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(54) Title: SOFT CHEWABLE DOSAGE FORM COMPOSITIONS OF CANNABINOID RECEPTOR TYPE 1 (CB-1) ANTAGONISTS

(57) Abstract: This invention relates to formulations to improve the bioavailability of the CB-1 antagonist compound in dogs through the use of a soft chewable dosage form.

SOFT CHEWABLE DOSAGE FORM COMPOSITIONS OF CANNABINOID RECEPTOR TYPE 1 (CB-1) ANTAGONISTS

Cross-Reference to Related Applications

This application claims benefit of U.S. Provisional Application Serial No. 61/556,967, filed on November 8, 2011, the contents of which are herein incoporated by reference in their entirety.

Background of the Invention

[001] Chewable dosage forms for drug delivery are well known to pharmaceutical technology. It is known in the pharmaceutical industry that the act of chewing increases the surface area of the available active ingredient and may increase the rate of absorption by the digestive tract. Chewable systems are also advantageous where it is desirable to make an active ingredient available topically to the mouth or throat areas for both local effects and/or systemic absorption. Further, chewable dosage forms are also utilized to ease drug administration in pediatric and geriatric patients. Examples of chewable dosage forms may be found in US Pat Nos. 6,387,381; 4,284,652; 4,327,076; 4,935,243; 6,270,790; 6,060,078; 4,609,543; and, 5753,255.

[002] A soft chewable dosage form utilizes a variety of excipients resulting in a tablet that can be easily chewed compared to a classic hard chew dosage form, similar to Children's Tylenol® Chewable Tablets. The texture of the soft chewable dosage form (also called soft chew) is firm enough to keep its form and imparts a more natural mouth feel for better palatability. Soft chews may use aqueous or non-aqueous components.

[003] Palatability and "mouth feel" are important characteristics to be considered in providing a dosage form, or matrix, for an active pharmaceutical or medicinal. Unfortunately, many pharmaceuticals and other active ingredients have a bitter or otherwise unpalatable taste, or an unacceptable mouth feel, due to the grittiness or chalkiness of the compound, or both. These

characteristics make it difficult to incorporate such active ingredients into the current state of the art for chewable dosage forms because the objectionable taste and/or mouth feel make it less likely to obtain compliance by the user.

[004] As a result, several approaches have been tried in attempting to overcome these problems. The poor taste of a pharmaceutical or other active ingredient may be masked by using suitable flavoring compounds and/or sweeteners. Encapsulation of the active ingredient may also serve to mask bitterness and other undesirable tastes. However, these approaches do not affect the physical state of the dosage form currently employed in the art. For example, chewable vitamin tablets are typically prepared as a compressed, compacted tablet, incorporating one or more active ingredients (e.g., vitamins), a sweetener and flavoring agent to mask the taste of the active ingredients, and a binder, typically microcrystalline cellulose.

[005] Generally, chewable tablets are made by direct compression of a mixture of tableting compounds including the active ingredient, flavorant, binders, etc. The mixture is fed into a die chamber of a tablet press and a tablet is formed by direct compaction. Hardness of the resulting tablet is a direct function of the compression pressure employed. A softer tablet, having an easier bite-through, may be prepared by adding a disintegrant, such as alginic acid, to the pre-tablet mix. Alternatively, a softer tablet may be formed by employing reduced compression pressures. In either case, the resultant tablet is softer, fragile, brittle and easily chipped. Compressed, chewable tablets generally suffer from less than desirable mouth feel, i.e., chalkiness, grittiness, and a dry, powdery taste. Antacid tablets are examples of typical compressed chewable tablets.

[006] Attempts have been made to reduce the grittiness and/or chalkiness of the compressed tablet by coating particles of the active ingredient with oils or fats, which coat the particles prior to incorporation into the delivery system. In this way, the grittiness or chalkiness of the particles is masked by the oil or fat while the particles are in the mouth. In addition, tablet softness is

improved. However, the addition of fats or oils to the pre-tablet mix can cause the tableting ingredients to adhere to the die chamber and cause a reduction in the binding action of the binders present in the mix.

[007] Other techniques for providing a chewable delivery system involve the use of a gum base. Gum bases are insoluble elastomers which form the essential element for chewing gum. The gum base is typically blended with one or more sweeteners to obtain a confectionery gum. A coating containing the active ingredient is then applied over the confectionery gum. As the dosage form is chewed, the coating fractures and/or is dissolved in the mouth and swallowed.

[008] Other delivery systems involve the used of layered, non-homogeneous structures. Another chewable delivery system is based on a nougat-type, chewy tablet. Such tablets generally employ a base of corn syrup (or a derivative). Such tablets are prepared as a confectionery, i.e., the corn syrup is cooked with water and a binder such as soy protein.

[009] However, the art field has experienced problems with delivering additives/active ingredients to animals because of palatability issues. Complex guidelines exist along the regulatory framework that make it very difficult to make and/or manufacture a palatable composition with an additive. Accordingly, the art field is in search of a method and/or composition of delivering an additive to an animal in a palatable format.

[0010] One part solution is in United States Patent No. 6,387,381 (hereinafter referred to as the '381 patent). The '381 patent discloses an extrudate formed from a matrix having starch, sugar, fat, polyhydric alcohol and water in suitable ratios such that there exists a water activity of 0.6-0.75, for carrying an active ingredient. The water activity of the product matrix may be adjusted up or down for the active ingredient, be it pharmaceutical, nutraceutical, or a vitamin mineral complex.

[0011] Soft chewable dosage forms have been developed for use in veterinary medicine because they can be formulated to be very palatable compared to traditional tablets. A disadvantage however is that they can have lower bioavailability of the active component that can reduce efficacy and sometimes require a higher dose, especially if the animal does not fully chew the dosage form. These soft chewable dosage forms are usually larger and have a longer disintegration time compared to tablets that are smaller and generally disintegrate very rapidly. It would be very unexpected if a moist chewable with a longer disintegrating time were to give a higher absorption, therefore allowing for a reduced dose. Soft chewable dosage form products often rely on chewing to improve absorption. It would be especially desirable to have a moist chewable that gives a high bioavailability even if the chewable tablet were swallowed whole without chewing.

[0012] An example that allows a direct comparison of a soft chewable dosage form to a tablet is Merials Heartgard® (ivermectin). Heartgard® Tablets (NADA 138-412) were the first product approved for the monthly prevention of heartworm. Several years later Merial launched Heartgard® Chewable (NADA 140-886). The dose of invermectin for both products is 6 mcg/kg. This shows that the soft chewable dosage form developed was unable to improve the bioavailability of the existing tablet dosage. A soft chewable dosage form that was able to improve bioavailability versus a tablet would be very valuable.

