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(71) Applicant (for all designated States except US): **YIS-SUM RESEARCH DEVELOPMENT COMPANY OF THE HEBREW UNIVERSITY OF JERUSALEM LTD.** [IL/IL]; Hi Tech Park, The Edmond J. Safra Campus, The Hebrew University of Jerusalem, Givat Ram, 91390 Jerusalem (IL).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **FRIEDMAN, Michael** [IL/IL]; 21 Revadim Street, 93391 Jerusalem (IL). **HOFFMAN, Amnon** [IL/IL]; 22 Anusei Mashad Street, 93784 Jerusalem (IL). **LAVY, Eran** [IL/IL]; 134 Yehuda Street, 71799 ModiIn (IL).

(74) Agents: **G.E EHRLICH (1995) LTD.** et al.; 11 Menachem Begin Street, 52521 Ramat Gan (IL).

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(54) Title: A GASTRORETENTIVE DOSAGE FORM FOR ORAL TREATMENT OF DOMESTIC ANIMALS

(57) Abstract: Gastroretentive oral dosage forms for an animal are described herein, as well as formulations and processes useful for preparation of same. The oral dosage form comprises a therapeutically active agent and a pharmaceutically acceptable solid carrier, and swells when in a stomach of the animal from a first size and shape to a second size and shape, wherein a short axis of the second size and shape is at least 50 % longer than a short axis of the first size and shape. The first size and shape of the dosage form are selected suitable for being swallowed as a whole by the animal, and the second size and shape are selected so as to prevent passage of the dosage form while in a stomach of the animal through the pylorus of the animal. The dosage form is capable of continuously releasing a therapeutically effective amount of the therapeutically active agent over a period of at least 2 days.



A GASTRORETENTIVE DOSAGE FORM FOR ORAL TREATMENT OF DOMESTIC ANIMALS

FIELD AND BACKGROUND OF THE INVENTION

5 The present invention, in some embodiments thereof, relates to a dosage form for oral administration of a drug, and more particularly, but not exclusively, to a gastroretentive dosage form suitable for sustained release of an orally administered drug, which is useful in the treatment of various medical conditions in animals such as domestic animals.

10 Many veterinary treatment protocols are performed on an "outpatient" basis, with the owners of the animals orally administering medications. Oral administration may be needed constantly, as for treatments of chronic diseases, or for a minimal period of time, as is the case for typical antibiotic treatments.

 Antibiotics (e.g., ampicillin, amoxicillin, amoxicillin-clavulanic acid, cephalexin
15 and cefuroxim) are the most commonly prescribed drugs in small animal medicine, and are applied in a variety of microbial infections, including gastrointestinal infections, urinary tract infections, wound infections, and pyodermas.

 The short biological half-life of many drugs and/or their pharmacodynamic properties require frequent exposure of the subject to the drug, so as to allow for the
20 presence of a minimum effective plasma concentration of the drug for a therapeutically effective period of time. For example, it is typically necessary for the concentration of an antibiotic to be above the minimal inhibitory concentration (MIC) of target pathogens, and preferably four times the minimal inhibitory concentration, for 25-50 % of the dosing interval (a parameter termed time above MIC, i.e., TaM), which
25 commonly necessitates multiple daily dosing of antibiotics throughout the treatment period, which usually lasts for 5 days.

 The need for multiple daily drug administrations is a major drawback of current treatment protocols in pets. As a result, a common reason for failure of therapy is low compliance by pet owners. In two canine studies, only 27 % of owners gave the
30 prescribed number of doses during short-term antibiotic treatment. The prime motives for this poor compliance are being out of the house during the day, difficulties with

restraining the animal, and lack of confidence. Another important factor influencing the thoroughness of compliance is related to the patient pet. For example, brachycephalic dog breeds and cats may pose particular challenges to administration of oral medications.

5 The polar chemical structure of many drugs (e.g., beta-lactam antibiotics) prevents absorption of the drug in the large intestine by passive diffusion. Consequently, the absorption of such drugs is confined to the small intestine, where they are actively absorbed by specific carriers. Hence, the drug effect terminates shortly after the formulation reaches the colon (2-4 hours after the drug administration) and is
10 no longer absorbed. Thus, the absorption of such drugs is limited to a narrow "absorption window" that is confined to the small intestine. Consequently, treatment strategies which do not require frequent drug administration have not been achieved for such drugs by conventional technologies of oral drug administration.

15 SUMMARY OF THE INVENTION

The currently available formulations for prolonged-release of a drug fail to provide an efficient solution to the drawbacks associated with repetitive administration of drugs to domestic and other animals that are characterized by short intestines, since the time during which drugs are released from such formulations is limited to the time the formulation paths through the intestines.

The present inventors have now surprisingly uncovered gastroretentive formulations that are capable of remaining in animal's stomach for prolonged time periods (e.g., at least 2 days, and optionally one week or more), and thus significantly
20 reduce the number of administrations required to achieve treatment of a disease in the animal.

According to an aspect of some embodiments of the present invention there is provided a gastroretentive oral dosage form for an animal comprising a therapeutically active agent and a pharmaceutically acceptable solid carrier, the oral dosage form swelling when in a stomach of the animal from a first size and shape to a second size
25 and shape, wherein a short axis of the second size and shape is at least 50 % longer than a short axis of the first size and shape, wherein the first size and shape are selected suitable for the oral dosage form to be swallowed as a whole by the animal, and the

second size and shape are selected so as to prevent passage of the dosage form while in a stomach of the animal through the pylorus of the animal, the dosage form being capable of continuously releasing a therapeutically effective amount of the therapeutically active agent over a period of at least 2 days.

5 According to an aspect of some embodiments of the present invention there is provided a method of treating a medical condition in an animal subject, the method comprising orally administering the gastroretentive oral dosage form described herein to the animal subject, wherein the medical condition is treatable by exposure to the therapeutically active agent for at least 2 days.

10 According to an aspect of some embodiments of the present invention there is provided a formulation comprising a therapeutically active agent and a pharmaceutically acceptable solid carrier which comprises a first polymer which swells upon contact with an aqueous solution by at least 100 %, and a second polymer which swells upon contact with an aqueous solution by up to 100%.

15 According to an aspect of some embodiments of the present invention there is provided a use of the formulation described herein in the manufacture of a gastroretentive oral dosage form for an animal which swells when in a stomach of the animal from a first size and shape to a second size and shape, wherein a short axis of the second size and shape is at least 50 % longer than a short axis of the first size and shape,
20 wherein the first size and shape are selected suitable for the oral dosage form to be swallowed as a whole by the animal, and the second size and shape are selected so as to prevent passage of the dosage form while in a stomach of the animal through the pylorus of the animal, the dosage form being capable of continuously releasing a therapeutically effective amount of the therapeutically active agent over a period of at least 2 days.

25 According to an aspect of some embodiments of the present invention there is provided a process of preparing the gastroretentive oral dosage form described herein, the process comprising:

a) providing a formulation comprising the therapeutically active agent and the pharmaceutically acceptable solid carrier; and

30 b) using a punch and die to shape the formulation into the dosage form having the first size and shape.

According to some embodiments of the invention, a shape of the first size and shape is eccentric.

According to some embodiments of the invention, the gastroretentive oral dosage form is kidney-shaped.

5 According to some embodiments of the invention, the dosage form is capable of continuously releasing a therapeutically effective amount of the therapeutically active agent over a period of at least 5 days.

10 According to some embodiments of the invention, the dosage form is capable of continuously releasing a therapeutically effective amount of the therapeutically active agent over a period of 7 days.

According to some embodiments of the invention, a length of the short axis of the first size and shape is no more than 75 % of a length of an axis perpendicular to the short axis.

15 According to some embodiments of the invention, a short axis of the second size and shape is at least 100 % longer than a short axis of the first size and shape.

According to some embodiments of the invention, each axis of the second size and shape is at least 20 % longer than a corresponding axis in the first size and shape.

According to some embodiments of the invention, a length of the short axis of the first size and shape is at least 10 mm.

20 According to some embodiments of the invention, a length of the short axis is in a range of 10 to 30 mm.

According to some embodiments of the invention, the solid carrier comprises a first polymer which swells upon contact with an aqueous solution by at least 100 %, and a second polymer which swells upon contact with an aqueous solution by up to 100 %.

25 According to some embodiments of the invention, the solid carrier comprises a first and a second polymer selected such that the first polymer swells upon contact with an aqueous solution to an extent larger than the second polymer.

According to some embodiments of the invention, at least one of two surfaces of the dosage form which are perpendicular to the short axis is a convex surface.

30 According to some embodiments of the invention, the gastroretentive oral dosage form is formed with a punch and die.

According to some embodiments of the invention, forming the dosage form as described herein from the formulation described herein comprises a punch and die.

According to some embodiments of the invention, the therapeutically active agent is an antibiotic.

5 According to some embodiments of the invention, the therapeutically active agent is hydrophilic.

According to some embodiments of the invention, the antibiotic is a beta-lactam antibiotic.

10 According to some embodiments of the invention, the gastroretentive oral dosage form is characterized by a gastric retention time of at least 3 days.

According to some embodiments of the invention, the therapeutically effective amount described herein provides the animal with a serum concentration of the therapeutically active agent which is at least a minimum effective concentration of the therapeutically active agent.

15 According to some embodiments of the invention, the serum concentration of the therapeutically active agent is at least the minimum effective concentration over a period of at least 40 hours.

20 According to some embodiments of the invention, the therapeutically effective amount provides the animal with a serum concentration of an antibiotic described herein which is at least a minimum inhibitory concentration of the antibiotic towards a pathogen which infects the animal, over a period time which is at least a treatment time of the antibiotic against the pathogen.

According to some embodiments of the invention, the animal is a carnivore.

25 According to some embodiments of the invention, the gastroretentive oral dosage form is packaged in a packaging material and identified in print, in or on the packaging material, for use in a treatment of a medical condition in the animal.

According to some embodiments of the invention, the medical condition described herein is treatable by exposure to the therapeutically active agent for at least 2 days.

30 According to some embodiments of the invention, the method described herein comprises a single administration of the dosage form or a plurality of administrations of

the dosage form, wherein the plurality of administrations are at intervals of at least 2 days.

