Pluronic 31R2, Pluronic C 121, Pluronic F, Pluronic F 108, Pluronic F 125, Pluronic F 127, Pluronic F 38, Pluronic F 68, Pluronic F 68LF, Pluronic F 87, Pluronic F 88, Pluronic F 98, Pluronic F-68, Pluronic F108, Pluronic F127, Pluronic F68, Pluronic F77, Pluronic F86, Pluronic F87, Pluronic F87-A7850, Pluronic F88, Pluronic L, Pluronic L 101, Pluronic L 121, Pluronic L 122, Pluronic L 24, Pluronic L 31, Pluronic L 35, Pluronic L 44, Pluronic L 61, Pluronic L 62, Pluronic L 64, Pluronic L 68, Pluronic L 92, Pluronic L-101, Pluronic L-81, Pluronic l44, Pluronic L62, Pluronic l62 (mw 2500), Pluronic L64, Pluronic l64 (mw 2900), Pluronic P, Pluronic P 104, Pluronic P 75, Pluronic P 85, Pluronic P-65, Pluronic P-75, Pluronic P103, Pluronic P104, Pluronic P105, Pluronic P123, Pluronic P65, Pluronic P84, Pluronic P85, Pluronic-68, Poloxalene, Poloxalene L64, Poloxalene [USAN:BAN:INN], Poloxalkol, Poloxamer, Poloxamer 101, Poloxamer 108, Poloxamer 182LF, Poloxamer 188, Poloxamer 331, Poloxamer 407, Poloxamer [USAN:BAN:INN], Poloxamer-188, Poly (propylene oxide-ethylene oxide), Poly(ethylene oxide-co-propylene oxide), Poly(mixed ethylene, propylene)glycol, Poly(oxyethylene)-poly(oxypropylene) glycol, Poly(oxyethylene)-poly(oxypropylene) polymer, Polyethylene glycol, propoxylated, Polyethylene oxide-polypropylene oxide, Polyethylene oxide-polypropylene oxide copolymer, Polyethylene-Pluronic L-62LF, Polyethylene-polypropylene glycol, Polykol, Polylon 13-5, Polyoxamer 108, Polyoxyethylenated poly (oxypropylene), Polyoxyethylene - polyoxypropylene block copolymer, Polyoxyethylene - polyoxypropylene copolymer, Polyoxyethylene polyoxypropylene, Polyoxyethylene-oxy-propylene [French], Polyoxyethylene-polyoxypropylene, Polyoxyethylene-polyoxypropylene polymer, Polyoxypropylene-polyoxyethylene block copolymer, Polypropoxylated, polyethoxylated propylene glycol, Polypropylene glycol, ethoxylated, Polypropylene glycol-ethylene oxide copolymer, PPG Diol 3000EO, Proksanol, Pronon, Pronon 102, Pronon 104, Pronon 201, Pronon 204, Pronon 208, Propane-1,2-diol, ethoxylated, propoxylated, Propylen M 12, Propylene glycol, propylene oxide, ethylene oxide polymer, Propylene oxide-ethylene oxide copolymer, Propylene oxide-ethylene oxide polymer, Proxanol, Proxanol 158, Proxanol 228, Proxanol Tsl-3, RC 102, Regulaid, Rokopol 16P, Rokopol 30P, Rokopol 30P9, SK and F 18,667, SK&F 18,667, SKandF 18,667, Slovanik, Slovanik 630, Slovanik 660, Slovanik M-640, Supronic B 75, Supronic E 400, Synperonic* PE 30/40, Tergitol* monionic XH, Tergitol nonionic XH, Tergitol XH, Tergitol XH (nonionic), Teric PE 61, Teric PE 62, Teric PE40, Teric PE60, Teric PE70, Thanol E

*Trade-mark

4003, Therabloat, TsL 431, TVM 370, Unilube* 50MB168X, Unilube 50MB26X, Velvetol OE 2NT1, Voranol* P 2001, WS 661, Wyandotte 7135.

Preferred formulations are those containing about 1 to 50% w/v of poloxamer and especially preferred formulations are those containing about 5 to about 40% w/v of poloxamer. Advantageously, the poloxamer is LUTROL® F 127 and LUTROL® F 68 and is suitably used in the formulation in the amounts ranging from about 10-30% w/v.

Most preferred is a LAI formulation, which comprises: clindamycin phosphate between 9 and 18%, LUTROL® between 5 and 30%, and sterile water for injection q.s. 100%.

The long-acting injectable formulation of the present invention may be prepared by adding the therapeutic agent with the poloxamer and mixing until uniform. Since the long acting formulation is intended for injection, it is necessary that it be sterilized. Heat sterilization is generally to be avoided in the situation where the therapeutic agent is unstable at autoclave temperatures. Rather, membrane sterilization is preferred in those situations. The sterile mixture is further mixed with sterile water for injection, q.s. to 100%.

In an alternative embodiment, the long-acting injectable veterinary formulation comprises the steps of:

(a) stirring the poloxamer into purified water at 5°C;

(b) optionally adding a second poloxamer to the mixture from step (a) and mixing the mixture; and

(c) optionally adding a polyacrylic acid into an aliquot of water, and completely hydrating the polyacrylic acid before mixing it into the poloxamer solution at 5°C;

(d) neutralizing the Carbopol using triethanolamine.

(e) dissolving the drug in ethanol/propylene glycol and adding it to the above solution.