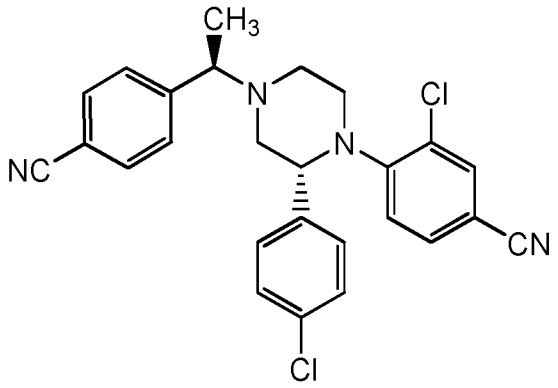
[0013] The CB-1 receptor is one of the most abundant neuromodulatory receptors in the brain, and is expressed at high levels in the hippocampus, cortex, cerebellum, and basal ganglia (e.g., Wilson et al., *Science*, **2002**, vol. 296, 678-682). Selective CB-1 receptor antagonists, for example pyrazole derivatives such as rimonabant (e.g., U.S. 6,432,984), can be used to treat various conditions, such as obesity and metabolic syndrome (e.g., Bensaid et al., *Molecular Pharmacology*, **2003** vol. 63, no. 4, pp. 908-914; Trillou et al., *Am. J. Physiol. Regul. Integr.*

Comp. Physiol. **2002** vol. 284, R345-R353; Kirkham, *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2002** vol. 284, R343-R344), neuroinflammatory disorders (e.g., Adam, et al., *Expert Opin. Ther. Patents*, **2002**, vol. 12, no. 10, 1475-1489; U.S. 6,642,258), cognitive disorders and psychosis (e.g., Adam et al., *Expert Opin. Ther. Pat.*, **2002**, vol. 12, pp. 1475-1489), addiction (e.g., smoking cessation; U.S. Patent Publ. 2003/0087933), gastrointestinal disorders (e.g., Lange et al., *J. Med. Chem.* **2004**, vol. 47, 627-643) and cardiovascular conditions (e.g., Porter et al., *Pharmacology and Therapeutics*, **2001** vol. 90, 45-60; Sanofi-Aventis Publication, Bear Stearns Conference, New York, September 14, 2004, pages 19-24).

[0014] WO 95/25443, U.S. 5,464,788, and U.S. 5,756,504 describe N-arylpiperazine compounds useful for treating preterm labor, stopping labor, and dysmenorrhea. WO 01/02372 and U.S. Published Application No. 2003/0186960 describe cyclized amino acid derivatives for treating or preventing neuronal damage associated with neurological diseases. WO 96/01656 describes radiolabelled substituted piperazines useful in pharmacological screening procedures, including labeled N-aryl piperazines. U.S. 5,780,480 describes N-aryl piperazines useful as fibrinogen receptor antagonists for inhibiting the binding of fibrinogen to blood platelets, and for inhibiting the aggregation of blood platelets. WO 03/008559 describes choline analogs useful for treating conditions or disorders. WO 97/22597 describes various 1,2,4-trisubstituted piperazine derivatives as tachykinin antagonists for treating tachykinin-mediated diseases such as asthma, bronchitis, rhinitis, cough, expectoration, etc. EP 0268222, WO 88/01131, U.S. 4,917,896, and U.S. 5,073,544 describe compositions for enhancing the penetration of active agents through the skin, comprising azacyclohexanes, including N-acyl and N,N'-diacylpiperazines. U.S. 6,528,529 describes compounds, including N,N'-disubstituted piperazines, which are selective for muscarinic acetylcholine receptors and are useful for treating diseases such as Alzheimer's disease. Wikström et al., J. Med. Chem. 2002, 45, 3280-3285, describe the synthesis of 1,2,3,4,10,14b-hexahydro-6-

methoxy-2-methyldibnzo[c,f]pyrazine[1,2-a]azepin. However, none of the references discloses the soft chewable dosage form compositions comprising a CB-1 antagonist compound.

[0015] 3-Chloro-4[(2R)-2-(4-chlorophenyl)-4-[(1R)-1-(4-cyanophenyl)ethyl]-1-piperazinyl]-benzonitrile, having the Formula A,



A

and related compounds are disclosed in US Patent 7,700,597, issued April 20, 2010. The compound of Example 392a in US Patent 7,700,597 is the CB-1 antagonist of Formula A and is indicated to be useful in the treatment of conditions such as metabolic syndrome (e.g. obesity), neuroinflammatory disorders and cognitive disorders.

[0016] Multiple polymorphs exist for CB-1 Antagonist of Formula A. Upon early salt and polymorph screening, crystalline Form 1 was initially identified as the stable form of the free base. Form 1 was not sensitive to mechanical stresses such as milling, pressure, heating at varying rates, or high humidity. As the process was scaled up, crystalline Form 3 was later isolated. Competition slurry study and temperature-solubility profiles suggested that Form 3 was the most stable form. Unfortunately, the bioavailability of Form 3 in animals was very low. A need was indentified to find a delivery system that would significantly improve the bioavailability of the Form 3 CB-1 antagonist compound of Formula A.

SUMMARY OF THE INVENTION

[0017] Embodiments of the present invention provide novel compositions and processes for the delivery of a CB-1 antagonist compound. An embodiment is a soft chewable dosage form composition comprising a CB-1 antagonist compound. In an embodiment, the CB-1 antagonist compound is a compound of Formula A. In another embodiment, the CB-1 antagonist is any compound that is active as an antagonist of the CB-1 receptor. In still another embodiment, the CB-1 antagonist compound is a compound selected from the following drinabant, ibipinabant, otenabant, rimonabant, rosonabant, surinabant and taranabant. In various embodiments, the CB-1 antagonist compound is combined with an additive.

[0018] This invention relates to formulations to improve the bioavailability of the CB-1 antagonist compound in animals through the use of a combination of at least one filler, at least one disintegrant, at least one lubricant, at least one flavor, and, optionally, at least one pH modifier, at least one surfactant, at least one humectant, at least one antioxidant, at least one solvent, and at least one coloring agent in a soft chewable dosage form.

[0019] In additional embodiments, the additive is selected from the group consisting of a pharmaceutical, a nutraceutical, a vitamin, and a mineral.

[0020] In a preferred embodiment, a soft chewable dosage form of the present invention comprises a filler component, a disintegrant component, a lubricant component, a flavor component, a pH modifier component, a surfactant component, a humectant component, an antioxidant component, a solvent component, and a color component.

[0021] The general process to manufacture the soft chewable dosage form involves the addition of the filler, the CB-1 antagonist compound, disintegrant, flavor, and lubricant into a mixing vessel to form a uniform mass. In a separate vessel, an additional lubricant is melted and added to the mass while molten. The mass is mixed and kept warm to form the final mass which will be formed into

the chewable tablets. In an embodiment, ingredients of a soft chewable dosage form of the present invention are uniformly dispersed throughout the soft chew. In another embodiment of a soft chewable dosage form of the present invention, ingredients are at least partially separated, such as when an embodiment has distinct layers, segments, and/or zones.

[0022] Further embodiments of the present invention comprise processes for treating and/or delivering an CB-1 antagonist compound to an animal, such process(es) being adaptable to the size of the animal for treatment and/or delivery of an appropriate amount of additive to the animal.

[0023] In a further embodiment, the present invention is a method of treating an animal for a disease comprising administrating to the animal in need thereof a pharmaceutically effect amount of the soft chewable dosage form composition described herein. In another embodiment, the disease is a metabolic syndrome (e.g. obesity, insulin resistance), a neuroinflammatory disorder or a cognitive disorder. In yet another embodiment, the animal is a dog or a cat.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is the x-ray diffraction pattern of CB-1 antagonist compound of Formula A (Crystalline Base Form 3).

Figure 2 is a comparative graph comparing the pharmacokinetic data of a chewable tablet formulation containing CB-1 antagonist compound of Formula A (form 3) with a standard tablet formulation at an oral dose of 1.0 mg/kg in dogs.

Figure 3 is a graph comparing the pharmacokinetic data of a chewable dosage form with the hydrochloric salt of CB-1 antagonist compound of Formula A with a standard tablet formulation with the hydrochloric salt of CB-1 antagonist compound of Formula A at an oral dose of 1.0 mg/kg in dogs.