According to some embodiments of the invention, the method is for treating a non-human animal.

5 According to some embodiments of the invention, the medical condition described herein is associated with a pathogen.

According to some embodiments of the invention, the formulation described herein is identified for use in the manufacture of a gastroretentive oral dosage form for an animal which swells when in a stomach of the animal from a first size and shape to a
10 second size and shape, wherein a short axis of the second size and shape is at least 50 % longer than a short axis of the first size and shape, wherein the first size and shape are selected suitable for the oral dosage form to be swallowed as a whole by the animal, and the second size and shape are selected so as to prevent passage of the dosage form while in a stomach of the animal through the pylorus of the animal, the dosage form being
15 capable of continuously releasing a therapeutically effective amount of the therapeutically active agent over a period of at least 2 days.

According to some embodiments of the invention, the first polymer is polycarbophil.

According to some embodiments of the invention, the second polymer is selected
20 from the group consisting of hydroxypropyl methyl cellulose, methyl cellulose and ethyl cellulose.

According to some embodiments of the invention, the punch is applied in a direction of the short axis of the first size and shape of the dosage form.

According to some embodiments of the invention, at least one of the punch and
25 the die is characterized by a concave surface, such that at least one of two surfaces of the dosage form which are perpendicular to the short axis of the dosage form is a convex surface.

Unless otherwise defined, all technical and/or scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which
30 the invention pertains. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments of the invention, exemplary methods and/or materials are described below. In case of conflict, the patent

specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and are not intended to be necessarily limiting.

BRIEF DESCRIPTION OF THE DRAWINGS

5 Some embodiments of the invention are herein described, by way of example only, with reference to the accompanying drawings. With specific reference now to the drawings in detail, it is stressed that the particulars shown are by way of example and for purposes of illustrative discussion of embodiments of the invention. In this regard, the description taken with the drawings makes apparent to those skilled in the art how
10 embodiments of the invention may be practiced.

 In the drawings:

 FIGs. 1A and 1B are schematic illustrations of a front view (FIG. 1A) and a side view (FIG. 1B) of an exemplary dosage form according to some embodiments of the invention;

15 FIGs. 2A and 2B are schematic illustrations of a front view (FIG. 1A) and a side view (FIG. 1B) of the exemplary dosage form shown in FIGs. 1 A and 1B, after swelling upon exposure to an aqueous solution, demonstrating a selective expansion of the dosage form along the short axis thereof;

 FIGs. 3A and 3B are schematic illustrations of a front view (FIG. 3A) and a side
20 view (FIG. 3B) of an exemplary kidney-shaped dosage form according to some embodiments of the invention;

 FIG. 4 presents comparative plots showing serum amoxicillin concentration in beagles as a function of time following oral administration of exemplary amoxicillin formulations according to some embodiments of the invention ("Formulation J" and
25 "Formulation K") or a standard amoxicillin tablet (minimum inhibitory concentration (MIC = 0.1 mg/l) and 4xMIC (0.4 mg/l) are shown for reference); and

 FIG. 5 presents comparative plots showing the cumulative release of amoxicillin from exemplary amoxicillin formulations according to some embodiments of the invention ("Formulation K" and "Formulation J"), as a function of time of incubation in
30 a U.S. Pharmacopeia (USP) buffer having a pH of 2 or 6.8.

DESCRIPTION OF SPECIFIC EMBODIMENTS OF THE INVENTION

The present invention, in some embodiments thereof, relates to a dosage form for oral administration of a drug, and more particularly, but not exclusively, to a gastroretentive dosage form suitable for sustained release of an orally administered drug, which is useful in the treatment of animals such as domestic animals.

In a search for new and improved formulations for administration of therapeutically active agents to animals, the present inventors have uncovered formulations for preparing gastroretentive oral dosage forms, which can remain in the stomach of an animal for a considerable time period and release a therapeutically active agent into the stomach for a considerable time period.

While reducing the present invention to practice, the inventors have demonstrated that gastroretentive oral dosage forms overcome the narrow "absorption window" which is characteristic of many therapeutically active agents, as well as the relatively short retention time of common therapeutically active agent in animals with short intestines, and provide sustained release and absorption of the agent into the bloodstream. Thus, the gastroretentive dosage forms allow for fewer and less frequent administrations of a therapeutically active agent, thereby resulting in more convenient and less costly treatment of animals.

The designed gastroretentive dosage forms advantageously address the limitations associated with frequent drug administrations to animals, particularly animals that are characterized by short small intestines (e.g., less than 8 times the length of the animal's torso) and/or short upper gastrointestinal transit times (i.e., times of transit for food through the stomach and small intestines), such as 6 hours or less, which limitations cannot be overcome by typical sustained release formulations.

Furthermore, the designed gastroretentive dosage forms are highly suitable for efficiently administering drugs directly to the stomach, for example, for treating stomach diseases and disorders (e.g., stomach ulcers, gastritis). The gastroretentive dosage forms advantageously deliver an agent specifically to the stomach, and overcome limitations associated with undesirable release of an agent into the intestines (where it has little or no beneficial effect), which limitations cannot be overcome by typical sustained release formulations.

Before explaining at least one embodiment of the invention in detail, it is to be understood that the invention is not necessarily limited in its application to the details set forth in the following description or exemplified by the Examples. The invention is capable of other embodiments or of being practiced or carried out in various ways.

5 Referring now to the drawings and tables, Figures 1A and 1B illustrate an exemplary dosage form according to some embodiments of the invention, from the front (Figure 1A) and from the side (Figure 1B). The dosage form comprises short axis **10** (see Figure 1B), which represents the width of the dosage form in the direction for which the dosage form is narrowest, as is further detailed hereinafter. In accordance with
10 optional embodiments of the invention, the dosage form comprises two convex surfaces **12** and **14** at either end of the short axis, as is further discussed in detail hereinafter.

Figures 2A and 2B illustrate the exemplary dosage form shown in Figures 1A and 1B following swelling of the dosage form upon exposure to an aqueous solution. The swollen dosage form comprises short axis **20** (see Figure 2B), which is considerably
15 longer than short axis **10** of the dosage form before swelling (shown in Figure 1B). In accordance with optional embodiments of the invention, the expansion of the short axis upon swelling is greater than the expansion of the dosage form in any other direction.

Figures 3A and 3B illustrate an exemplary kidney-shaped dosage form according to some embodiments of the invention, from the front (Figure 3A) and from the side (Figure 3B). The kidney-shaped dosage form comprises a convex side **30** and a concave side **32**, as viewed from the front (see Figure 3A). The dosage form comprises short axis **34** (see Figure 3B), which represents the width of the dosage form in the direction for which the dosage form is narrowest, as is further detailed hereinafter. In accordance
20 with optional embodiments of the invention, short axis **34** is perpendicular to an axis connecting convex side **30** and a concave side **32**. In accordance with optional
25 embodiments of the invention, the dosage form comprises two convex surfaces **36** and **38** at either end of the short axis (seen in the side view of Figure 3B), as is further discussed in detail hereinafter. Table 1 presents exemplary formulations for preparing a dosage form for administration of amoxicillin. Tables 2 and 3 show the gastric retention
30 times of dosage forms prepared from the formulations presented in Table 1. As shown therein, gastric retention times of over 300 hours can be obtained.

Figure 4 and Table 4 show that administration of exemplary gastroretentive oral dosage forms results in a therapeutically active agent (amoxicillin) being present in the blood at significant concentrations (e.g., above a minimum inhibitory concentration for amoxicillin) for a longer period of time (e.g., 100 hours) than for standard tablets.

5 Figure 5 shows that exemplary gastroretentive oral dosage forms gradually release a therapeutically active agent, and that the rate of the release is pH-dependent in some cases.

Thus, as exemplified in the Examples section that follows, the oral dosage forms according to embodiments of the present invention are both gastroretentive (i.e., remain
10 in the stomach for a long period of time), and are capable of releasing a therapeutically active agent for a long period of time. Hence, the dosage forms are suitable for releasing a therapeutically active agent into the stomach for a long period of time.

Without being bound by any particular theory, it is believed that sustained release of a therapeutically active agent into the stomach is advantageous in that the
15 entire length of the intestines lies after the point of release, thereby facilitating absorption of the agent by the intestines. In particular, it is believed that release into the stomach avoids the risk of missing an "absorption window" in the intestines, that is, a particular section of the intestines to which absorption is limited.

Hence, according to one aspect of embodiments of the invention, there is
20 provided a gastroretentive oral dosage form for an animal (e.g., a non-human animal) comprising a therapeutically active agent and a pharmaceutically acceptable solid carrier. The dosage form swells when in a stomach of the animal from a first size and shape to a second size and shape.

As used herein, the term "gastroretentive" refers to an object which, when
25 swallowed by an animal, remains in a stomach for a longer period of time than do other swallowed substances, such as typical food of the animal (e.g., chewed food).

Accordingly, a gastric retention time defines the time an object (or the digestion products thereof) remains in the stomach after being swallowed.

As used herein and in the art, the phrase "dosage form" describes a final physical
30 form a drug for consumption by a subject.

Examples of acceptable oral dosage forms include, but are not limited to, pills, caplets, or tablets.

Herein, the term “pharmaceutically acceptable solid carrier” refers to a solid carrier (e.g., a polymer or mixture of polymers) that does not cause significant irritation to an organism and does not abrogate the biological activity and properties of the therapeutically active agent. Examples of suitable carriers are described in detail
5 hereinafter.

Optionally, the dosage form is for an animal which is a mammal.

In some embodiments, the animal is characterized in that it is not capable of digesting cellulose. In some embodiments, the animal is characterized by a protein-based diet.

10 Optionally, the animal is a carnivore (e.g., a strict carnivore, an omnivore, an insectivore).

Examples of carnivores include felids (e.g., domestic cats, wild cats), canids (e.g., domestic dogs, foxes, wolves), mustelids (e.g., weasels, mink, martens, stoats, ferrets, polecats), hyenas, herpestids (e.g., mongoose, meerkats), procyonids (e.g.,
15 raccoons, ringtails), genets, civets, bears, pinnipeds (e.g., seals, sea lions), hedgehogs, and skunks.