In an alternative embodiment, the long-acting injectable veterinary formulation comprises the steps of:

(a) dissolving LUTROL® F 127 completely in water at room temperature or water pre-cooled to approximately 5°C

(b) dissolving active substances that are insoluble in water, in ethanol, isopropanol or propylene glycol

(c) mixing the therapeutic agent solution with the aqueous phase at 5°C to form a homogeneous mass.

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In an alternative embodiment, the long-acting injectable veterinary formulation comprises the steps of:

(a) dissolving LUTROL® F 127 in water at room temperature at approximately 70°C

(b) dissolving active substances that are insoluble in water, in ethanol, isopropanol or propylene glycol at 70°C

(c) mixing the therapeutic agent solution with the warm aqueous phase to form a homogeneous mass.

The inventive formulations herein described may be used to treat a number of disease states by administering to the host in need thereof an effective amount of the formulation containing the pharmaceutical agent. The determining of a treatment protocol of a specific indication would be well within the skill level of a practitioner in the pharmaceutical or veterinary arts. The hosts include all animals, e.g. cats, dogs, cattle, sheep, horses, and pigs.

The inventive formulations herein described may be administered to a warm-blooded animals, such as cattle, sheep, pigs, cats, dogs, horses, llamas, deer, rabbits, skunks, raccoons, camels and the like, or birds. The amount of pharmaceutical active agent depends on the individual therapeutic agent, the animal being treated, the disease state, and the severity of the disease state. The determination of those factors is well within the skill level of the practitioner.

EXAMPLES

Example 1: Tablet And Soft Chewable Formulations Demonstrate Comparable Bioavailability To A Conventional Capsule Product.

Six healthy Beagle or mongrel dogs, 6.3 to 15.0 months of age, weighing 7.8 to 10.0 kg were studied in this randomized, five-period crossover study. Dogs were randomly assigned to one of three treatment sequences by lottery. Within each sequence, dogs received one of three treatments on Days 0, 7, 14, 21 and 28. On each treatment day, dogs received either clindamycin capsules (Group 1), soft chewables (Group 2) or chewable tablets (Group 3). All treatments were administered orally at a dose rate of at least 10 mg/kg.

Blood samples were collected prior to each treatment and at 0.5, 1, 1.5, 3, 6, 12 and 24 hours after each treatment. Figure 1 provides plasma concentration levels (ng/ml) of clindamycin at each time point. The results indicate that the mean concentration-time profiles were parallel, with the mean Cmax slightly higher for the commercial product, ANTIROBE.

The pharmacokinetic parameters among the three treatment groups were similar with average terminal half lives of 5-7 hr and average times to maximum concentration of 1.1-1.6 hr. The relative bioavailabilities of the soft and hard chews are 87 and 110% w/v, respectively compared to ANTIROBE. Additionally, the pharmacokinetic parameters were broadly similar between groups fed 1.5-3 hour post dose versus 6 hours post dose for all formulations.

Analysis of Plasma Concentration of Clindamycin

A bioanalytical method for the determination of clindamycin from canine serum samples was developed using Reversed-Phase HPLC with UV Detection. All serum samples were extracted using a liquid-liquid extraction procedure and injected on an HPLC with UV absorption at 210 nm. Sets of fortified control samples to assess method performance, along with an unfortified control sample were included to assess any inherent interference.

Pharmacokinetic analysis was performed using WinNonlin software, version 4.0 (Pharsight Corporation, Mountain View, CA, 2002). The area under the plasma concentration-time curve (AUC) was calculated using the linear/logarithmic trapezoidal method from 0 to the last point at which drug concentration was quantified [AUC(0-t_{last})]. Clearance and volume of distribution values, not corrected for bioavailability, were also calculated for each animal. The terminal elimination half life was calculated via linear regression of the last two to four nonzero values. C_{max} and T_{max} for each animal were taken as the highest observed concentration and time to that observation.

Table 1. Summary of pharmacokinetic parameters for a capsule (ANTIROBE), soft chewable, or hard chewable at 10 mg/kg (nominal) clindamycin to dogs

	Antirobe Avg±SD (n=10)	Soft chew Avg±SD (n=10)	Hard chew Avg±SD (n=10)
AUC(0-t_{last}) (ng·hr/mL)	17400±10400	18300±9410	17300±10300
C_{max} (ng/mL)	3720±1380	3070±981	3640±1060
T_{max} (hr)	1.25±0.72	1.55±0.80	1.10±0.32
T ½ (hr)	5.02±2.26	5.75±4.65	6.97±6.82
V/F (mL/kg)	4700±2760	4340±3640	5800±5330
Cl/F (mL/hr/kg)	678±341	644±393	740±498

Arithmetic averages; Values rounded to 3 significant digits;
AUC = Area Under the Curve;
C_{max} = Peak Concentration;
T_{max} = Time to Peak Concentration;

$T_{½}$ = terminal elimination half life;
V/F = apparent volume of distribution (not corrected for bioavailability);
CL/F = clearance (not corrected for bioavailability)

Example 2: Preferred Soft Chewable Formulation

Table 2 provides the preferred concentrations of active ingredient and excipients for soft chewable formulations.

Table 2.

#	**Ingredient**	**%**
1	Clindamycin HCl	1 - 5%
2	Hydrogenated vegetable Oil	2 – 15%
3	Soy Protein Fines	20 – 60%
4	Flavor	5 – 30%
5	Preservative	0.2 – 1.0%
6	Disintegrant	2 – 10%
7	Propylene Glycol / Purified water / other ingredients	2 – 20%

Example 3: Preferred Tablet Formulation

Table 3 provides the preferred concentrations of active ingredient and excipients for tablet formulations.

Table 3.