Figure 4 is a graph comparing the pharmacokinetic data of 4 formulations, 2 chewable and 2 direct compression tablets, with the hydrochloric salt and crystalline base of CB-1 antagonist compound of Formula A at an oral dose of 1.0 mg/kg in dogs.

Detailed Description of the Invention

[0024] Embodiments of a composition of the present invention are soft chewable dosage form or soft chews for the delivery of a CB-1 antagonist compound of Formula A to an animal. Such animal may be any animal. Especially considered animals include livestock, pets, farm animals, and the like, including, but not limited to, horses, cows, pigs, goats, sheep, llamas, deer, ducks, chickens, dogs, cats, lions, tigers, bears, oxen, buffalo, fish, birds, insects, and the like.

[0025] In an embodiment of the composition, the therapeutically effective amount of the CB-1 antagonist of Formula A is 0.01 to 30 mg/kg. In an embodiment of the composition, the therapeutically effective amount of the CB-1 antagonist of Formula A is 0.1 to 10 mg/kg. In an embodiment of the composition, the therapeutically effective amount of the CB-1 antagonist of Formula A is 0.5 to 2 mg/kg. In another embodiment of the composition, the therapeutically effective amount of the CB-1 antagonist of Formula A is 1 mg/kg.

[0026] In further embodiments, the CB-1 antagonist compound of Formula A is combined with an additive. In various embodiments, the additive is selected from the group consisting of a pharmaceutical, a nutraceutical, a vitamin, a mineral and a filler. Embodiments of the soft chew of the present invention deliver reasonable levels of the CB-1 antagonist compound of Formula A and/or the additive, thereby producing the desired effect for the CB-1 antagonist compound of Formula A and/or the additive. The soft chew, in various embodiments, may be pleasant tasting and/or palatable to an animal.

[0027] In various alternative embodiments, a composition of the present invention contains at least one other component as disclosed below. Unless otherwise indicated, the percentages of these other components are w/w percentages.

[0028] In an embodiment, a composition of the present invention contains at least one filler or diluent. In another embodiment, the diluent is selected from a group as listed in the "Handbook of Pharmaceutical Excipients", page 758. In another embodiment, the filler is selected from a group consisting of soy meal/grits, corn meal/gluten, flour, white sugar, corn syrup, sorbitol, maltitol, oligosaccharide, isomaltooligosaccharide, glucose, lycasin, erythritol, isomaltose, raffinose, galactose, honey, molasses, polyhydric alcohols and other similar saccharides oligomers and polymers, and mixtures thereof. In another embodiment, the filler comprises about 10 percent to about 60 percent of the soft chew. In an alternate embodiment, the filler comprises about 20 percent to about 50 percent of the soft chew. In a further embodiment, the filler comprises about 25 percent to about 45 percent of the soft chew.

[0029] In an embodiment, a composition of the present invention contains at least one disintegrant. In another embodiment, the disintegrant is selected from a group as listed in Handbook of Pharmaceutical Excipients, 4th Edition, edited by Rowen et al, Pharmaceutical Press, London, UK, 2003 (hereafter "the Handbook of Pharmaceutical Excipients"), page 758. In an alternate embodiment, the disintegrant comprises about 5 percent to about 50 percent of the soft chew. In an alternate embodiment, the disintegrant comprises about 10 percent to about 40 percent of the soft chew. In a further embodiment, the disintegrant comprises about 10 percent to about 20 percent of the soft chew. In a further embodiment, the disintegrant comprises about 15 percent to about 30 percent of the soft chew.

[0030] In an embodiment, a composition of the present invention contains at least one lubricant. In another embodiment, the lubricant is selected from a group as listed in the "Handbook of

Pharmaceutical Excipients", page 764. In an alternate embodiment, the lubricant is selected from a group consisting of soybean oil, corn oil, sesame oil, ne glycol 3350, Dow Chemical Co. Midland, MI), derived palm oil, palm hydrogenated oil, corn germ hydrogenated oil, castor hydrogenated oil, cotton-seed oil, olive oil, peanut oil, palm olein oil, Cacao fat, margarine, butter, shortening and palm stearin oil, fish oil, chicken fat, tallow, choice white grease, prime steam lard, and mixtures thereof. In an embodiment, the lubricant comprises about 1 percent to about 40 percent of the soft chew. In an alternate embodiment, the lubricant comprises about 2 percent to about 35 percent of the soft chew. In a further embodiment, the lubricant comprises about 5 percent to about 30 percent of the soft chew. In a further embodiment, the lubricant comprises about 1 percent to about 10 percent of the soft chew. In a further embodiment, the lubricant comprises about 10 percent to about 20 percent of the soft chew. In a further embodiment, the lubricant comprises about 20 percent to about 30 percent of the soft chew.

[0031] In an embodiment, a composition of the present invention contains at least one flavor. In another embodiment, the flavor is selected from a group as listed in the "Handbook of Pharmaceutical Excipients", page 760. In alternate embodiment, the flavor is selected from a group consisting of natural and/or artificial flavors such as by-products of beef liver, pork liver, garlic, malt, peanuts, chocolate, hickory (Chartor, Red Arrow International, Manitowoc, WI), fruit, meat (including, but not limited to pork, beef, chicken, fish, poultry, and the like), vegetable, cheese, bacon and/or artificial flavorings, strawberry flavor, tutti fruity flavor, orange flavor, banana flavor, mint flavor, and an apple-molasses. In an alternate embodiment, the flavor comprises about 1 percent to about 40 percent of the soft chew. In an alternate embodiment, the flavor comprises about 2 percent to about 20 percent of the soft chew. In a further embodiment, the flavor comprises about 1 percent to about 5 percent of the soft chew. In a further embodiment, the flavor comprises about 10 percent to about 20 percent of the soft chew.

[0032] In an embodiment, a composition of the present invention contains at least one pH modifier. In another embodiment, the pH modifier is selected from a group as listed in the "Handbook of Pharmaceutical Excipients" as Acidifying Agents and Acidulants, page 767. In an embodiment, the pH modifier comprises about 0.5 percent to about 30 percent of the soft chew. In an alternate embodiment, the pH modifier comprises about 2 percent to about 20 percent of the soft chew. In a further embodiment, the pH modifier comprises about 2 percent to about 10 percent of the soft chew. In a further embodiment, the pH modifier comprises about 0.5 percent to about 5 percent of the soft chew.

[0033] In an embodiment, a composition of the present invention contains at least one surfactant. In another embodiment, the surfactant is selected from a group as listed in the "Handbook of Pharmaceutical Excipients", page 773. In an embodiment, the surfactant comprises about 0.5 percent to about 20 percent of the soft chew. In an alternate embodiment, the surfactant comprises about 1 percent to about 15 percent of the soft chew. In a further embodiment, the surfactant comprises about 10 percent to about 20 percent of the soft chew. In a further embodiment, the surfactant comprises about 0.5 percent to about 5 percent of the soft chew.

[0034] In an embodiment, a composition of the present invention contains at least one humectant. In another embodiment, the humectant is selected from a group as listed in the "Handbook of Pharmaceutical Excipients", page 762. In an embodiment, the humectant comprises about 1 percent to about 30 percent of the soft chew. In an alternate embodiment, the humectant comprises about 5 percent to about 15 percent of the soft chew. In a further embodiment, the humectant comprises about 1 percent to about 10 percent of the soft chew. In a further embodiment, the humectant comprises about 10 percent to about 20 percent of the soft chew.