Carnivores typically have small intestines (typically 3-6 times the length of the torso) which are comparatively shorter than the small intestines of herbivores (typically at least about 10 times the length of the torso), and shorter mean transit times through
20 the stomach and small intestines (e.g., 6 hours or less), due to the more readily digestible nature of a carnivorous diet, and are therefore more vulnerable to “absorption windows”.

Thus, in some embodiments, the animal is characterized by a ratio between the length of the small intestine and the length of the torso that is less than 8, optionally in a range of from 2 to 6, and optionally in a range of from 3 to 6.

25 In some embodiments, the animal is characterized by a small intestinal transit time of 6 hours or less, optionally 4 hours or less, optionally 3 hours or less, and optionally 2 hours or less.

In some embodiments, the dosage form is for a domestic animal. Optionally, the dosage form is for a domestic animal that is a carnivore, for example, a cat, a dog, a
30 domesticated ferret, a domesticated mink, a domesticated hedgehog, a pet skunk, and/or a domesticated fox. Optionally, the dosage form is for a dog and/or a cat.

The first size and shape are selected suitable for the oral dosage form to be swallowed as a whole by the animal. For example, the width is selected so as not so large as to make swallowing too difficult. Optionally, the shape is relatively rounded, so as to facilitate swallowing.

5 The second size and shape (obtained following swelling of the dosage form in the stomach) are selected so as to prevent passage of the dosage form while in a stomach of the animal through the pylorus of the animal, into the intestines.

 The dosage form is preferably capable of continuously releasing a therapeutically effective amount of the therapeutically active agent over a period of at least 2 days, optionally at least 3 days, optionally at least 4 days, optionally at least 5 days, and
10 optionally at least 7 days.

 The time period during which a dosage form continuously releases a therapeutically effective amount of the therapeutically active agent may optionally be determined using the U.S. Pharmacopeia (USP) basket method I, as exemplified in the
15 Examples section herein (e.g., rotation speed 100 rotations per minute, dissolution medium 900 ml of USP buffer pH 2, at 37 °C). Alternatively, determination can be made by simply placing the dosage form in distilled water or a buffer and measuring continuously the amount of the therapeutically active agent in the solution.

 The swelling of the dosage form is such that a short axis of the second size and
20 shape is at least 50 % longer than a short axis of the first size and shape. Optionally, a short axis of the second size and shape is at least 100 % (twice) longer than a short axis of the first size and shape, optionally at least 150 % longer and optionally at least 200 % (x4) longer. Other percentage values between 20 % and 200%, or between 50 % and 200 %, and even higher, are also contemplated.

25 As used herein, the phrase "short axis" refers to an axis passing through the dosage form in a direction for which the dosage form is narrowest. Thus, the length of a short axis is defined herein as the width of the dosage form in a direction for which the dosage form is narrowest. Thus, for example, the direction for which the dosage form shown in Figures 1A and 1B is narrowest is the direction shown as horizontal in Figure
30 1B (and which is perpendicular to the plane of the figure in Figure 1A). Hence, the short axis is shown as a horizontal line in Figure 1B.

Herein, the width of the dosage form in any given direction refers to the width at the widest part of the dosage form in that direction. Thus, for example, in the direction for which the dosage form shown in Figure 1B is narrowest (i.e., the horizontal direction in Figure 1B), the dosage form is widest in the center thereof. Hence, the length of the short axis of the dosage form shown in Figure 1B equals the width of the dosage in the horizontal direction at the center of the dosage form.

Without being bound by any particular theory, it is believed that the length of the short axis is particularly relevant to the ability of a dosage form to pass through a narrow passage, such as an esophagus or a pylorus, and that a considerable increase (e.g., at least 50 %) in the length of the short axis is particularly advantageous in converting a readily swallowable dosage form (e.g., capable of passing through the esophagus) into a gastroretentive dosage form (e.g., not capable of passing through a pylorus).

Optionally, the length of the short axis before swelling is considerably shorter than a length of an axis perpendicular to the short axis, so as to facilitate swallowing.

In some embodiments, the length of a short axis (in the first size and shape) is no more than 75 % of a length of any axis perpendicular to the short axis (in the first size and shape), and optionally no more than 50 %, optionally no more than 40 %, optionally no more than 30 %, and optionally no more than 20 % of a length of any axis perpendicular to the short axis.

Herein, the length of an axis perpendicular to the short axis refers to a width of the dosage form in a direction perpendicular to the direction of the short axis, i.e., the direction for which the dosage form is narrowest.

Although the lengthening of a short axis is believed to be particularly relevant to the function of the gastroretentive dosage form, swelling of the dosage form in directions other than the direction of the short axis may optionally contribute to the advantageous properties (e.g., gastroretention) of dosage forms according to embodiments of the invention.

Hence, according to some embodiments, each axis of the second size and shape is at least 20 % longer than a corresponding axis in the first size and shape. That is, the dosage form increases in width by at least 20 % in the direction of the short axis, as well as in the directions perpendicular to the short axis. Optionally, each axis of the second size and shape is at least 30 % longer, optionally 40 % longer, optionally 50 % longer,

optionally 75 % longer, and optionally 100 % longer, than a corresponding axis in the first size and shape.

The dosage form comprises a surface at each end of the short axis, each surface being perpendicular to the short axis. The surfaces may be flat (e.g., two parallel flat surfaces) or curved (e.g., convex or concave surfaces). Optionally, the surface
5 comprises both flat and curved portions.

In some embodiments, at least one of the two surfaces which are perpendicular to the short axis is curved so as to be a convex surface. Optionally, both of the two surfaces are convex surfaces.

10 Optionally, the convex surface is such that an average width of the dosage form in the direction parallel to the short axis is less than 90 % of the length of the short axis, and optionally less than 80 %, optionally less than 70 %, and optionally less than 60 %, of the length of the short axis (as defined herein).

In some embodiments, the shape of the dosage form prior to exposure to an aqueous solution (i.e., the shape of the abovementioned first size and shape) is a
15 generally rounded shape (e.g., spheroid, ovoid, ellipsoid, oblate spheroid, prolate spheroid, cylinder).

In some embodiments, the first shape is eccentric (e.g., having an axis that is not centrally placed).

20 An exemplary eccentric shape is a kidney-like shape,

In some embodiments, the dosage form is kidney-shaped, for example, having a cross-section with a substantially concave edge and a substantially convex edge on opposite sides (e.g., as exemplified in Figures 3A and 3B). Optionally, the cross-section is perpendicular to the short axis. Optionally the kidney shape, or any other eccentric
25 shape is substantially rounded, for example, comprising no acute angles, and optionally no angles.

In some embodiments, the length of the short axis is at least 10 mm, optionally at least 15 mm, and optionally at least 20 mm.

In some embodiments, the length of the short axis is no more than 30 mm, so as
30 to facilitate swallowing by a domestic animal (e.g., a dog).

Alternatively, the length of the short axis may be more than 30 mm. Such embodiments are optionally designed suitable for exotic animals (e.g., large zoo

animals). One of skill in the art of veterinary medicine will be capable of selecting a first size and shape for a dosage form, such that the dosage form can be swallowed by a given animal.

5 The gastric retention time of the dosage form (i.e., the time the dosage form remains in the stomach) is optionally at least 2 days, optionally at least 3 days, optionally at least 5 days, and optionally at least 7 days. Higher retention times are also contemplated.

10 In some embodiments, the dosage form exits the stomach through the pylorus when the dosage form has sufficiently decreased in size so as to allow passage through the pylorus. The decrease in size may be due to any of a variety of factors, such as release (e.g., by diffusion) of the therapeutically active agent (and optionally, one or more additional components of the dosage form) out of the dosage form, biodegradation of the dosage form (e.g., via enzymatic hydrolysis of at least one polymer in the dosage form), and optionally by mechanical forces in the stomach.

15 Optionally, the gastric retention time is controlled by modulating the rate at which the dosage form decreases in size.

20 For example, a biodegradation rate may optionally be modulated according to an amount of digestible polymer included in the dosage form, whereby the biodegradation rate correlates to an amount of digestible polymer. Whether a polymer is digestible may depend on the animal in question. Thus, protein and starches are examples of digestible polymers, whereas many polysaccharides and derivatives thereof (e.g., cellulose and derivatives thereof) are digestible only for certain herbivores (e.g., ruminants).

25 In addition, a rate at which a dosage form decreases in size due to mechanical forces may optionally be modulated according to a rigidity of the dosage form, whereby a relatively high rigidity is associated with a relatively high gastric retention time.

30 The dosage form will release the therapeutically active agent into the stomach (from where the agent can be absorbed after passing into the intestines) until the end of the gastric retention time, provided that the dosage form is capable of continuously releasing a therapeutically active agent over such a period of time. However, it is to be appreciated that the time during which the therapeutically active agent is absorbed into the body may in some embodiments be longer than the gastric retention time, as absorption of the agent into the body may continue for a significant time period when

the dosage form (or the remaining portion of the dosage form) is in the intestines. The duration of the time period during which absorption occurs after the dosage form has exited the stomach will depend on various factors, such as the length of the "absorption window" and the speed at which intestinal contents pass through the intestines.

5 Optionally, the gastric retention time is at least 50 %, optionally at least 75 %, and optionally at least 90 % of the time period during which the therapeutically active agent is absorbed into the body.

 In some embodiments, the dosage form is in the intestines for about 12-36 hours after exiting the stomach. Thus, for example, for a dosage form characterized by a
10 gastric retention time of about 300 hours (as exemplified below in the Examples section), the gastric retention time represents about 90-96 % of the total time in the gastrointestinal tract.

 It is to be further appreciated that a therapeutically effective level of the agent may remain in the body after absorption has ceased. The duration of the time period
15 during which a therapeutically effective level of the agent remains in the body after absorption has ceased will depend, for example, on the half-life of the agent in the body, and the amount of the agent present in the body at around the time absorption ceased.

 In some embodiments, the therapeutically effective amount of the therapeutically active agent provides the animal with a serum concentration of the agent which is at
20 least a minimum effective concentration (MEC) of the agent.

 MEC values for various agents will be known to one of skill in the art. Preferably, the MEC value is calculated for the animal. Optionally, an MEC can be determined from an MEC value determined in another animal (e.g., humans).