#	**Ingredient**	**% (w/w)**
1	Clindamycin HCl	4 – 15%
2	Lactose Carrier	40 – 80%
3	Mannitol	5 – 15%
4	Binder and disintegrant	3 – 10%
5	Flavor	10 – 20%
6	Color	0.1 - 0.5%
7	Purified water / other ingredients	Qs. 100%

Example 4: Preferred Long-Acting Injectable Formulation

Table 4 provides the preferred concentrations of active ingredient and excipients for long-acting injectable formulations.

Table 4.

Clindamycin Phosphate	9 - 18%
LUTROL® F 127 or LUTROL® F 127 and F 68	5 – 30%
Sterile water for injection	Qs. 100%

Various kinds of LUTROL® are available for use in the LAI formulation. In the present example, preferred poloxamers were LUTROL® F 127 (poloxamer 407) and F 68 (poloxamer 188). LUTROL® F 127 is soluble in water, ethanol (95%) and isopropanol. It is used primarily as a thickening agent and gel former. In particular, LUTROL® F 127 is suitable for the formulation of active substances that show reduced solubility as a result of neutralization. Owing to its ability to affect viscosity, LUTROL® F 127 is suitable as a stabilizer for topically and orally administered suspensions.

LUTROL® F 68 is readily soluble in water. It is primarily applied as an emulsifier, solubilizer, and suspension stabilizer in liquid oral, topical and parenteral dosage forms. It is particularly useful for enhancing the solubility and bioavailability of sparingly water soluble active drugs. LUTROL® F 68 has a low toxicity profile with minimal side effects.

In the present example, LUTROL® F 127 and F 68 may be used in combination. When LUTROL® F 68 is used in combination with a gel-forming poloxamer, like LUTROL® F 127, it strongly influences the thermorheological properties of F127 preparations, resulting in an increase of the sol-gel transition temperature. At constant amounts of F 127, the viscosity and thermo-reversible gelling temperature are functions of the LUTROL® F 68 concentration.

Gel Preparation Method 1:

LUTROL® F 127 will be stirred into purified water at 5°C and LUTROL® F 68 will be added. For the bioadhesive formulations, a polyacrylic acid (PAA) will be dispersed into an aliquot of water, completely hydrated, and mixed with the LUTROL® solution at 5°C. The Carbopol will be neutralized using triethanolamine. The drug will be dissolved in ethanol/propylene glycol and the solution added.

Gel Preparation Method 2: "Cold Process"

LUTROL® F 127 will be dissolved completely in water at room temperature or water pre-cooled to approximately 5°C. Active substances that are insoluble in water will be dissolved in ethanol, isopropanol or propylene glycol and mixed with the aqueous phase at 5°C to form a homogeneous mass.

Gel Preparation Method 3: "Hot Process"

LUTROL® F 127 will be dissolved in water at approximately 70°C. Active substances that are insoluble in water will be dissolved in ethanol, isopropanol or propylene glycol at 70°C and mixed with the warm aqueous phase to form a homogeneous mass. The gel will form when the solution cools to room temperature.

Rheology: Using a rotation viscosimeter equipped with a probe the thermorheological behavior will be measured by adjusting a temperature interval from 0 - 90°C with a ramp of 1°C per minute. The rotation speed will be kept constant at 250 rpm. The rheological studies will be examined at a temperature of 40°C using a shear rate from 0 - 65 - 0 rpm within 120 s.

Gel strength: The resistance to penetration of the gels at 40°C will be performed by means of asoftware-controlled penetrometer with a 5 kg load cell and a 20 mm probe. The pre-test speed will be adjusted at 5 mm/s and the test speed will be 1 mm/s. The chosen penetration depth will be 5 mm.

Thermorheological properties: The addition of LUTROL® F 68 is expected to strongly influence the thermorheological properties of F 127 formulations. In contrast to the effect of common used salts (e. g. NaCl) the addition of LUTROL ® F 68 to LUTROL® F 127 formulations is expected to result in an increase of the sol-gel-transition temperature. At constant amounts of LUTROL ® F 68 the thermoreversible gelling temperature can be adjusted by varying the LUTROL ® F 127 concentration.

The addition of small amounts of PAA as bioadhesive polymer is expected to lead to a further decrease of the gelling temperature of the LUTROL® F 127 / F 68 combinations.

Viscosity: A considerable increase of the viscosity is expected to be observed with rising amounts of LUTROL® F 68. At high concentrations of LUTROL® F 68 a sharp gelling temperature and a strong viscosity increase is expected. The viscosity of the gel form is expected to be higher when small quantities of PAA are present. With increasing amount of PAA these effects are expected to be reinforced. The influence of the different F 127 / F 68 combinations and the addition of PAA on the viscosity of the gels will be confirmed by penetration resistance measurements.

Therapeutic Agent: The choice of therapeutic agent is expected to strongly influence the properties of the LUTROL® F 127 / F 68 mixtures by lowering the gelling temperature. The required amount of LUTROL F 127 will have to be adapted.

The viscosity of Lutrol F 127 gels may be affected by the addition of electrolytes, moisturizers, alcohols and surfactants. Thus, the addition of more than 1% sodium chloride will reduce the gel formation temperature as well as the viscosity and pour point. Similar

effects are also seen with potassium chloride. In contrast to this, ethanol will increase the gel formation temperature. The use of anionic surfactants may inhibit gel formation, even at Lutrol F 127 concentrations of over 20 %. This is true, for example, for sodium lauryl sulphate at concentrations above 2 %. Low pH values affect both the gel formation temperature and the viscosity.