[0035] In an embodiment, a composition of the present invention contains at least one antioxidant. In another embodiment, the antioxidant is selected from a group as listed in the "Handbook of

Pharmaceutical Excipients", page 752. In an embodiment, the antioxidant comprises about 0.01 percent to about 10 percent of the soft chew. In an alternate embodiment, the antioxidant comprises about 0.02 percent to about 10 percent of the soft chew. In a further embodiment, the antioxidant comprises about 0.05 percent to about 5 percent of the soft chew.

[0036] In an embodiment, a composition of the present invention contains at least one solvent. In another embodiment, the solvent is selected from a group as listed in the "Handbook of Pharmaceutical Excipients", page 771. In an alternate embodiment, the solvent is selected from a group consisting of 2-pyrollidone, glycerol formal, methanol, acetonitrile, dimethylacetamide, and ethyl lactate. In an embodiment, the solvent comprises about 1 percent to about 20 percent of the soft chew. In an alternate embodiment, the solvent comprises about 2 percent to about 20 percent of the soft chew. In a further embodiment, the solvent comprises about 2 percent to about 10 percent of the soft chew.

[0037] In an embodiment, a composition of the present invention contains at least one coloring agent. In another embodiment, the coloring agent is selected from a group as listed in the "Handbook of Pharmaceutical Excipients", page 165. In an embodiment, the coloring agent comprises about 0.01 percent to about 5 percent of the soft chew. In an alternate embodiment, the coloring agent comprises about 0.1 percent to about 5 percent of the soft chew. In a further embodiment, the coloring agent comprises about 0.1 percent to about 3 percent of the soft chew.

[0038] In an embodiment, a composition of the present invention comprises at least one filler component, at least one disintegrant component, at least one lubricant component, at least one flavor component, and optionally, a pH modifier, a surfactant, a humectant, an antioxidant, a solvent, and a coloring agent. Generally, in various embodiments, the filler component comprises about 10 percent to about 60 percent of the soft chew, the disintegrant component comprises about 5 percent to about 50 percent of the soft chew, the lubricant component comprises about 5 percent

to about 40 percent of the soft chew, the flavor component comprises about 1 percent to about 40 percent of the soft chew, the pH modifier component comprises about 0.5 percent to about 30 percent of the soft chew, the surfactant component comprises about 1 percent to about 20 percent of the soft chew, the humectant component comprises about 1 percent to about 30 percent of the soft chew, the antioxidant component comprises about 0.01 percent to about 10 percent of the soft chew, the solvent component comprises about 1 percent to about 20 percent of the soft chew, and the coloring component comprises about 0.01 percent to about 5 percent of the soft chew. The percentages of these components may be varied depending upon the end use and desired consistency of the soft chew.

[0039] In an alternate embodiment, the filler component comprises about 20 percent to about 50 percent of the soft chew, the disintegrant component comprises about 10 percent to about 40 percent of the soft chew, the lubricant component comprises about 10 percent to about 40 percent of the soft chew, the flavor component comprises about 1 percent to about 30 percent of the soft chew, the pH modifier component comprises about 2 percent to about 20 percent of the soft chew, the surfactant component comprises about 2 percent to about 20 percent of the soft chew, the humectant component comprises about 5 percent to about 30 percent of the soft chew, the antioxidant component comprises about 0.02 percent to about 10 percent of the soft chew, the solvent component comprises about 2 percent to about 20 percent of the soft chew, and the coloring component comprises about 0.1 percent to about 5 percent of the soft chew.

[0040] In an another embodiment, the filler component comprises about 30 percent to about 40 percent of the soft chew, the disintegrant component comprises about 20 percent to about 30 percent of the soft chew, the lubricant component comprises about 20 percent to about 30 percent of the soft chew, the flavor component comprises about 1 percent to about 20 percent of the soft chew, the pH modifier component comprises about 2 percent to about 10 percent of the soft chew,

the surfactant component comprises about 2 percent to about 10 percent of the soft chew, the humectant component comprises about 10 percent to about 20 percent of the soft chew, the antioxidant component comprises about 0.05 percent to about 5 percent of the soft chew, the solvent component comprises about 2 percent to about 10 percent of the soft chew, and the coloring component comprises about 0.1 percent to about 3 percent of the soft chew.

[0041] In various embodiments, one or more components and/or additives are added to the composition. The additive components are selected from the group consisting of a pharmaceutical, a nutraceutical, a vitamin, a mineral and/or a filler that can be orally administered. In this regard, an additive component may be an active ingredient or an inactive ingredient.

[0042] Exemplary pharmaceuticals may include, but are not limited to, parasiticides, insecticides, anthelmintics, therapeutic agents, non-steroidal anti-inflammatory drugs, antibiotics, corticosteroids, and other compounds such as magnesium hydroxide, stranozole, furosemide, , acepromazine, aspirin, PROZAC, ZANTACS, BENADRYL, and omyprazole.

[0043] In various embodiments, the additive is coated. Any suitable coating may be used. In an embodiment, a coating is chosen that will not interfere with an additive. In another embodiment, an additive is chosen that can modify the time for digestion of the additive(s), thereby at least partially controlling the release of the additive(s). Suitable coatings include, but are not limited to, and may be any pharmaceutically acceptable, and/or neutraceutically acceptable coating, as is common in the art.

[0044] In an embodiment, the soft chew composition is manufactured without any water-based components. In another embodiment, the soft chew composition is substantially free of aqueous components. In an embodiment, the moisture level of the soft chew is 1 – 10%. In another embodiment, the moisture level of the soft chew is 1 – 8%. In a further embodiment, the moisture level of the soft chew is 1 – 5%.

[0045] An embodiment of a process for forming a soft chew of the present invention comprises the steps of:

Mix the API, and at least one filler component, at least one disintegrant component, at least one lubricant component, at least one flavor component, and optionally, at least one pH modifier component, one surfactant component, one humectant component, one antioxidant component, one solvent component, and one coloring agent.

Heat the resulting mass prior to forming.

Form the soft chews into the desired weights.

In an alternative, the lubricant may be heated prior to addition to the formulation.

[0046] If an additive is present in the embodiment of the soft chew, the additive component may be mixed along with the other components or at a later step and/or time in the process. In an alternate embodiment, the components are mixed completely to produce a dough. In a most preferred embodiment, the dough is mixed until there is a uniform dispersal of the components in the dough.

[0047] Embodiments of processes of the present invention may further comprise mixing a pH modifier component, a surfactant component, a humectant component, an antioxidant component, and a coloring component.

[0048] In an embodiment, the dry components are mixed and the liquid components are mixed separately. In an embodiment, the lubricant component is heated when mixing and added, at sufficient temperature, to the dry components. The liquid and dry components are then mixed together until a desired dough is obtained. However, the process by which the components are mixed and/or heated into a dough may be varied. Moreover, the degree of mixing may be varied, such that, in various embodiments, the dough is not uniformly mixed and remains striated.

Likewise, various embodiments of dough of the present invention have discrete zones and/or layers.

[0049] In an embodiment, an additive(s) component is added during mixing of the components. In an alternate embodiment, an additive component is injected into the soft chew after forming. In an alternate embodiment, a dough is formed about an additive component. In another embodiment, an additive(s) is mixed and/or dissolved in an ingredient prior to adding with a dough and/or components of the present invention. In alternate embodiments, an additive(s) component is sprayed into a dough while mixing. The particular process for mixing the additive in the dough may be dependant upon considerations, including the stability of the additive, the temperature sensitivity of the additive, and/or the like. In a preferred embodiment, the additive is uniformly mixed and/or dispersed in the dough.