 In embodiments wherein the therapeutically active agent is for inhibiting a
25 pathogen which infects the animal (e.g., an antibiotic), the therapeutically effective amount optionally provides the animal with a serum concentration of the agent which is at least a minimum inhibitory concentration (MIC) of the agent towards the pathogen, over a period of time which is at least a treatment time for treatment of with said antibiotic against said pathogen.

30 MIC values for various therapeutically active agents (e.g., antibiotics) and pathogens will be available to one of skill in the art. Optionally, a MIC value may be determined experimentally, for example, by administering different levels of a

therapeutically active agent to infected animals and monitoring the serum concentration of the agent.

As discussed herein and exemplified in the Examples section, dosage forms described herein combine both an ability to release a therapeutically effective amount of
5 a therapeutically active agent for an extended period of time (e.g., at least 2 days) with a relatively long gastric retention time (e.g., at least 2 days). Consequently, such dosage forms can provide an effective serum concentration of the agent (e.g., at least the MEC for the agent) for an extended period of time (e.g., at least 40 hours, at least 48 hours, at least 3 days, at least 5 days, at least 7 days).

10 The dosage form is optionally formed with a punch and die (e.g., mechanically operated, manually operated). For example, a dosage form with a convex surface is optionally formed with a punch and/or die having a concave surface, as exemplified in the Examples section herein.

15 In some embodiments, the solid pharmaceutically acceptable carrier in the dosage form is selected so as to affect the gastroretentive features of the dosage form as described herein.

In some embodiments, the solid carrier comprises one or more polymers that together with the therapeutically active agent impart to the dosage form the desired gastroretentive features as described herein.

20 In some embodiments, the one or more polymers are biocompatible polymers.

According to optional embodiments, the solid carrier comprises at least a first polymer and a second polymer selected such that the first polymer swells upon contact with an aqueous solution to an extent larger than the second polymer. Optionally, a first polymer in the carrier swells upon contact with an aqueous solution by at least 100 % (in
25 diameter). Optionally, the first polymer swells by at least 150 %, and optionally, by at least 200 %. Any other percentage value higher than 100 % is also contemplated.

Optionally, a second polymer in the carrier swells upon contact with an aqueous solution by up to 100 % (in diameter). Optionally, the second polymer swells by up to 75 %, optionally by up to 50 %, optionally by up to 25 %, and optionally by 10 %. Any
30 other percentage value lower than 100 % is also contemplated.

Optionally, the second polymer does not swell at all upon contact with an aqueous solution.

The degree to which a polymer swells in diameter is optionally determined by immersing a spherical sample of the polymer in an aqueous solution, and measuring the increase in diameter of the spherical sample upon water absorption. The diameter of the spherical sample prior to immersion is optionally in a range of 0.5 to 4 cm (e.g., 1.2 cm).

5 Optionally, the immersion is performed in distilled water at 23 °C for 24 hours or until water absorption essentially ceases (in accordance with the ISO 62 test standards). Alternatively, a temperature of 37 °C and U.S. Pharmacopeia (USP) buffer with a pH of 2 are used instead, in order to mimic conditions in the stomach.

10 Alternatively or additionally, the degree to which a polymer swells is optionally determined for the polymer in the dosage form. Thus, a dosage form is immersed as described hereinabove, and then separated into its different components, for example, by separating grains of a polymer from grains of other components (e.g., other polymer(s) and/or therapeutically active agent). Polymer grains before immersion are then compared to polymer grains after immersion, in order to determine the increase in
15 diameter of the grains caused by swelling of the grains, and thus, the swelling of the polymer.

The dosage form is preferably sufficiently swellable so as to swell in the stomach to a degree described hereinabove. The dosage form is further preferably sufficiently rigid (e.g., resistant to mechanical forces in the stomach) and insoluble (e.g., in the
20 stomach) so as to retain a size and shape while in the stomach of the animal which prevents passage through the pylorus for at least a time period described herein.

The rigidity of the dosage form and/or polymers in the dosage form is optionally determined using a texture analyzer. A texture analyzer may penetrate a probe (e.g., 2-mm diameter probe) into a sample (e.g., dosage form or individual polymer) at a
25 selected speed (e.g., 0.5 mm/second) while measuring the applied force, until a given force is reached (e.g., 10 newtons). The rigidity can then be quantified as the total work of penetration, which equals the area under the curve of force as a function of penetration depth (units are of force x distance, e.g., newtons·mm). In some embodiments, the rigidity is determined for a sample which has been immersed in an
30 aqueous solution (e.g., water, USP buffer) as described herein.

In some embodiments, a rigidity of the dosage form (subsequent to immersion) is in a range of from 4 to 9 newtons·mm.

In some embodiments, a rigidity of the second polymer (subsequent to immersion) is in a range of from 6 to 9 newtons·mm.

As the first polymer absorbs considerably amounts of water, a rigidity of the first polymer subsequent to immersion may be relatively low, for example, less than 1
5 newton·mm, and optionally in a range of from 0.5 to 0.8 newtons·mm.

In some embodiments, the first polymer enhances the ability of the dosage form to swell, such that the dosage form can swell to a degree described herein, while the second polymer provides a rigidity to the dosage form, such that the dosage form retains a size and shape which prevents passage through the pylorus.

10 It is to be understood that the phrases “first polymer” and “second polymer” may each independently refer to a plurality of polymers, wherein each polymer of the plurality of polymers exhibits characteristics of the first polymer or second polymer, as described herein.

Optionally, the first polymer is selected from the group consisting of
15 polycarbophil, carboxymethyl cellulose, cross-linked carboxymethyl cellulose (e.g., croscarmellose), tragacanth gum, pectins, pectinate salts, and alginic acid and salts thereof, and optionally from the group consisting of polycarbophil, carboxymethyl cellulose, and tragacanth gum.

Optionally, the second polymer is selected from the group consisting of
20 hydroxypropyl methyl cellulose, ethyl cellulose, methyl cellulose, cellulose (e.g., microcrystalline cellulose), hydroxyethyl cellulose, hydroxypropyl cellulose, crospovidone, proteins (e.g., zein, egg albumin, serum albumin, casein and gelatin), guar gum, cross-linked guar gum, locust bean gum, carrageenans (e.g., kappa and iota carrageenans), starch, and dextrans, and optionally from the group consisting of
25 hydroxypropyl methyl cellulose, methyl cellulose and ethyl cellulose.

Polymers which may be incorporated into the dosage form described herein include polysaccharides and non-polysaccharides. Suitable polysaccharides include cellulosic and non-cellulosic polysaccharides.

Examples of suitable cellulosic polysaccharides include, without limitation,
30 cellulose (e.g., microcrystalline cellulose), methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, carboxymethyl cellulose, and cross-linked carboxymethyl cellulose.

Examples of suitable non-cellulosic polysaccharides include, without limitation, starches (e.g., microcrystalline starch), dextrans, pectins, pectinate salts (e.g., calcium pectinate), alginic acid and salts thereof (e.g., calcium alginate, sodium alginate), guar gum, cross-linked guar gum, xanthan gum, locust bean gum, tragacanth gum, and
5 carrageenans (e.g., kappa, iota and lambda carrageenans).

Examples of suitable non-polysaccharide polymers include proteins (e.g., zein, egg albumin, serum albumins such as bovine serum albumin, casein and gelatin), polyvinyl alcohol, polyethylene glycol, polyvinylpyrrolidone, crospovidone, and copolymers thereof.

10 Optionally, the first and/or second polymers are selected so as not to be digestible in a stomach of the animal.

In some embodiments, the carrier further includes a polymer which enhances dissolution and release of the therapeutically active agent. Optionally, the polymer which enhances dissolution is water-soluble. In exemplary embodiments, the polymer
15 which enhances dissolution is polyethylene glycol (e.g., polyethylene glycol having a molecular weight in a range of 300-10,000 Da). Optionally, a polymer which enhances dissolution is included so as to increase the percentage of therapeutically active agent which is released from the dosage form in the stomach of the animal, as opposed, for example, to the intestines of the animal.

20 In some embodiments, the solid carrier further comprises thickeners, diluents, flavorings, dispersing aids, emulsifiers or binders. The additional ingredients (e.g., the aforementioned ingredients) should not result in the dosage form having substantially different performance than as described herein.

In some embodiments, the solid carrier consists of the polymers as described
25 herein.

The dosage form may comprise any therapeutically active agent which is suitable for oral administration to the animal.

Optionally, the therapeutically active agent is characterized as being absorbed in a gastrointestinal tract of the animal primarily (e.g., by more than 50 %) by active
30 transport, rather than by passive diffusion. As discussed hereinabove, absorption of such drugs is confined to the small intestine, and therefore limited absorption to a relatively narrow "absorption window" is more likely.

Optionally, the therapeutically active agent is hydrophilic, being characterized, for example, by a water-solubility of at least 1 weight percent (e.g., in solution at pH 7). Optionally, the water-solubility is tested in phosphate buffered saline at pH 7.

Alternatively or additionally, a hydrophilic agent is characterized by an inability
5 to undergo absorption in the gastrointestinal tract of the animal by passive diffusion across an intestinal wall. Optionally, less than 50 % of the agent undergoes passive diffusion, optionally less than 10 %, and optionally less than 1 %.

In some embodiments, the therapeutically active agent is an antibiotic (e.g., a beta-lactam antibiotic).