The invention is further described by the following numbered paragraphs:

1. A chewable antibiotic formulation comprising an antibiotic, hydrophobic material, soy protein fines, a disintegrant, a solvent, and optionally a flavor, and optionally a preservative.

2. The formulation according to paragraph 1 wherein the antibiotic is between 1 and 5% of the formulation, the hydrophobic material is between 2 and 15%, the soy protein fines is between 20-60%, the flavor is between 5-30%, the preservative is between 0.2 to 1%, the disintegrant is between 2 and 10%, and the humectant is between 2 and 20%.

3. The formulation according to paragraph 2 wherein the antibiotic is selected from the group consisting of amikacin, aminosalicyclic acid, amoxicillin, amoxicillin and clavulanate potassium, ampicillin, azithromycin, bacampicillin, bacitracin, capreomycin, carbenicillin, carbenicillin indanyl sodium, cefaclor, cefadroxil, cefaloridine, cefamandole, cefazolin, cefazolin sodium, cefepime, cefinetazole, cefixime, cefmetazole, cefodizime, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotetan, cefoxitin, cefoxitin sodium, cefpirome, cefpodoxime, cefpodoxime proxetil, cefquinome, ceftaxidime, ceftibuten, ceftiofur, ceftizoxime, ceftriaxone, cefuroxime, cephacelor, cephadrine, cephalexin, cephalothin, cephamandole, cephapirin, cepharadine, cephprozil, chloramphenicol, chlortetracycline, ciprofloxacin, clarithromycin, clindamycin HCl, clindamycin or salts thereof, clindamycin phosphate, clofazimine, cloxacillin, colistin, co-triamoxazole, cycloserine, dalfopristin, danofloxacin, demeclocycline, dicloxacillin, difloxacin, dihydro-streptomycin, dirithromycin, docycycline, efrotomycin, enoxacin, enrofloxacin, ertapenem, erythromycin and salts thereof, ethambutol HCl and other salts, ethionamide, florfenicol, flumequine, fosfomycin, fosfomycin, gamithromycin, gatifloxacin, gentamycin, imipenem, imipenem-cilastin, isoniazid, kanamycin, levofloxacin, lincomycin, linezolid, lomefloxacin, loracarbef mafenide, marbofloxacin, meropenem, methenamine, methicillin, metronidazole, mezlocillin, minocycline, moxifloxacin, nafcillin, nalidixic acid, neomycin, netilmicin, nitrofurantoin, norfloxacin, novobiocin, ofloxacin, orbifloxacin, ormetoprim, oxacillin, oxytetracycline, paromomycin, penicillin G, penicillin G aqueous, penicillin G benzatine, penicillin G procaine, penicillin V, penicillin V penicillin salts and complexes, pentamidine,

piperacillin, piperacillin sodium, piperacillin-tazobactam, polymixin B, pyrazinamide, rifampin, roxithromycin, salts of carbenicillin, silver sulfadiazine, sparfloxacin, spectinomycin, spiramycin, streptomycin, streptozocin, sufadimethoxine-ormetoprim, sulfacetamide, sulfacytine, sulfadiazine, sulfadimethoxine, sulfadimethoxine-trimethoprim, sulfamerazine, sulfamethazine, sulfamethixole, sulfapyridine, sulfapyrizine, sulfasalazine, sulfinethoxazole, sulfisoxazole, tazobactam, teicoplanin, , tetracycline, tetracycline HCl, tiamulin, ticarcillin, ticarcillin and clavulanate potassium, tilmicosin, tobramycin, trimethoprim, trimetrexate and ketolides, troleanomycin, trovafloxacin, tulathromycin, tylosin, vancomycin and ketolides such as telithromycin and HMR 3004.

4. The formulation according to paragraph 2 wherein the antibiotic is clindamycin or a pharmaceutically acceptable salt or hydrate thereof.

5. The formulation according to paragraph 2 wherein the hydrophobic material is selected from the group consisting of glyceryl behenate, hydrogenated vegetable oil, stearic acid, glyceryl monostearate, glycerylpalmito stearate or cetyl alcohol.

6. The formulation according to paragraph 2 wherein the hydrophobic material is hydrogenated vegetable oil.

7. The formulation according to paragraph 2 where in the filler is selected from the group consisting of soy protein, corn cob, or corn gluten meal.

8. The formulation according to paragraph 2 where in the filler is soy protein.

9. The formulation according to paragraph 2 wherein the flavor is a hickory smoke flavor or a beef flavor.

10. The formulation according to paragraph 2 wherein the preservative is selected from the group consisting of parabens (methylparaben and/or propylparaben), benzalkonium chloride, benzethonium chloride, benzoic acid, benzyl alcohol, bronopol, butylparaben, cetrimide, chlorhexidine, chlorobutanol, chlorocresol, cresol, ethylparaben, imidurea, methylparaben, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric acetate, phenylmercuric borate, phenylmercuric nitrate, potassium sorbate, sodium benzoate, sodium propionate, sorbic acid, thimerosal, propyl paraben, myristyl gama-picolinium chloride, paraben methyl, paraben propyl and quaternary ammonium compounds.

11. The formulation according to paragraph 2 wherein the preservative is methylparaben and/or propylparaben.

12. The formulation according to paragraph 2 wherein the disintegrant is selected from the group consisting of sodium starch glycolate, crospovidone, croscarmellose sodium,

starch, micocrystalline cellulose, alginic acid, veegum, crospovidone, bentonite, and pregelatinized starch.

13. The formulation according to paragraph 2 wherein the disintegrant is crospovidone.

14. The formulation according to paragraph 2 wherein the humectant is selected from the group consisting of propylene glycol, glycerin, polyethylene glycol 400 and polyethylene glycol 3350.