[0050] In another embodiment, the lubricant component is heated prior to mixing the components, whereby the dough is then formed into a soft chew of the present invention. In an embodiment, the dough is formed while still warm. The dough may be formed into a soft chew by any means or method common in the art, such as by hand or by machine. In an embodiment, a forming machine or patty machine is utilized, such that the soft chew is formed out of the dough. In a most preferred embodiment, the dough (or mass) is kept at a warm temperature suitable for forming the soft chews. Suitable examples of forming machines are exemplified in U.S. Pat. Nos. 5,165,218, 7,780,931, 4,523,520, and 3,887,964.

[0051] Embodiments of a soft chew of the present invention may have different textures, crispness, hardness, and the like. In an embodiment texture of the soft chew will be smooth. In other embodiments, the texture of the soft chew will be rough.

[0052] Further embodiments of the present invention are for a process of introducing an additive to an animal. Suitable examples of animals are livestock, pets, farm animals, and the like,

including, but not limited to, horses, cows, pigs, goats, sheep, llamas, deer, ducks, chickens, dogs, cats, lions, tigers, bears, oxen, buffalo, fish, birds, insects, and the like.

[0053] Dosage requirements for embodiments of the present invention will vary and should be chosen to be within established veterinary parameters. In various embodiments, dosage delivered to an animal may be adjusted by offering more or less units of soft chews to the animal, one soft chew supplies enough additive for a certain weight animal.

[0054] While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and the appended Claims are intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth whether now existing or after arising. Furthermore, all patents mentioned herein are herby incorporated by reference.

[0055] For a further understanding of an embodiment of the present invention, reference should be had to the following examples:

Example 1: Chewable (Base- crystalline Form 3) Tablet A

Material	Functional group	% w/w
CB-1 antagonist compound of Formula A, form 3	API	0.5
Glycerin	Humectant	5.0
Sucrose	Filler	7.0
Lactose (Spray-dried)	Filler	26.5
Sodium lauryl sulfate	Surfactant	1.0
Citric acid, monohydrate	pH modifier	1.0
Soybean oil	Lubricant	15.0
Polyethylene glycol 3350	Lubricant	14.0
Sodium starch glycolate	Disintegrant	15.0
SPF liver flavor	Flavor	15.0

[0056] The process used for making Soft Chewable dosage form Tablet A was as follows:

1. In a mixing vessel, add Glycerin. CB-1 antagonist compound of Formula A, Sucrose, Sodium starch gylcolate, Liver flavor, Sodium lauryl sulfate, and Citric acid. Mix until uniform to form a mass.
2. Add Soybean oil. Mix until uniform.
3. Add Lactose. Mix until uniform.
4. In a separate vessel, melt Polyethylene glycol 3350 and add while molten into the mass. Mix until uniform.
5. Adjust consistency of blend by adding Lactose or Soybean oil. Mix until uniform.
6. While warm, form the mass into chewable tablets.

Physical Characteristics of the Soft Chewable Dosage Form Tablet A:

[0057] The soft chews formed from the above section had the following general characteristics:

Chewable Tablet Weight: 2.5 g

Amount of CB-1 antagonist compound of Formula A: 12.5 mg

Time to Disintegrate: 16 min

Example 2: Soft Chewable Dosage Form (HCl salt) Tablet B

Material	Functional group	% w/w
CB-1 antagonist compound of Formula A (HCl salt)	API	0.27
Cremaphor RH40	Surfactant	15.00
Glycerol formal	Solvent	2.50
Soy grits	Filler	15.13
Corn gluten	Filler	20.00
Fructose	Filler	5.00
Glycerin	Humectant	10.00
Propylene glycol	Humectant	5.00
Sodium starch glycolate	Disintegrant	20.00
Miglyol 812	Lubricant	5.00
Red iron oxide	Color	0.10
Chartor hickory flavor	Flavor	2.00

[0058] The process used for making the Soft Chewable Dosage Form Tablet B was as follows:

1. In a small vessel, add Glycerol formal.
2. Add CB-1 antagonist compound of Formula A. Mix until clear.

3. Add Propylene glycol. Mix until clear.
4. In a large vessel, add Soy grits, Corn gluten, and Sodium starch glycolate. Mix until uniform.
5. Use a portion of blend from large vessel to "wash" small vessel.
6. Return blend from small vessel to large vessel.
7. Add Glycerin. Mix until uniform.
8. Add Cremaphor. Mix until uniform.
9. Add Miglyol. Mix until uniform.
10. Add Red iron Oxide and Chartor. Mix until uniform.
11. While warm, form the mass into chewable tablets.

Example 3: Direct Compression (Base – crystalline Form 3) Tablet

Material	Functional group	% w/w
CB-1 antagonist compound of Formula A, form 3	API	5.0
Avicel PH 102	Binder/Disintegrant	37.0
Lactose (spray dried)	Filler	47.0
SPF liver flavor	Flavor	10.0
Magnesium stearate	Lubricant	1.0

Physical Characteristics of the Direct Compression (Base – crystalline Form 3) **tablet:**

[0059] The tablets formed from the above section had the following general characteristics:

Direct Compression Tablet Weight: 250 mg

Amount of CB-1antagonist compound of Formula A: 12.5 mg

Time to Disintegrate: 1 min

Example 4: Direct Compression (HCl) Tablet

Material	Functional group	% w/w
CB-1 antagonist of Formula A (HCl salt)	API	5.00
Avicel PH 102	Binder/Disintegrant	40.00
Lactose (spray dried)	Filler	49.55
Sodium lauryl sulfate	Surfactant	1.00
Hickory flavor	Flavor	2.00
Liver flavor	Flavor	2.00
Aspartame	Flavor	0.10
Magnesium stearate	Lubricant	0.35

Example 5: Comparison of pK data

[0060] Table 1 summarizes the 24 hour pK data comparing the direct compression (base) tablet of Example 3 and soft chewable dosage form (base) tablet of Example 1. This was a 20 day study, with 5 dogs per group, where the dogs were dosed once daily for the first 7 days and then weekly up to day 20. Figure 2 depicts the improved Cmax of the chewable tablet compared to the direct compression tablet. Both dosage forms contained CB-1, formula A (base – form 3). Both samples were dosed at 1 mg/kg orally to beagle dogs and were dosed whole, without allowing the dogs to chew.

Table 1: pK Data of Direct Compression & Soft Chewable Tablet

Formulation	Cmax (ng/mL)	Tmax (hr)	AUC (ng/hr/mL)	Disintegration time (min)
Direct compression (base)	218	4	1580	1
Soft Chewable (base)	576	2	3601	16

[0061] Formulations using the soft chewable dosage form resulted in the highest drug absorption. Disintegration time comparing soft chewable tablet A and the direct compression tablet was evaluated based on USP <701>, Disintegration, using a disintegration apparatus with water at 37°C. The results showed that the direct compression tablet disintegrated in 1 minute, while the chewable tablet A disintegrated in 16 minutes. Although its disintegration time was later than the direct compression tablet, the chewable tablet had a significantly better pharmacokinetic profile. Interestingly, the Tmax of the compressed tablet was longer (4 hours) compared to the chewable tablet at 2 hours. Both formulations were dosed orally without chewing. Additionally, the Cmax of the chewable tablet was 576 ng/mL compared to a much lower Cmax of 218 ng/mL for the direct compression tablet. These unexpected results allow for a much lower dose of CB-1 to be used to reach the necessary therapeutic endpoint

[0062] Table 2 summarizes the 24 hour pK data comparing the direct compression (HCl & base) tablets and the soft chewable (HCl & base) tablets. Figure 3 depicts the improved Cmax of the soft chewable (HCl) tablets compared to the direct compression (HCl) tablets. This data is based on a compilation of studies, wherein 1 study included 5 dogs per group dosed over 20 days with blood samples taken at various time points over the 20 days and 2 other studies included 4 dogs per group dosed over 7 days with blood samples taken at various time points across the 7 days. With the exception of the soft chewable (HCl) tablets of Example 2, the samples were dosed at 1

mg/kg orally to beagle dogs and were dosed whole, without allowing the dogs to chew. Data from the soft chewable (HCl) tablets of Example 2, which were dosed at 0.2 mg/kg, was normalized to 1.0 mg/kg for comparative purposes. All tablets were dosed whole, without allowing the dogs to chew. Figure 4 is a comparison of the mean Cmax of all the dosage forms.