10 Non-limiting examples of antimicrobial and antibiotic agents that are suitable for use in this context of the present invention include, without limitation, mandelic acid, 2,4-dichlorobenzenemethanol, 4-[bis(ethylthio)methyl]-2-methoxyphenol, 4-epi-tetracycline, 4-hexylresorcinol, 5,12-dihydro-5,7,12,14-tetrazapentacen, 5-chlorocarvacrol, 8-hydroxyquinoline, acetarsol, acetylkidasamycin, acriflavin,
15 alatrofloxacin, ambazon, amfomycin, amikacin, amikacin sulfate, aminoacridine, aminosalicylate calcium, aminosalicylate sodium, aminosalicylic acid, ammoniumsulfobituminat, amorolfen, amoxicillin, amoxicillin sodium, amoxicillin trihydrate, amoxicillin-potassium clavulanate combination, amphotericin B, ampicillin, ampicillin sodium, ampicillin trihydrate, ampicillin-sulbactam, apalcillin, arbekacin,
20 asproxillin, astromicin, astromicin sulfate, azanidazole, azidamfenicol, azidocillin, azithromycin, azlocillin, aztreonam, bacampicillin, bacitracin, bacitracin zinc, bekanamycin, benzalkonium, benzethonium chloride, benzoxonium chloride, berberine hydrochloride, biapenem, bibrocathol, biclotymol, bifonazole, bismuth subsalicylate, bleomycin antibiotic complex, bleomycin hydrochloride, bleomycin sulfate,
25 brodimoprim, bromochlorosalicylanilide, bronopol, broxyquinolin, butenafine, butenafine hydrochloride, butoconazol, calcium undecylenate, candididin antibiotic complex, capreomycin, carbenicillin, carbenicillin disodium, carfecillin, carindacillin, carumonam, carzinophilin, caspofungin acetate, cefacetril, cefaclor, cefadroxil, cefalexin, cefalexin hydrochloride, cefalexin sodium, cefaloglycin, cefaloridine,
30 cefalotin, cefalotin sodium, cefamandole, cefamandole nafate, cefamandole sodium, cefapirin, cefapirin sodium, cefatrizine, cefatrizine propylene glycol, cefazedone, cefazedone sodium salt, cefazolin, cefazolin sodium, cefbuperazone, cefbuperazone

sodium, cefcapene, cefcapene pivoxil hydrochloride, cefdinir, cefditoren, cefditoren
pivoxil, cefepime, cefepime hydrochloride, cefetamet, cefetamet pivoxil, cefixime,
cefmenoxime, cefmetazole, cefmetazole sodium, cefminox, cefminox sodium,
cfmolexin, cfodizime, cfodizime sodium, cfonicid, cfonicid sodium, cfoperazone,
5 cfoperazone sodium, ceforanide, cfoselis sulfate, cfotaxime, cfotaxime sodium,
cfotetan, cfotetan disodium, cfotiam, cfotiam hexetil hydrochloride, cfotiam
hydrochloride, cffoxitin, cffoxitin sodium, cfzopran hydrochloride, cfpiramide,
cfpiramide sodium, cfpirome, cfpirome sulfate, cfpodoxime, cfpodoxime proxetil,
cfprozil, cfquinome, cfradine, cfroxadine, cfsulodin, ceftazidime, cefteram,
10 cefteram pivoxil, ceftezole, ceftibuten, ceftizoxime, ceftizoxime sodium, ceftriaxone,
ceftriaxone sodium, cfuroxime, cfuroxime axetil, cfuroxime sodium, cetalkonium
chloride, cetrimide, cetrimonium, cetylpyridinium, chloramine T, chloramphenicol,
chloramphenicol palmitate, chloramphenicol succinate sodium, chlorhexidine,
chlormidazole, chlormidazole hydrochloride, chloroxylenol, chlorphenesin,
15 chlorquinaldol, chlortetracycline, chlortetracycline hydrochloride, ciclacillin, ciclopirox,
cinoxacin, ciprofloxacin, ciprofloxacin hydrochloride, citric acid, clarithromycin,
clavulanate potassium, clavulanate sodium, clavulanic acid, clindamycin, clindamycin
hydrochloride, clindamycin palmitate hydrochloride, clindamycin phosphate,
clioquinol, cloconazole, cloconazole monohydrochloride, clofazimine, clofoctol,
20 clometocillin, clomocycline, clotrimazol, cloxacillin, cloxacillin sodium, colistin,
colistin sodium methanesulfonate, colistin sulfate, cycloserine, dactinomycin,
danofloxacin, dapson e, daptomycin, daunorubicin, DDT, demeclocycline,
demeclocycline hydrochloride, dequalinium, dibekacin, dibekacin sulfate,
dibrompropamidine, dichlorophene, dicloxacillin, dicloxacillin sodium,
25 didcyldimethylammonium chloride, dihydrostreptomycin, dihydrostreptomycin sulfate,
diiodohydroxyquinolin, dimetridazole, dipyrithione, dirithromycin, DL-menthol, D-
menthol, dodecyltriphenylphosphonium bromide, doxorubicin, doxorubicin
hydrochloride, doxycycline, doxycycline hydrochloride, econazole, econazole nitrate,
enilconazole, enoxacin, enrofloxacin, eosine, epicillin, ertapenem sodium,
30 erythromycin, erythromycin estolate, erythromycin ethyl succinate, erythromycin
lactobionate, erythromycin stearate, ethacridine, ethacridine lactate, ethambutol,
ethanoic acid, ethionamide, ethyl alcohol, eugenol, exalamide, faropenem,

fenticonazole, fenticonazole nitrate, fezatione, fleroxacin, flomoxef, flomoxef sodium, florfenicol, flucloxacillin, flucloxacillin magnesium, flucloxacillin sodium, fluconazole, flucytosine, flumequine, flurithromycin, flutrimazole, fosfomycin, fosfomycin calcium, fosfomycin sodium, framycetin, framycetin sulphate, furagin, furazolidone, fusafungin, fusidic acid, fusidic acid sodium salt, gatifloxacin, gemifloxacin, gentamicin antibiotic complex, gentamicin c1a, gentamicin sulfate, glutaraldehyde, gramicidin, grepafloxacin, griseofulvin, halazon, haloprogine, hetacillin, hetacillin potassium, hexachlorophene, hexamidine, hexetidine, hydrargaphene, hydroquinone, hygromycin, imipenem, isepamicin, isepamicin sulfate, isoconazole, isoconazole nitrate, isoniazid, isopropanol, itraconazole, josamycin, josamycin propionate, kanamycin, kanamycin sulphate, ketoconazole, kitasamycin, lactic acid, lanoconazole, lenampicillin, leucomycin A1, leucomycin A13, leucomycin A4, leucomycin A5, leucomycin A6, leucomycin A7, leucomycin A8, leucomycin A9, levofloxacin, lincomycin, lincomycin hydrochloride, linezolid, liranafate, l-menthol, lomefloxacin, lomefloxacin hydrochloride, loracarbef, lymecyclin, lysozyme, mafenide acetate, magnesium monoperoxophthalate hexahydrate, mecetronium ethylsulfate, mecillinam, meclocycline, meclocycline sulfosalicylate, mepartricin, merbromin, meropenem, metalkonium chloride, metampicillin, methacycline, methenamin, methyl salicylate, methylbenzethonium chloride, methylrosanilinium chloride, meticillin, meticillin sodium, metronidazole, metronidazole benzoate, mezlocillin, mezlocillin sodium, miconazole, miconazole nitrate, micronomicin, micronomicin sulfate, midecamycin, minocycline, minocycline hydrochloride, miocamycin, miristalkonium chloride, mitomycin c, monensin, monensin sodium, morinamide, moxalactam, moxalactam disodium, moxifloxacin, mupirocin, mupirocin calcium, nadifloxacin, nafcillin, nafcillin sodium, naftifine, nalidixic acid, natamycin, neomycin a, neomycin antibiotic complex, neomycin C, neomycin sulfate, neticonazole, netilmicin, netilmicin sulfate, nifuratel, nifuroxazide, nifurtoinol, nifurzide, nimorazole, niridazole, nitrofurantoin, nitrofurazone, nitroxolin, norfloxacin, novobiocin, nystatin antibiotic complex, octenidine, ofloxacin, oleandomycin, omoconazol, orbifloxacin, ornidazole, ortho-phenylphenol, oxacillin, oxacillin sodium, oxiconazole, oxiconazole nitrate, oxoferin, oxolinic acid, oxychlorosene, oxytetracycline, oxytetracycline calcium, oxytetracycline hydrochloride, panipenem, paromomycin, paromomycin sulfate, pazufloxacin,

pefloxacin, pefloxacin mesylate, penamecillin, penicillin G, penicillin G potassium, penicillin G sodium, penicillin V, penicillin V calcium, penicillin V potassium, pentamidine, pentamidine diisetonate, pentamidine mesilas, pentamycin, phenethicillin, phenol, phenoxyethanol, phenylmercuriborat, PHMB, phthalylsulfathiazole, picloxydin,
5 pipemidic acid, piperacillin, piperacillin sodium, piperacillin sodium - tazobactam sodium, piromidic acid, pivampicillin, pivcefalexin, pivmecillinam, pivmecillinam hydrochloride, policresulen, polymyxin antibiotic complex, polymyxin B, polymyxin B sulfate, polymyxin B1, polynoxilin, povidone-iodine, propamidin, propenidazole, propicillin, propicillin potassium, propionic acid, prothionamide, protiofate,
10 pyrazinamide, pyrimethamine, pyrithion, pyrrolnitrin, quinoline, quinupristin-dalfopristin, resorcinol, ribostamycin, ribostamycin sulfate, rifabutin, rifampicin, rifamycin, rifapentine, rifaximin, ritiometan, rokitamycin, rolitetracycline, rosoxacin, roxithromycin, rifloxacin, salicylic acid, secnidazol, selenium disulphide, sertaconazole, sertaconazole nitrate, siccanin, sisomicin, sisomicin sulfate, sodium
15 thiosulfate, sparfloxacin, spectinomycin, spectinomycin hydrochloride, spiramycin antibiotic complex, spiramycin b, streptomycin, streptomycin sulphate, succinylsulfathiazole, sulbactam, sulbactam sodium, sulbenicillin disodium, sulbentin, sulconazole, sulconazole nitrate, sulfabenzamide, sulfacarbamide, sulfacetamide, sulfacetamide sodium, sulfachlorpyridazine, sulfadiazine, sulfadiazine silver,
20 sulfadiazine sodium, sulfadicramide, sulfadimethoxine, sulfadoxine, sulfaguanidine, sulfalene, sulfamazone, sulfamerazine, sulfamethazine, sulfamethazine sodium, sulfamethizole, sulfamethoxazole, sulfamethoxazol-trimethoprim, sulfamethoxypyridazine, sulfamonomethoxine, sulfamoxol, sulfanilamide, sulfaperine, sulfaphenazol, sulfapyridine, sulfaquinoxaline, sulfasuccinamide, sulfathiazole,
25 sulfathiourea, sulfatolamide, sulfatriazin, sulfisomidine, sulfisoxazole, sulfisoxazole acetyl, sulfonamides, sultamicillin, sultamicillin tosilate, tacrolimus, talampicillin hydrochloride, teicoplanin A2 complex, teicoplanin A2-1, teicoplanin A2-2, teicoplanin A2-3, teicoplanin A2-4, teicoplanin A2-5, teicoplanin A3, teicoplanin antibiotic complex, telithromycin, temafloxacin, temocillin, tenoic acid, terbinafine, terconazole,
30 terizidone, tetracycline, tetracycline hydrochloride, tetracycline metaphosphate, tetramethylthiuram monosulfide, tetroxoprim, thiabendazole, thiamphenicol, thiaphenicol glycinate hydrochloride, thiomersal, thiram, thymol, tibeonium iodide,

ticarcillin, ticarcillin - clavulanic acid mixture, ticarcillin disodium, ticarcillin monosodium, tilbroquinol, tilmicosin, tinidazole, tioconazole, tobramycin, tobramycin sulfate, tolclate, tolindate, tolnaftate, toloconium metilsulfat, toltrazuril, tosufloxacin, triclocarban, triclosan, trimethoprim, trimethoprim sulfate, triphenylstibinsulfide, troleandomycin, trovafloxacin, tylosin, tyrothricin, undecoylium chloride, undecylenic acid, vancomycin, vancomycin hydrochloride, viomycin, virginiamycin antibiotic complex, voriconazol, xantocillin, xibornol and zinc undecylenate.