15. The formulation according to paragraph 2 wherein the humectant is propylene glycol or purified water.

16. A process for preparing a chewable veterinary formulation according to paragraph 1 which comprises the steps of:

(a) blending the pharmaceutical agent, hydrophobic material, disintegrant, flavor;

(b) adding the water, preservative, and the humectant to the mixture from step (a) and mixing the mixture; and

(c) without drying, extruding the mixture.

17. A method of achieving bioavailability in an animal of a therapeutic agent that is comparable to commercially available products, comprising administering to an animal any one of the formulations of paragraphs 1 through 15.

18. A method for treating a bacterial infection in an animal comprising administering to the animal any one of the formulations of paragraphs 1 through 15.

19. The method of paragraph 18 wherein the animal receives treatment on days 0 ,7, 14, 21, and 28 comprising administering any of the formulations of paragraphs 1 through 15.

20. An antibiotic formulation comprising an antibiotic, a lactose carrier, mannitol, a binder and disintegrant, an aqueous solvent, and optionally a flavor, and optionally color.

21. The formulation according to paragraph 21 wherein the antibiotic is between 4 and 15%, the lactose carrier is between 40 and 80%, mannitol is between 5 and 15%, the binder and disintegrant are between 3 and 10%, the flavor is between 10 and 20%, the color is between 0.1 and 0.5%, and the aqueous solvent is of a concentration sufficient to q.s. to 100%.

22. The formulation according to paragraph 21 wherein the antibiotic is selected from the group consisting of amikacin, aminosalicyclic acid, amoxicillin, amoxicillin and clavulanate potassium, ampicillin, azithromycin, bacampicillin, bacitracin, capreomycin, carbenicillin, carbenicillin indanyl sodium, cefaclor, cefadroxil, cefaloridine, cefamandole, cefazolin, cefazolin sodium, cefepime, cefinetazole, cefixime, cefmetazole, cefodizime,

cefonicid, cefoperazone, ceforanide, cefotaxime, cefotetan, cefoxitin, cefoxitin sodium, cefpirome, cefpodoxime, cefpodoxime proxetil, cefquinome, ceftaxidime, ceftibuten, ceftiofur, ceftizoxime, ceftriaxone, cefuroxime, cephacelor, cephadrine, cephalexin, cephalothin, cephamandole, cephapirin, cepharadine, cephprozil, chloramphenicol, chlortetracycline, ciprofloxacin, clarithromycin, clindamycin HCl, clindamycin or salts thereof, clindamycin phosphate, clofazimine, cloxacillin, colistin, co-triamoxazole, cycloserine, dalfopristin, danofloxacin, demeclocycline, dicloxacillin, difloxacin, dihydro-streptomycin, dirithromycin, docycycline, efrotomycin, enoxacin, enrofloxacin, ertapenem, erythromycin and salts thereof, ethambutol HCl and other salts, ethionamide, florfenicol, flumequine, fosfomycin, fosfomycin, gamithromycin, gatifloxacin, gentamycin, imipenem, imipenem-cilastin, isoniazid, kanamycin, levofloxacin, lincomycin, linezolid, lomefloxacin, loracarbef mafenide, marbofloxacin, meropenem, methenamine, methicillin, metronidazole, mezlocillin, minocycline, moxifloxacin, nafcillin, nalidixic acid, neomycin, netilmicin, nitrofurantoin, norfloxacin, novobiocin, ofloxacin, orbifloxacin, ormetoprim, oxacillin, oxytetracycline, paromomycin, penicillin G, penicillin G aqueous, penicillin G benzatine, penicillin G procaine, penicillin V, penicillin V penicillin salts and complexes, pentamidine, piperacillin, piperacillin sodium, piperacillin-tazobactam, polymixin B, pyrazinamide, rifampin, roxithromycin, salts of carbenicillin, silver sulfadiazine, sparfloxacin, spectinomycin, spiramycin, streptomycin, streptozocin, sufadimethoxine-ormetoprim, sulfacetamide, sulfacytine, sulfadiazine, sulfadimethoxine, sulfadimethoxine-trimethoprim, sulfamerazine, sulfamethazine, sulfamethixole, sulfapyridine, sulfapyrizine, sulfasalazine, sulfinethoxazole, sulfisoxazole, tazobactam, teicoplanin, , tetracycline, tetracycline HCl, tiamulin, ticarcillin, ticarcillin and clavulanate potassium, tilmicosin, tobramycin, trimethoprim, trimetrexate and ketolides, troleanomycin, trovafloxacin, tulathromycin, tylosin, vancomycin and ketolides such as telithromycin and HMR 3004.

23. The formulation according to paragraph 21 wherein the antibiotic is clindamycin or a pharmaceutically acceptable salt or hydrate thereof.

24. The formulation according to paragraph 21 wherein the antibiotic is clindamycin HCl.

25. The formulation according to paragraph 21 wherein the filler is selected from the group consisting of anhydrous lactose, hydrated lactose, sprayed dried lactose, crystalline maltose and maltodextrins.

26. The formulation according to paragraph 21 wherein the filler is lactose.

27. The formulation according to paragraph 21 wherein the binder is selected from the group consisting of polyvinyl pyrrolidone, povidone, starch, pregelatinized starch, gelatin, methylcellulose, hydroxypropyl cellulose, carboxymethyl cellulose sodium, ethylcellulose, sodium alginate, tragacanth, and acacia.