Table 2: Mean Cmax of CB-1 dosage forms

Dosage form	Actual dose (mg/kg)	Cmax (ng/mL)	
		Unadjusted	Adjusted to 1 mg/kg
Chewable (HCl)	0.2	82.0	410.0
Chewable (base)	1.0	576.0	576.0
Direct compression (HCl)	1.0	177.0	177.0
Direct compression (base)	1.0	218.0	218.0

Claims:

What is claimed is:

1. A soft chewable dosage form comprising a CB-1 antagonist compound at least one filler, at least one disintegrant, at least one lubricant and at least one flavor.

2. The composition of claim 1, further comprising at least one pH modifier.

3. The composition of claim 1, further comprising at least one surfactant.

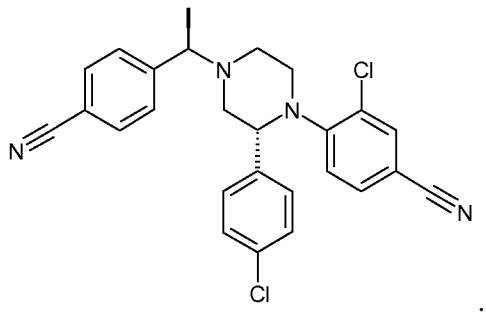
4. The composition of claim 1, further comprising at least one humectant.

5. The composition of claim 1, further comprising at least one antioxidant

6. The composition of claim 1, further comprising at least one solvent.

7. The composition of claim 1 further comprising at least one coloring agent.

8. The composition of claim 1, wherein the CB-1 antagonist compound is a compound of formula A.



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9. The composition of claim 8, wherein the compound of formula A is the *Form 3* polymorph that exhibits a powder x-ray diffraction pattern substantially the same as the pattern shown in Figure 1.

10. The composition of claim 1, wherein the soft chewable dosage form is substantially free of aqueous components.

11. The composition of claim 1, wherein the oral bioavailability of the CB-1 antagonist compound is greater than 50% as compared to IV administration.

12. The composition of claim 1 wherein the Cmax of the CB-1 antagonist compound is greater than 200 – 900 ng/mL orally at the dose of 1 mg/kg for dogs.

13. The composition of claim 1 wherein the bioavailability of CB-1 antagonist compound is greater than 50% when not chewed as compared to IV administration.

14. The composition of claim 1 wherein the filler is selected from a group consisting of lactose, sucrose, sorbitol, maltose, maltodextrin, starch, soy meal/grits, corn meal/gluten, flour, white sugar, corn syrup, sorbitol, maltitol, oligosaccharide, isomaltooligosaccharide, fructose, lactose, glucose, lycasin, xylitol, lactitol, erythritol, mannitol, isomaltose, polydextrose, raffinose, dextrin, galactose, sucrose, invert sugar, honey, molasses, polyhydric alcohols and other similar saccharides oligomers and polymers, and mixtures thereof.

15. The composition of claim 1 wherein the disintegrant is selected from a group consisting of sodium starch glycolate, crospovidone, croscarmellose sodium, pregelatinized starch, and microcrystalline cellulose.

16. The composition of claim 1 wherein the lubricant is selected from a group consisting of soybean oil, corn oil, sesame oil, polyethylene glycol, sodium lauryl sulfate, polyvinyl alcohol, polaxamer, miglyol, derived palm oil, palm hydrogenated oil, corn germ hydrogenated oil, castor hydrogenated oil, cotton-seed oil, olive oil, peanut oil, palm olein

oil, Cacao fat, margarine, butter, shortening and palm stearin oil, fish oil, chicken fat, tallow, choice white grease, prime steam lard, and mixtures thereof.

17. The composition of claim 1 wherein the flavor is selected from a group consisting of natural and/or artificial flavors such as by-products of beef liver, pork liver, garlic, malt, peanuts, chocolate, hickory, fruit, meat (including, but not limited to pork, beef, chicken, fish, poultry, and the like), vegetable, cheese, bacon and/or artificial flavorings, strawberry flavor, tutti fruity flavor, orange flavor, banana flavor, mint flavor, and an apple-molasses.

18. The composition of claim 2, wherein the pH modifier is selected from a group consisting of citric acid, malic acid, fumaric acid, phosphoric acid, hydrochloric acid, ascorbic acid, or lactic acid.

19. The composition of claim 3, wherein the surfactant is selected from a group consisting of polyoxyethylene sorbitan fatty acid esters, sodium lauryl sulfate, docusate sodium, polaxamers, polyethylene alkyl ethers, and polyoxyethylene castor oil derivatives.

20. The composition of claim 4, wherein the humectant is selected from a group consisting of glycerin, polydextrose, propylene glycol, sorbitol, triacetin, or xylitol.

21. The composition of claim 5, wherein the antioxidant is selected from a group consisting of alpha tocopherol, ascorbic acid, butylated hydroxyanisole, butylated hydroxytoluene, monothioglycerol, propyl gallate, sodium busulfite, or vitamin E.

22. The composition of claim 6, wherein the solvent is selected from a group consisting of 2-pyrollidone, glycerol formal, polyethylene glycol, medium-chain triglycerides, methanol, acetonitrile, dimethylacetamide, and ethyl lactate.

23. The composition of claim 7, wherein the coloring agent is selected from a group consisting of red #40, red iron oxide, brown iron oxide, and caramel.

24. The composition of claim 1 wherein the composition comprises an effective amount of CB-1 antagonist compound, about 10 – 60% filler, about 5 – 50% disintegrant, 5 – 40% lubricant, and 1 – 40% flavor based upon the total weight of the formulation.

25. A soft chewable dosage form composition comprising, a CB-1 antagonist compound, sucrose, sodium starch glycolate, soybean oil, polyethylene glycol, pork liver powder, citric acid, sodium lauryl sulfate, glycerin, propyl gallate, and red iron oxide.

26. A soft chewable dosage form composition comprising, a CB-1 antagonist compound, soy grits, corn gluten, fructose, sodium starch glycolate, miglyol 812, hickory powder, polyoxyethylene castor oil, glycerin, propylene glycol, glycerol formal, and red iron oxide.

27. A soft chewable dosage form composition comprising

a) a theraputically effective amount of the CB-1 antagonist compound of Form A;

b) 1-10 % w/w glycerin;

c) 1-10 % w/w sucrose;

d) 20-30 % w/w lactose;

e) 0.5-5 % w/w sodium lauryl sulfate;

f) 0.5-5 % w/w citric acid, monohydrate;

g) 10-20 % w/w soybean oil;

f) 10-20 % w/w polyethylene glycol 3350;

g) 10-20 % w/w sodium starch glycolate; and

`h) 10-20 % w/w SPF liver flavor.