Non-limiting examples of beta lactam antibiotic agents include, for example, benzathine penicillin, benzylpenicillin, phenoxymethylpenicillin, procaine penicillin, methicillin, oxacillin, nafcillin, cloxacillin, dicloxacillin, flucloxacillin, temocillin, amoxicillin, ampicillin, azlocillin, carbenicillin, ticarcillin, mezlocillin, piperacillin, cephalexin, cephalothin, cefazolin, cefaclor, cefuroxime, cefamandole, cefotetan, cefoxitin, ceftriaxone, cefpodoxime, ceftazidime, cefepime, cefpirome, imipenem (optionally with cilastatin), meropenem, ertapenem, faropenem, doripenem, aztreonam, tigemonam, nocardicin A, tabtoxinine beta-lactam.

Optionally, the dosage form further comprises a beta-lactamase inhibitor (e.g., clavulanic acid, tazobactam, sulbactam), in order to inhibit enzymatic degradation of the beta-lactam agent.

Diseases which are caused by bacterial infections and may be treated with one or more antibiotic agents include, for example, actinomycosis, anthrax, bacteremia, bacterial skin diseases, bartonella infections, botulism, brucellosis, burkholderia infections, campylobacter infections, candidiasis, cat-scratch disease, chlamydia infections, cholera, clostridium infections, coccidioidomycosis, cryptococcosis, dermatomycoses, diphtheria, ehrlichiosis, epidemic louse borne typhus, *Escherichia coli* infections, fusobacterium infections, gangrene, general infections, general mycoses, gonorrhea, gram-negative bacterial infections, gram-positive bacterial infections, histoplasmosis, impetigo, kennel cough, klebsiella infections, legionellosis, leprosy, leptospirosis, listeria infections, Lyme disease, malaria, maduromycosis, melioidosis, mycobacterium infections, mycoplasma infections, necrotizing fasciitis, nocardia infections, onychomycosis, ornithosis, pneumococcal infections, pneumonia, pseudomonas infections, Q fever, rat-bite fever, relapsing fever, rheumatic fever, rickettsia infections, Rocky-mountain spotted fever, salmonella infections, scarlet fever,

scrub typhus, sepsis, sexually transmitted bacterial diseases, staphylococcal infections, streptococcal infections, surgical site infection, tetanus, tick-borne diseases, tuberculosis, tularemia, typhoid fever, urinary tract infection, vibrio infections, yaws, yersinia infections, Yersinia pestis plague, zoonoses and zygomycosis.

5 Diseases which are caused by fungal infections and may be treated with one or more anti-fungal therapeutically active agents include, for example, aspergillosis, blastomycosis, coccidiomycosis, cryptococcosis, histoplasmosis, mucormycosis, pythiosis, ringworm, and sporotrichosis.

10 Non-limiting examples of antifungal agents that are suitable for use in this context of the present invention include, without limitation, amphotericin B, caspofungin, fluconazole, flycytosine, itraconazole, ketoconazole, posaconazole, terbinafine, and voriconazole.

15 Diseases which are caused by protozoa and may be treated with one or more anti-protozoal therapeutically active agents include, for example, babesiosis, coccidiosis, giardiasis, leishmaniasis, neosporosis and toxoplasmosis.

20 Non-limiting examples of anti-protozoal agents that are suitable for use in this context of the present invention include, without limitation, albendazole, amphotericin, atovaquone, azithromycin, clindamycin, diminazen, furazolidone, imidocarb, mebendazole, metronidazole, miltefosine, niazoxanide, paromomycin, pentavalent antimonials (e.g., meglumine antimoniate, sodium stibogluconate), pyrimethamine, quinacrine, quinine, spiramycin, sulfonamides (e.g., sulfadiazine), tinidazole, trypan blue, and zoalene.

25 Parasite infestations which may be treated with one or more therapeutically active agents in a dosage form described herein include, for example, hookworm infestations, tapeworm infestations, and roundworm infestations (e.g., trichinosis, heartworm infestations).

30 Non-limiting examples of anti-parasitic agents (e.g., anti-helminthic agents) that are suitable for use in this context of the present invention include, without limitation, abamectin, albendazole, diethylcarbamazine, emodepside, flubendazole, fenbendazole, ivermectin, levamisole, mebendazole, melarsomine, milbemycin, monepantel, moxidectin, niclosamide, praziquantel, pyrantel pamoate, suramin, thiabendazole, thiacetarsamide, and triclabendazole.

As discussed herein, the gastroretentive dosage forms described herein are particularly suitable for delivering an active agent to the stomach.

Hence in some embodiments, the therapeutically active agent is an agent for acting on or in the stomach.

5 Non-limiting examples of suitable therapeutically active agents for acting on or in the stomach include, without limitation, H₂-receptor antagonists (e.g., cimetidine, ranitidine), proton pump inhibitors (e.g., omeprazole, lansoprazole, dexlansoprazole, esomeprazole, pantoprazole, rabeprazole), anti-inflammatory agents (steroidal and non-steroidal) and antibiotics (e.g., as described herein).

10 Non-limiting examples of disorders treatable by action of a therapeutically active agent on or in a stomach include, for example, gastritis, gastric ulcers, heartburn, reflux, and infections (e.g., *H. pylori* infections).

 Further non-limiting examples of therapeutically active agents that are suitable for use in this context of the present embodiments include, without limitation, beta
15 blockers (e.g., metoprolol, atenolol, bisoprolol, propranolol) and calcium channel blockers (e.g., verapamil), which may be used to treat cardiomyopathy (e.g., feline hypertrophic cardiomyopathy); anti-diabetic agents (e.g., glipizide); anti-epileptic agents; anti-depressant agents; antihypertensive agents; and analgesics and anti-inflammatory agents (e.g., non-steroidal anti-inflammatory drugs, COX-2 inhibitors,
20 glucocorticosteroids, opioid analgesics), which may be used to treat a variety of painful and/or inflammatory disorders (e.g., arthritis, hip or elbow dysplasia, panosteitis, back pain, myositis, spondylosis, asthma), anti-Parkinsonian agents, and any other therapeutically active agent useful in the treatment of a medical condition, as described hereinbelow.

25 According to some embodiments, the dosage form is packaged in a packaging material and identified in print, in or on said packaging material, for use in a treatment of a medical condition in the animal.

 Gastroretentive dosage forms described herein are advantageous, for example, for treating a medical condition which is treatable by exposure to the therapeutically
30 active agent for an extended period of time (e.g., at least 2 days, at least 3 days, at least 5 days, at least 7 days, at least 10 days).

In some embodiments, the medical condition which is treatable by exposure to the therapeutically active agent for a period of time which is considerably longer (e.g., 3 times as long, 10 times as long, 30 times as long) than a serum half-life of the therapeutically active agent in the animal.

5 Herein, a medical condition is considered treatable by exposure to the therapeutically active agent for a given period of time, when exposure must be for at least the given period of time in order for a successful treatment (and/or optimal treatment) to be reliably expected. Such periods of time can be determined by one of ordinary skill in the art for a given medical agent and a given therapeutically active agent.

10 It is to be appreciated that treatment of such medical conditions typically requires multiple administrations of a dosage form when standard dosage forms are used, particularly when a serum half-life of the therapeutically active agent is considerably shorter than the necessary time of exposure to the agent. In contrast, gastroretentive dosage forms described herein are capable of providing exposure to the therapeutically active agent for an extended period of time from a reduced number of administrations, and even from a single administration.

15 Hence, according to another aspect of embodiments of the present invention, there is provided a method of treating a medical condition in an animal subject (e.g., a non-human animal, such as animals described herein), the method comprising orally administering a gastroretentive dosage form described herein to the animal subject, wherein the medical condition is treatable by exposure to the therapeutically active agent for at least 2 days (e.g., a medical condition described herein).

20 In some embodiments, the medical condition to be treated is chronic (e.g., cancers, mental disorders, Parkinson's disease, arthritis, chronic infections and/or parasite infestations), such that treatment of the medical condition is by exposure to the therapeutically active agent for at least 1 month, optionally at least one year, and optionally for a lifetime.

25 The method may optionally be effected by a single administration of a dosage form described herein, for example, when the medical condition is treatable by exposure to the therapeutically active agent for a period of time which is equal to, or shorter than, a period of time for which the dosage form provides a serum concentration of the

therapeutically active agent at a level of at least a minimum effective concentration (MEC) of the agent.

Alternatively, the method may be effected by a plurality of administrations of a dosage form described herein, for example, when the medical condition is treatable by exposure to the therapeutically active agent for a period of time which is longer than a period of time for which the dosage form provides a serum concentration of the therapeutically active agent at a level of at least a MEC of the agent. Such medical conditions include, for example, chronic medical conditions (e.g., as described herein), but are not limited to chronic medical conditions.