28. The formulation according to paragraph 21 wherein the binder is polyvinyl pyrrolidone.

29. The formulation according to paragraph 21 wherein the disintegrant is selected from the group consisting of sodium starch glycolate, crospovid one, croscarmellose sodium, starch, micocrystalline cellulose, alginic acid, veegum, crospovidone, bentonite, and pregelatinized starch.

30. The formulation according to paragraph 21 wherein the disintegrant is crospovidone.

31. The formulation according to paragraph 21 wherein the flavor is a hickory smoke flavor or a beef flavor.

32. The formulation according to paragraph 21 wherein the colorant is selected from the group consisting of dyes, an aluminum lake, caramel, colorant based upon iron oxide or a mixture of any of the foregoing.

33. The formulation according to paragraph 21 wherein the colorant is selected from the group consisting of organic dyes and titanium dioxide.

34. A process for preparing the chewable veterinary formulation according to paragraph 20 which comprises mixing the ingredients intimately and pressing into single scored tablets.

35. A method of achieving bioavailability in an animal of a therapeutic agent that is comparable to commercially available products, comprising administering to an animal any one of the formulations of paragraphs 20 through 33.

36. A method for treating a bacterial infection in an animal comprising administering to the animal any one of the formulations of paragraphs 20 through 33.

37. The method of paragraph 36 wherein the animal receives treatment on days 0 ,7, 14, 21, and 28 comprising administering any of the formulations of paragraphs 20 through 33.

38. An antibiotic formulation comprising an antibiotic, a poloxamer, and sterile water for injection.

39. The formulation according to paragraph 38 wherein the antibiotic is between 9 and 18%, the poloxamer is between 5 and 30%, and sterile water for injection is of a concentration sufficient to q.s. to 100%.

40. The formulation according to paragraph 19 wherein the antibiotic is selected from the group consisting of amikacin, aminosalicyclic acid, amoxicillin, amoxicillin and

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clavulanate potassium, ampicillin, azithromycin, bacampicillin, bacitracin, capreomycin, carbenicillin, carbenicillin indanyl sodium, cefaclor, cefadroxil, cefaloridine, cefamandole, cefazolin, cefazolin sodium, cefepime, cefinetazole, cefixime, cefmetazole, cefodizime, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotetan, cefoxitin, cefoxitin sodium, cefpirome, cefpodoxime, cefpodoxime proxetil, cefquinome, ceftaxidime, ceftibuten, ceftiofur, ceftizoxime, ceftriaxone, cefuroxime, cephacelor, cephadrine, cephalexin, cephalothin, cephamandole, cephapirin, cepharadine, cephprozil, chloramphenicol, chlortetracycline, ciprofloxacin, clarithromycin, clindamycin HCl, clindamycin or salts thereof, clindamycin phosphate, clofazimine, cloxacillin, colistin, co-triamoxazole, cycloserine, dalfopristin, danofloxacin, demeclocycline, dicloxacillin, difloxacin, dihydro-streptomycin, dirithromycin, docycycline, efrotomycin, enoxacin, enrofloxacin, ertapenem, erythromycin and salts thereof, ethambutol HCl and other salts, ethionamide, florfenicol, flumequine, fosfomycin, fosfomycin, gamithromycin, gatifloxacin, gentamycin, imipenem, imipenem-cilastin, isoniazid, kanamycin, levofloxacin, lincomycin, linezolid, lomefloxacin, loracarbef mafenide, marbofloxacin, meropenem, methenamine, methicillin, metronidazole, mezlocillin, minocycline, moxifloxacin, nafcillin, nalidixic acid, neomycin, netilmicin, nitrofurantoin, norfloxacin, novobiocin, ofloxacin, orbifloxacin, ormetoprim, oxacillin, oxytetracycline, paromomycin, penicillin G, penicillin G aqueous, penicillin G benzatine, penicillin G procaine, penicillin V, penicillin V penicillin salts and complexes, pentamidine, piperacillin, piperacillin sodium, piperacillin-tazobactam, polymixin B, pyrazinamide, rifampin, roxithromycin, salts of carbenicillin, silver sulfadiazine, sparfloxacin, spectinomycin, spiramycin, streptomycin, streptozocin, sufadimethoxine-ormetoprim, sulfacetamide, sulfacytine, sulfadiazine, sulfadimethoxine, sulfadimethoxine-trimethoprim, sulfamerazine, sulfamethazine, sulfamethixole, sulfapyridine, sulfapyrizine, sulfasalazine, sulfinethoxazole, sulfisoxazole, tazobactam, teicoplanin, , tetracycline, tetracycline HCl, tiamulin, ticarcillin, ticarcillin and clavulanate potassium, tilmicosin, tobramycin, trimethoprim, trimetrexate and ketolides, troleanomycin, trovafloxacin, tulathromycin, tylosin, vancomycin and ketolides such as telithromycin and HMR 3004.

41. The formulation according to paragraph 39 wherein the antibiotic is clindamycin or a pharmaceutically acceptable salt or hydrate thereof.

42. The formulation according to paragraph 39 wherein the antibiotic is clindamycin phosphate.

43. The formulation according to paragraph 39 wherein the poloxamer is selected from any available poloxamer.

44. The formulation according to paragraph 39 wherein the poloxamer is poloxamer 407 or poloxamer 188 or a combination thereof.

45. A process for preparing the long-acting injectable veterinary formulation according to paragraph 38 which comprises the steps of:

(a) stirring the poloxamer into purified water at 5°C;

(b) optionally adding a second poloxamer to the mixture from step (a) and mixing the mixture; and

(c) optionally adding a polyacrylic acid into an aliquot of water, and completely hydrating the polyacrylic acid before mixing it into the poloxamer solution at 5°C;

(d) neutralizing the Carbopol using triethanolamine.