28. A soft chewable dosage form composition comprising

a) a theraputically effective amount of the CB-1 antagonist compound of Form A;

b) 10-20 % w/w Cremaphor RH40;

c) 2-10 % w/w glycerol formal;

d) 10-20 % w/w soy grits;

e) 5-30 % w/w corn gluten;

f) 1-10 % w/w fructose;

g) 5-15 % w/w glycerin;

h) 1-10 % w/w propylene glycol;

i) 15-30 % w/w sodium starch glycolate;

j) 1-10 % w/w Miglyol 812;

k) 0.01-5 % w/w red iron oxide; and

l) 1-5 % w/w Chartor hickory flavor.

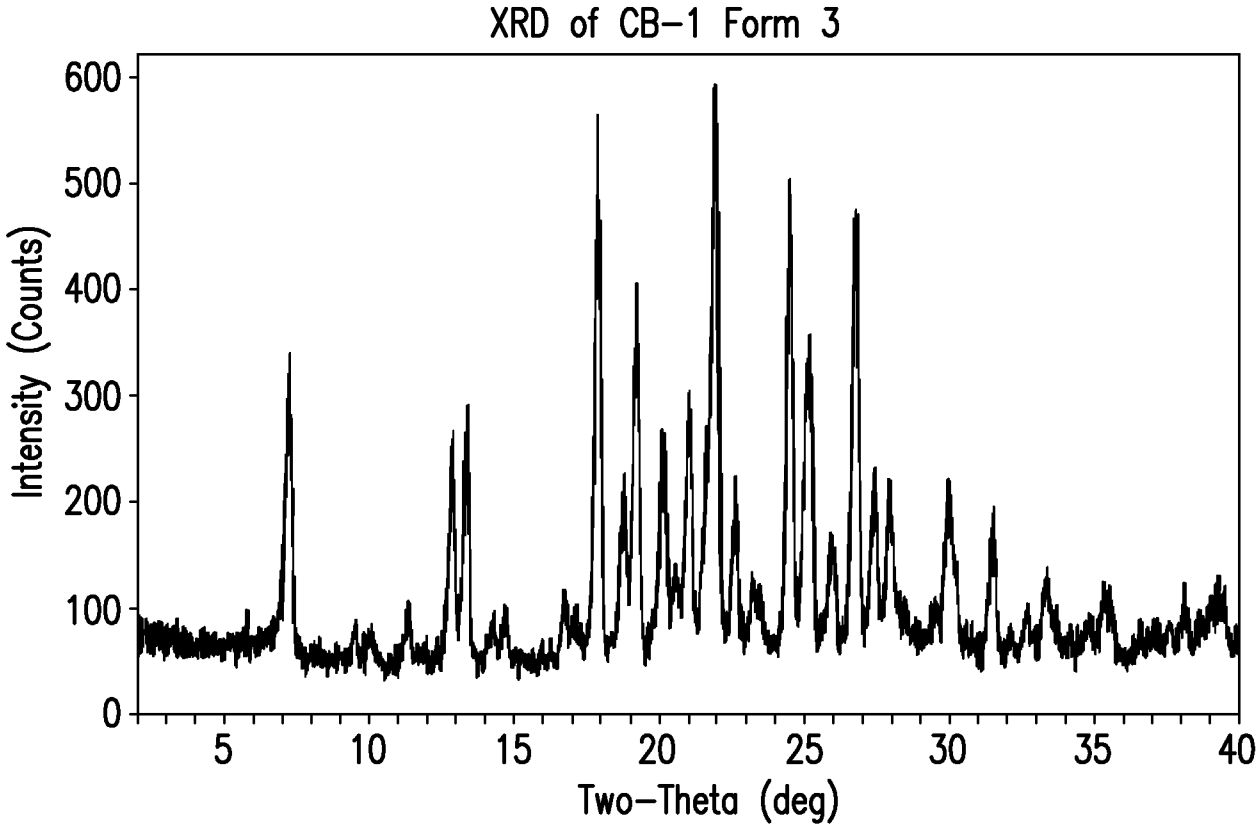

XRD of CB-1 Form 3
Intensity (Counts)
600
500
400
300
200
100
0
5
10
15
20
25
30
35
40
Two-Theta (deg)