In embodiments wherein the method is effected by a plurality of administrations, the intervals between administrations may optionally be determined according the period of time for which the dosage form provides a serum concentration of the therapeutically active agent at a level of at least a minimum effective concentration of the agent.

Thus, the intervals between administrations may be equal to, or shorter than, the period of time for which the serum concentration is above a MEC of the agent, such that the serum concentration is constantly above the MEC.

Alternatively, the intervals between administrations are determined such that the serum concentration is above the MEC for at least a predetermined percentage of time (e.g., at least 10 % of the time, optionally at least 25 %, optionally at least 50 %, optionally at least 75 %).

In some embodiments, the intervals between administrations are determined such that the serum concentration is above the MEC for no more than a predetermined percentage of time (e.g., no more than 75 % of the time, optionally no more than 50 %, optionally no more than 25 %). Such a time intervals may be selected, for example, in order to avoid administering a dosage form more often than is necessary.

Optionally, the time intervals between administrations are in a range of from 2 to 4 times the period of time for which the serum concentration is above a MEC of the agent, such that the serum concentration will be above the MEC 25-50 % of the time during the treatment.

Optionally, the times of administration of the dosage form are determined as described hereinabove, but calculated based on a minimal desired level of the agent

other than a MEC (e.g., 2 x MEC, 4 x MEC, a minimum inhibitory concentration towards a pathogen, 4 times a minimum inhibitory concentration).

In some embodiments, the plurality of administrations are at intervals of at least 2 days, optionally at least 3 days, optionally at least 5 days, optionally at least 7 days, and optionally at least 14 days.

According to optional embodiments, the medical condition is associated with a pathogen (e.g., a prokaryotic pathogen, a eubacterium, an archaeobacterium, a eukaryotic pathogen, a yeast, a fungus, an alga, a protozoon, a parasite). Thus, the therapeutically active agent may be an agent selected to kill and/or inhibit growth of the pathogen (e.g., an antibiotic, an antiviral agent, an antifungal agent, an antiprotozoal agent, an antihelminthic agent, an insecticide), as delineated hereinabove.

Optionally, a medical condition associated with a pathogen is treated with an administration of a single dosage form, which maintains a sufficiently high level of the therapeutically active agent (e.g., a minimum inhibitory concentration (MIC), 2 x MIC, 4 x MIC) in the body (e.g., in serum) for a period of time long enough to treat the medical condition (e.g., eliminate the pathogen).

According to another aspect of the present invention, there is provided a formulation comprising a therapeutically active agent (e.g., as described herein) and a pharmaceutically acceptable solid carrier which comprises a first polymer (as described herein) and a second polymer (as described herein).

Optionally, the first polymer swells upon contact with an aqueous solution by at least 100 % and the second polymer swells upon contact with an aqueous solution by up to 100 %, as described herein.

As described hereinabove, such formulations are useful in the manufacture of gastroretentive oral dosage forms, e.g., dosage forms for an animal.

Hence, the formulation is optionally identified for use in the manufacture of a gastroretentive oral dosage form described herein, for example, a dosage form which swells when in a stomach of an animal from a first size and shape to a second size and shape, the dosage form being capable of continuously releasing a therapeutically effective amount of the therapeutically active agent over a period of at least 2 days. Optionally, a short axis of the second size and shape is at least 50 % longer than a short axis of the first size and shape, the first size and shape are selected suitable for the oral

dosage form to be swallowed as a whole by the animal, and the second size and shape are selected so as to prevent passage of the dosage form while in a stomach of the animal through the pylorus of the animal.

According to another aspect of the present invention, there is provided a use of a formulation described herein in the manufacture of a gastroretentive dosage form described herein.

As exemplified in the Examples section below, gastroretentive oral dosage forms may optionally be formed from a formulation using a punch and die.

Hence, according to another aspect of the present invention, there is provided a process for forming a gastroretentive oral dosage form (e.g., as described herein), the process comprising providing a formulation (e.g., as described herein) comprising a therapeutically active agent and a pharmaceutically acceptable solid carrier, and using a punch and die to shape the formulation into the dosage form (e.g., a dosage form having a first size and shape described herein).

According to optional embodiments, the dosage form is characterized by a short axis (as described herein), and the punch is applied in a direction of the short axis.

Optionally, the punch and/or the die are characterized by a concave surface, such that at least one of the two surfaces of the dosage form which are formed by the punch and die (e.g., the surfaces which are perpendicular to the short axis) is a convex surface. Optionally, both the punch and die are characterized by a concave surface, and the resulting dosage form therefore comprises two corresponding convex surfaces (e.g., convex surfaces described herein).

Techniques for formulation and administration of drugs may be found in "Remington's Pharmaceutical Sciences" Mack Publishing Co., Easton, PA, latest edition, which is incorporated herein by reference.

Dosage forms of the present invention may, if desired, be presented in a pack or dispenser device, such as an FDA (the U.S. Food and Drug Administration) approved kit, which may contain one or more unit dosage forms described herein. The pack may, for example, comprise metal or plastic foil, such as, but not limited to a blister pack. The pack or dispenser device may be accompanied by instructions for administration. The pack or dispenser may also be accompanied by a notice associated with the container in a form prescribed by a governmental agency regulating the manufacture,

use or sale of pharmaceuticals for humans and/or for non-human animals, which notice is reflective of approval by the agency of the form of the compositions for human or veterinary administration. Such notice, for example, may be of labeling approved by the U.S. Food and Drug Administration for a dosage form such as described herein or of
5 an approved product insert. Dosage forms described herein may also be prepared, placed in an appropriate container, and labeled for treatment of a medical condition (as described herein), and optionally for a recommended dosage regimen (e.g., reflecting the exhibited gastroretentive effect).

It is expected that during the life of a patent maturing from this application many
10 relevant therapeutically active agents will be developed and the scope of the term "therapeutically active agent" is intended to include all such new agents *a priori*.

The terms "comprises", "comprising", "includes", "including", "having" and their conjugates mean "including but not limited to".

The term "consisting of" means "including and limited to".

15 The term "consisting essentially of" means that the composition, method or structure may include additional ingredients, steps and/or parts, but only if the additional ingredients, steps and/or parts do not materially alter the basic and novel characteristics of the claimed composition, method or structure.

The word "exemplary" is used herein to mean "serving as an example, instance or
20 illustration". Any embodiment described as "exemplary" is not necessarily to be construed as preferred or advantageous over other embodiments and/or to exclude the incorporation of features from other embodiments.

The word "optionally" is used herein to mean "is provided in some embodiments and not provided in other embodiments". Any particular embodiment of the invention
25 may include a plurality of "optional" features unless such features conflict.

As used herein, the singular form "a", "an" and "the" include plural references unless the context clearly dictates otherwise. For example, the term "a compound" or "at least one compound" may include a plurality of compounds, including mixtures thereof.

30 Throughout this application, various embodiments of this invention may be presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible

limitation on the scope of the invention. Accordingly, the description of a range should be considered to have specifically disclosed all the possible subranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed subranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 3, 4, 5, and 6. This applies regardless of the breadth of the range.

Whenever a numerical range is indicated herein, it is meant to include any cited numeral (fractional or integral) within the indicated range. The phrases "ranging/ranges between" a first indicate number and a second indicate number and "ranging/ranges from" a first indicate number "to" a second indicate number are used herein interchangeably and are meant to include the first and second indicated numbers and all the fractional and integral numerals therebetween.

As used herein the term "method" refers to manners, means, techniques and procedures for accomplishing a given task including, but not limited to, those manners, means, techniques and procedures either known to, or readily developed from known manners, means, techniques and procedures by practitioners of the chemical, pharmacological, biological, biochemical and medical arts.

As used herein, the term "treating" includes abrogating, substantially inhibiting, slowing or reversing the progression of a condition, substantially ameliorating clinical or aesthetical symptoms of a condition or substantially preventing the appearance of clinical or aesthetical symptoms of a condition.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination or as suitable in any other described embodiment of the invention. Certain features described in the context of various embodiments are not to be considered essential features of those embodiments, unless the embodiment is inoperative without those elements.

Various embodiments and aspects of the present invention as delineated hereinabove and as claimed in the claims section below find experimental support in the following examples.

5

EXAMPLES

Reference is now made to the following examples, which together with the above descriptions illustrate some embodiments of the invention in a non-limiting fashion.

MATERIALS AND METHODS

10

Materials:

Ethyl cellulose was obtained from Dow Chemical Co.;

Hydroxypropyl methyl cellulose (HPMC) (Methocel™ K100M) was obtained from Colorcon;

Polycarbophil (Noveon®) was obtained from BF Goodrich;

15

Polyethylene glycol 400 (PEG400) was obtained from J.T. Baker.

In vitro dissolution assay:

20

Dissolution rates of tablets were monitored using a tablet dissolution tester (Caleva), according to the U.S. Pharmacopeia (USP) basket method I. Rotation speed was 100 rotations per minute. Dissolution medium was either 900 ml of USP buffer pH 2 or 900 ml of USP buffer pH 6.8 maintained at 37 °C.

Amoxicillin release was monitored spectrophotometrically at a wavelength of 272 nm.

In vivo gastroretentivity assay:

25

Beagles (13-19 kg) were deprived of food (with *ad libitum* access to water) 12 hours before the experiment. Before administration of the tested formulation, the dogs were given 20 ml of water by syringe. In order to determine the anatomical location of a tablet formulation in the gastrointestinal tract, three pieces of 0.5 cm long radiopaque threads were incorporated into the tablet. X-rays pictures from two perpendicular recumbencies (right lateral & ventral-dorsal) were taken 24 hours post-administration and every 24 hours thereafter, until the formulation was not seen in the stomach, and an additional radiograph was taken to ascertain that the formulation exited the gastrointestinal tract).

30

EXAMPLE 1***Preparation of polymeric swelling tablets***

Polymeric mixtures comprising from 30 to 44 % amoxicillin were prepared from one or more of the following polymers: polycarbophil (Noveon®) was used as an exemplary highly swellable polymer, hydroxypropyl methyl cellulose (Methocel™ K100M and K4M) was used as an exemplary moderately swellable polymer, and ethyl cellulose were used as an exemplary non-swellable polymer. In addition, polyethylene glycol 400 was used as an exemplary dissolution enhancer.