(e) dissolving the drug in ethanol/propylene glycol and adding it to the above solution.

46. A process for preparing the long-acting injectable veterinary formulation according to paragraph 38 which comprises the steps of:

(a) dissolving poloxamer 407 completely in water at room temperature or water pre-cooled to approximately 5°C

(b) dissolving active substances that are insoluble in water, in ethanol, isopropanol or propylene glycol

(c) mixing the therapeutic agent solution with the aqueous phase at 5°C to form a homogeneous mass.

47. A process for preparing the long-acting injectable veterinary formulation according to paragraph 38 which comprises the steps of:

(a) dissolving poloxamer 407 in water at room temperature at approximately 70°C

(b) dissolving active substances that are insoluble in water, in ethanol, isopropanol or propylene glycol at 70°C

(c) mixing the therapeutic agent solution with the warm aqueous phase to form a homogeneous mass.

48. A method for treating a bacterial infection in an animal comprising administering to the animal any one of the formulations of paragraphs 38 through 44.

49. The method of paragraph 22 wherein the animal receives treatment on any of days 0 ,7, 14, 21, and 28 comprising administering any of the formulations of paragraphs 38 through

44, wherein the formulation provides sustained concentrations of therapeutic agents for 7-10 days.

* * *

Having thus described in detail preferred embodiments of the present invention, it is to be understood that the invention defined by the above paragraphs is not to be limited to particular details set forth in the above description as many apparent variations thereof are possible without departing from the scope of the present invention, which is as defined by the appended claims.

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CLAIMS:

1. A chewable antibiotic veterinary formulation comprising:

an antibiotic between 1 and 5%, a hydrophobic material between 2 and 15%, soy protein fines between 20-60%, a flavor between 5-30%, a preservative between 0.2 to 1%, a disintegrant between 2 and 10%, and a humectant between 2 and 20% of the formulation;

wherein the antibiotic is clindamycin or a pharmaceutically acceptable salt or hydrate thereof.

2. The formulation according to claim 1, wherein the hydrophobic material is selected from the group consisting of glyceryl behenate, hydrogenated vegetable oil, stearic acid, glyceryl monostearate, glycerylpalmito stearate and cetyl alcohol.

3. The formulation according to claim 2, wherein the hydrophobic material is hydrogenated vegetable oil.

4. The formulation according to any one of claims 1 to 3 further comprising a filler selected from the group consisting of soy protein, corn cob, or corn gluten meal.

5. The formulation according to claim 4, wherein the filler is soy protein.

6. The formulation according to any one of claims 1 to 5, wherein the flavor is a hickory smoke flavor or a beef flavor.

7. The formulation according to any one of claims 1 to 6, wherein the preservative is selected from the group consisting of parabens (methylparaben and/or propylparaben), benzalkonium chloride, benzethonium chloride, benzoic acid, benzyl alcohol, bronopol, butylparaben, cetrimide, chlorhexidine, chlorobutanol, chlorocresol, cresol, ethylparaben, imidurea, methylparaben, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric acetate, phenylmercuric borate, phenylmercuric nitrate, potassium sorbate, sodium benzoate, sodium propionate, sorbic acid, thimerosal, propyl paraben, myristyl gama-picolinium chloride, paraben methyl, paraben propyl and quaternary ammonium compounds.

8. The formulation according to claim 7, wherein the preservative is methylparaben and/or propylparaben.

9. The formulation according to any one of claims 1 to 8, wherein the disintegrant is selected from the group consisting of sodium starch glycolate, crospovidone, croscarmellose sodium, starch, micocrystalline cellulose, alginic acid, veegum, crospovidone, bentonite, and pregelatinized starch.

10. The formulation according to claim 9, wherein the disintegrant is crospovidone.

11. The formulation according to any one of claims 1 to 10, wherein the humectant is selected from the group consisting of propylene glycol, glycerin, polyethylene glycol 400 and polyethylene glycol 3350.

12. The formulation according to any one of claims 1 to 10, wherein the humectant is propylene glycol or purified water.

13. A process for preparing a chewable veterinary formulation according to any one of claims 1 to 12 which comprises the steps of:

(a) blending the antibiotic, hydrophobic material, disintegrant, and flavor;