FIG. 1

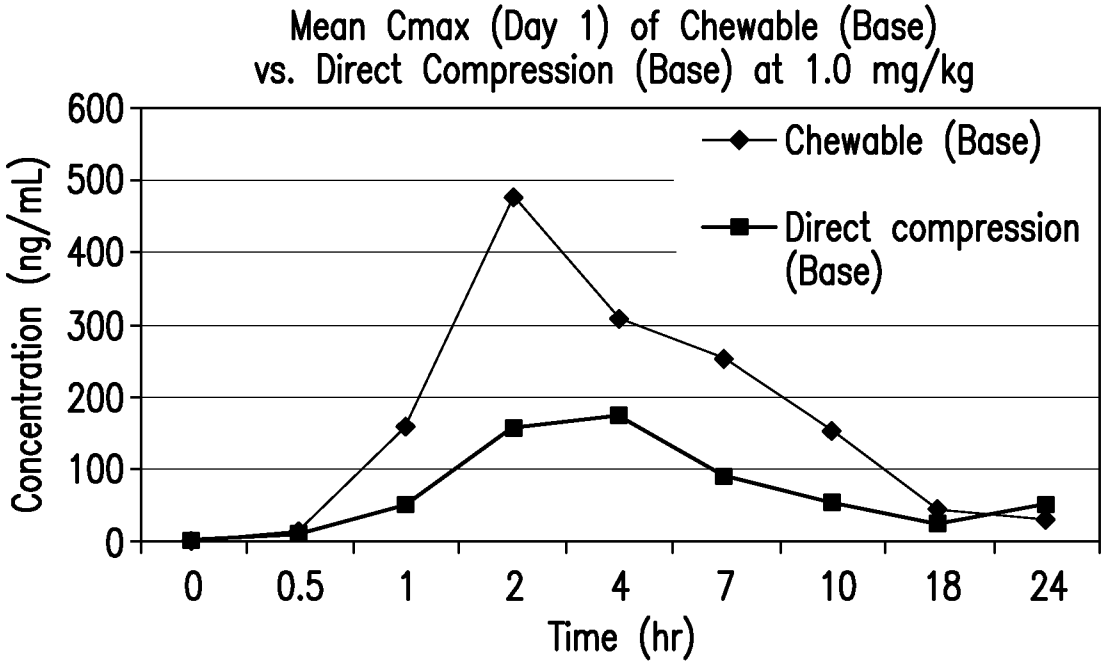
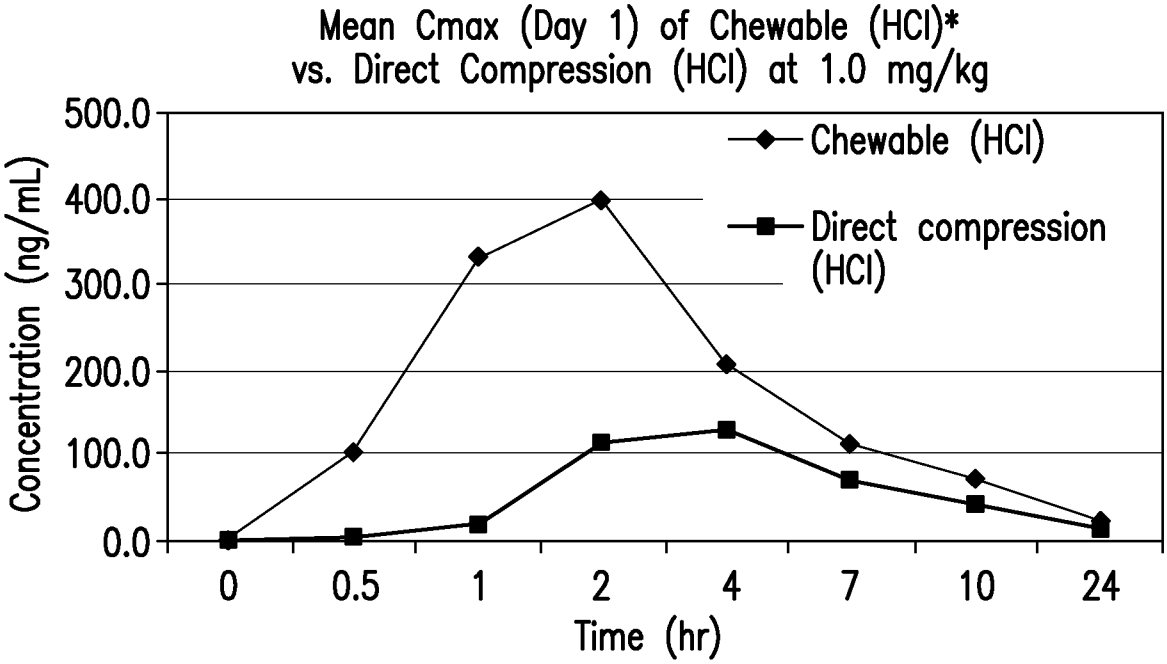
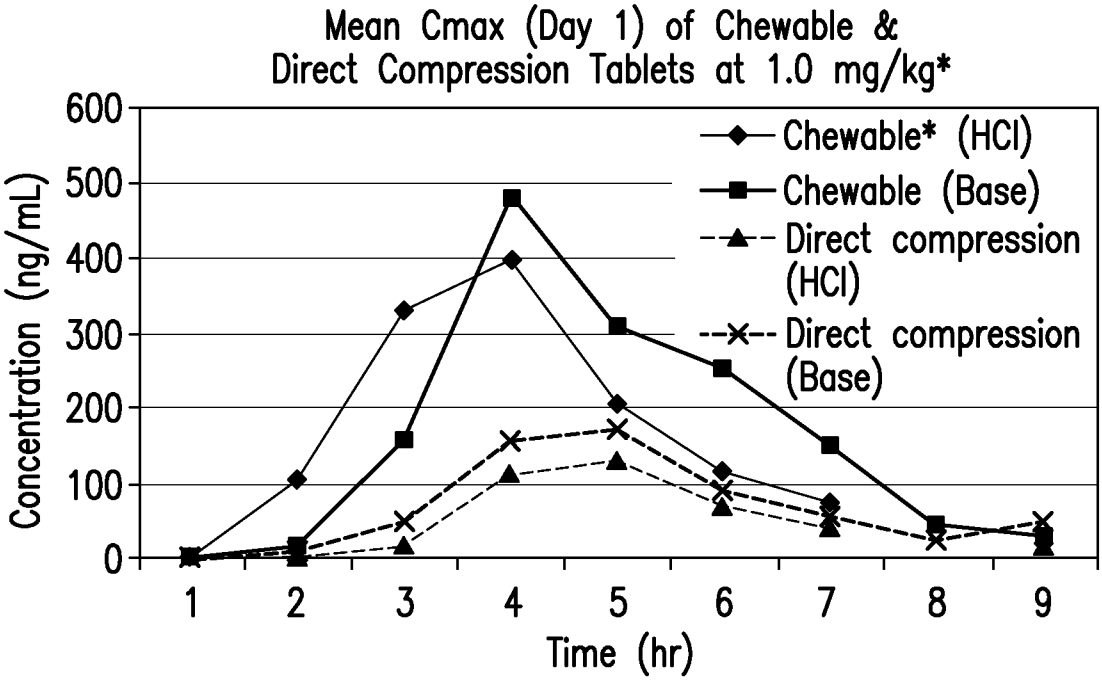

Mean Cmax (Day 1) of Chewable (Base)
vs. Direct Compression (Base) at 1.0 mg/kg
Concentration (ng/mL)
600
500
400
300
200
100
0
0
0.5
1
2
4
7
10
18
24
Time (hr)
Chewable (Base)
Direct compression (Base)

FIG.2



*Chewable pK data is normalized from 0.2 mg/kg to 1.0 mg/kg to match data from direct compression tablets.

FIG.3



*Chewable pK data is normalized from 0.2 mg/kg to 1.0 mg/kg to match the data from the other dosage forms.

FIG.4

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/071970

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K31/495
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 642 258 B1 (BOURRIE BERNARD [FR] ET AL) 4 November 2003 (2003-11-04) cited in the application	1-7,9-26
Y	examples 1-4	8

Y	US 2006/241121 A1 (GREENLEE WILLIAM J [US] ET AL GILBERT ERIC J [US] ET AL) 26 October 2006 (2006-10-26) cited in the application	8
A	example 392	27,28

A	US 2008/075759 A1 (PAULSEN NEIL E [US] ET AL) 27 March 2008 (2008-03-27) example 1	1-28

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 April 2013	25/04/2013

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Frelichowska, J

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2012/071970

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6642258 B1	04-11-2003	AR 025883 A1	18-12-2002
		AT 295170 T	15-05-2005
		AU 7667300 A	10-05-2001
		DE 60020145 D1	16-06-2005
		DE 60020145 T2	16-02-2006
		DK 1221952 T3	29-08-2005
		EP 1221952 A1	17-07-2002
		ES 2240176 T3	16-10-2005
		FR 2799124 A1	06-04-2001
		JP 2003510361 A	18-03-2003
		PT 1221952 E	31-08-2005
		US 6642258 B1	04-11-2003
		WO 0124798 A1	12-04-2001
US 2006241121 A1	26-10-2006	AR 054998 A1	01-08-2007
		AU 2005311930 A1	08-06-2006
		AU 2009230816 A1	19-11-2009
		CA 2589483 A1	08-06-2006
		CN 101115726 A	30-01-2008
		CN 102558075 A	11-07-2012
		CN 102633730 A	15-08-2012
		EP 1819684 A1	22-08-2007
		JP 2008521910 A	26-06-2008
		JP 2011251994 A	15-12-2011
		KR 20070090176 A	05-09-2007
		MY 144301 A	29-08-2011
		NZ 555320 A	26-11-2010
		SG 163577 A1	30-08-2010
		TW I343379 B	11-06-2011
		US 2006241121 A1	26-10-2006
		US 2010029607 A1	04-02-2010
		WO 2006060461 A1	08-06-2006
		ZA 200705002 A	25-09-2008
US 2008075759 A1	27-03-2008	AU 2008320992 A1	22-05-2009
		CA 2705724 A1	22-05-2009
		CN 101909605 A	08-12-2010
		EP 2219626 A1	25-08-2010
		JP 2011503197 A	27-01-2011
		RU 2010123868 A	20-12-2011
		US 2008075759 A1	27-03-2008
		US 2011223234 A1	15-09-2011
		US 2012141574 A1	07-06-2012
		WO 2009064859 A1	22-05-2009