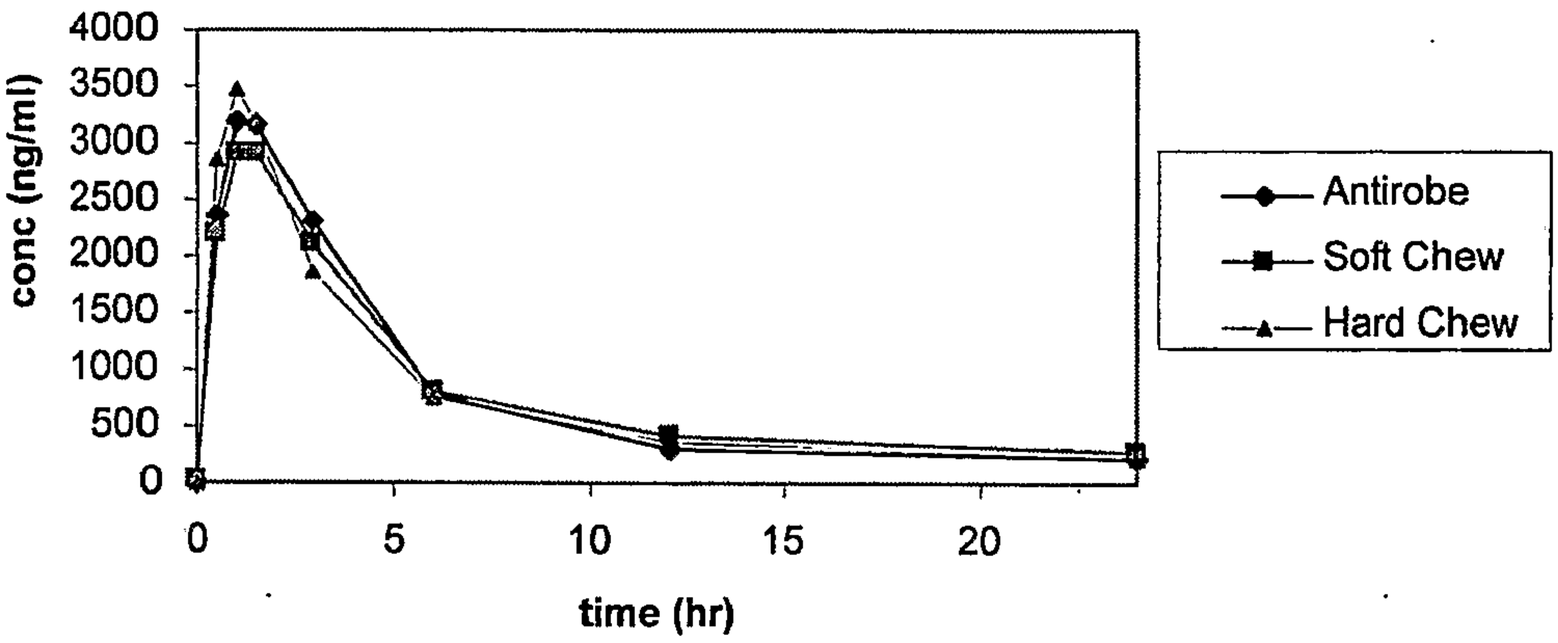
(b) adding water, the preservative, and the humectant to the mixture from step (a) and mixing the mixture; and

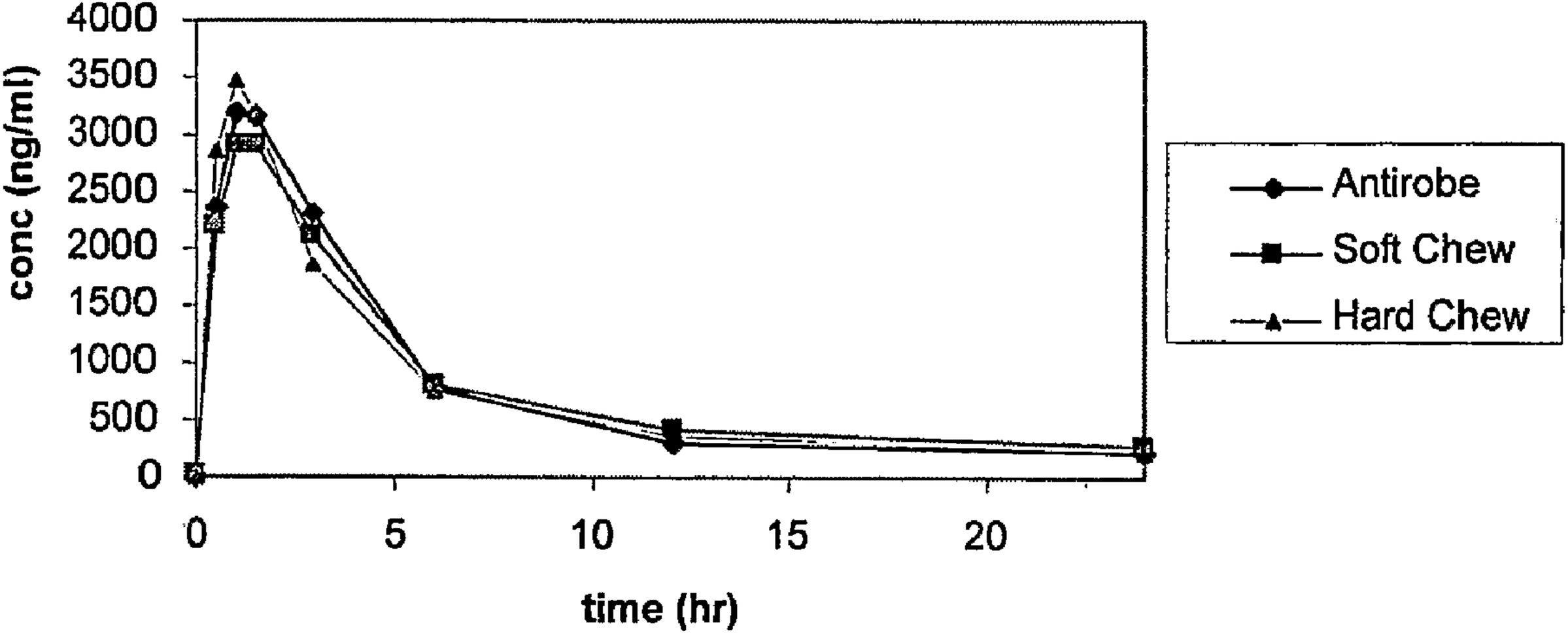
(c) without drying, extruding the mixture.

14. The formulation according to any one of claims 1 to 12 for use in treating a bacterial infection in an animal.

FIGURES

Figure 1.




4000
3500
3000
2500
2000
1500
1000
500
0
conc (ng/ml)
0
5
10
15
20
time (hr)
Antirobe
Soft Chew
Hard Chew