The compositions of different tablets prepared are summarized in Table 1.

Table 1: composition of exemplary tablet formulations

Formulation	A	B	C	D	E	F	G	H	I	J	K
	Amount (grams/tablet)										
Amoxicillin	2.5	3.8	2.5	3.75	1.65	1.65	2.5	2.5	2.5	2.5	2.5
HPMC (Methocel™ K100M)	3.5	5.2					2	2	2	2	1.75
HPMC (Methocel™ K4M)						3.85					
Polycarbophil (Noveon®)			3.5	5.25	3.85		2			2	1.75
Ethyl Cellulose											
Polyethylene Glycol 400											0.5
Lactose									1.5		
Total	6	9	6	9	5.5	5.5	6.5	4.5	6	6.5	6.5
%Amoxicillin	42%	42%	42%	30%	30%	30%	38%	44%	42%	38%	38%

Swelling tablets with amoxicillin were prepared by direct compression of the abovementioned polymeric mixtures. Formulations A-I were prepared using a laboratory press with a flat-faced punch and die, and formulations J and K were prepared using a laboratory press fitted with a 3x2 cm oval-faced punch and die, with a 0.25-0.5

cm depression in the center which resulted in a convex face comprising a corresponding protrusion around the equator of the tablet, as illustrated in FIG. 1A.

EXAMPLE 2

In vivo gastroretentivity and pharmacodynamics of swelling tablets

In a preliminary study, tablets consisting of formulations A-F, which comprised polycarbophil (Noveon®) or hydroxypropyl methyl cellulose (Methocel™ K100M or K4M), tested *in vivo* in dogs, using the procedures described in the above Materials and Methods section. Standard, immediate release amoxicillin tablets were also tested *in vivo* (at a dose of 20 mg/kg) as a control. Blood samples were obtained periodically, centrifuged immediately and kept at -70 °C pending analysis.

In all dogs the formulations were evacuated spontaneously from the stomach and then from the gastrointestinal tract. The gastric retention times of the tablets are summarized in Table 2 below.

In a further study, tablets consisting of formulations G-K were tested *in vivo* as described above.

As shown in Tables 2 and 3 below, a formulation comprising both hydroxypropyl methyl cellulose and polycarbophil (e.g., formulation G) exhibited a longer retention time than formulations comprising either hydroxypropyl methyl cellulose (e.g., formulations A, B, F, H, I) or polycarbophil (e.g., formulations C, D, E) alone.

These results indicate that polymers having different swelling properties act in combination to provide a longer gastric retention time than would be obtained with any one polymer alone.

Table 2: Gastric retention time (in hours) of exemplary tablets

Formulation	A	B	C	D	E	F
Dog 1	48	55	0	60	36	36
Dog 2	12	12	0	55	24	36
Dog 3	37	36	12	12	36	24
Dog 4	60	26	55	48	36	36
Mean	39.25	32.25	16.75	43.75	33.00	33.00
Median	42.50	31.00	6.00	51.50	36.00	36.00
Standard deviation	20.45	18.08	26.12	21.73	6.00	6.00
Standard error	10.23	9.04	13.06	21.88	3.00	3.00

Table 3: Gastric retention time (in hours) of exemplary tablets

Formulation	G	H	I	J	K
Dog 1	12	36	24	132	108
Dog 2	60	24	36	480	84
Dog 3	108	24	36	396	36
Dog 4	60	48	48	396	84
Dog 5	60	24	36	180	96
Dog 6	12			264	96
Dog 7					96
Dog 8					108
Mean	52.00	31.20	36.00	308.00	88.50
Median	60.00	24.00	36.00	330.00	96.00
Standard deviation	36.13	10.73	8.49	137.38	23.07
Standard error	14.75	4.80	3.79	56.09	8.16

As further shown in Table 3, tablets having a convex face (formulations J and K) exhibited considerably higher gastric retention times than did tablets having a flat face. Thus, formulation J tablets, prepared with a convex face, exhibited a mean ($\pm$ standard deviation) gastric retention time of 308 ± 137 hours, whereas tablets prepared from formulation G, comprising the same ingredients as formulation J, exhibited a mean ($\pm$ standard deviation) gastric retention time of 52 ± 36 hours.

These results indicate that a convex face provides swellable tablets with a considerably longer gastric retention time than does a flat face.

As shown in Figure 4 and in Table 4 herein, Formulations J and K caused serum amoxicillin levels to reach a moderately high peak in about 4 hours, and then decline slowly (with an apparent half-life of 61 hours and 7.1 hours, respectively), whereas a standard amoxicillin tablet caused serum amoxicillin levels to reach a very high peak and then drop sharply (with an apparent half-life of only 1.6 hours) to below detection levels. The AUC (area under curve) values of serum amoxicillin levels were comparable for all of the tested tablets. As further shown therein, Formulations J and K considerably lengthened the time above minimum inhibitory concentration (MIC = 0.1 $\mu\text{g/l}$) and the time above 4xMIC (i.e., 0.4 $\mu\text{g/ml}$) for serum amoxicillin. Thus, Formulations J and K resulted in a time above 4xMIC of 36-48 hours (within the target range of 30-60 hours), whereas the standard amoxicillin tablet resulted in an insufficient time above 4xMIC of approximately 12 hours.

These results indicate that the formulations described hereinabove can maintain serum amoxicillin levels for extended periods of time (over 5 days for Formulation J) above the MIC for many clinically relevant Gram-positive pathogens, such as most strains of *Staphylococci*, *Streptococci*, *Pasteurella* and other species. The relatively low C_{max} values exhibited by the formulations described hereinabove may also diminish concentration-dependent adverse side effects.

Table 4: Pharmacokinetic-pharmacodynamic parameters of exemplary tablets and a standard immediate-release amoxicillin tablet

Parameter	Formulation J (n=8)	Formulation K (n=6)	Standard tablet (n=6)
C _{max} (µg/ml)	0.86	4.84	18.6
T _{max} (hours)	4	4	2
T _{1/2} (hours)	61	7.1	1.6
Area under curve (AUC) (µg/ml x hour)	74	62	69
Time above minimum inhibitory concentration (MIC = 0.1 µg/ml) (% of 120-hour test interval)	100	40	10
Time above 4xminimum inhibitory concentration (4xMIC = 0.4 µg/ml) (% of 120-hour test interval)	40	30	10

EXAMPLE 3

In vitro dissolution and drug release of swelling tablets

Dissolution and release of amoxicillin was tested for formulations J and K described in Example 1, using the procedures described in the Materials and Methods section hereinabove.

As shown in Figure 5, Formulation K exhibited faster release of amoxicillin at pH 2 than at pH 6.8, with approximately 90 % release within 96 hours at pH 2, whereas Formulation J exhibited a relatively pH-independent release of amoxicillin, with approximately 70 % release within 96 hours at both pH 2 and pH 6.8.

Although the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all

such alternatives, modifications and variations that fall within the spirit and broad scope of the appended claims.

5 All publications, patents and patent applications mentioned in this specification are herein incorporated in their entirety by reference into the specification, to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein by reference. In addition, citation or identification of any reference in this application shall not be construed as an admission that such reference is available as prior art to the present invention. To the extent that section headings are used, they should not be construed as necessarily limiting.

WHAT IS CLAIMED IS:

1. A gastroretentive oral dosage form for an animal comprising a therapeutically active agent and a pharmaceutically acceptable solid carrier, the oral dosage form swelling when in a stomach of the animal from a first size and shape to a second size and shape, wherein a short axis of said second size and shape is at least 50 % longer than a short axis of said first size and shape, wherein said first size and shape are selected suitable for said oral dosage form to be swallowed as a whole by said animal, and said second size and shape are selected so as to prevent passage of said dosage form while in a stomach of the animal through the pylorus of said animal, the dosage form being capable of continuously releasing a therapeutically effective amount of said therapeutically active agent over a period of at least 2 days.
2. The gastroretentive oral dosage form of claim 1, wherein a shape of said first size and shape is eccentric.
3. The gastroretentive oral dosage form of claim 2, wherein said shape of said first size and shape is a kidney-like shape.
4. The gastroretentive oral dosage form of claim 1, wherein the dosage form is capable of continuously releasing a therapeutically effective amount of said therapeutically active agent over a period of at least 5 days.
5. The gastroretentive oral dosage form of claim 1, wherein the dosage form is capable of continuously releasing a therapeutically effective amount of said therapeutically active agent over a period of 7 days.
6. The gastroretentive oral dosage form of claim 1, wherein a length of said short axis of said first size and shape is no more than 75 % of a length of an axis perpendicular to said short axis.

7. The gastroretentive oral dosage form of any of claims 1 to 6, wherein a short axis of said second size and shape is at least 100 % longer than a short axis of said first size and shape.

8. The gastroretentive oral dosage form of any of claims 1 to 7, wherein each axis of said second size and shape is at least 20 % longer than a corresponding axis in said first size and shape.

9. The gastroretentive oral dosage form of any of claims 1 to 8, wherein a length of said short axis of said first size and shape is at least 10 mm.

10. The gastroretentive oral dosage form of any of claims 1 to 8, wherein a length of said short axis is in a range of 10 to 30 mm.

11. The gastroretentive oral dosage form of any of claims 1 to 10, wherein said solid carrier comprises a first polymer which swells upon contact with an aqueous solution by at least 100 %, and a second polymer which swells upon contact with an aqueous solution by up to 100 %.

12. The gastroretentive oral dosage form of any of claims 1 to 10, wherein said solid carrier comprises a first and a second polymer selected such that said first polymer swells upon contact with an aqueous solution to an extent larger than said second polymer.

13. The gastroretentive oral dosage form of any of claims 1 to 12, wherein at least one of two surfaces of said dosage form which are perpendicular to said short axis is a convex surface.

14. The gastroretentive oral dosage form of any of claims 1 to 13, being formed with a punch and die.

15. The gastroretentive oral dosage form of any of claims 1 to 14, wherein said therapeutically active agent is an antibiotic.

16. The gastroretentive oral dosage form of any of claims 1 to 15, wherein said therapeutically active agent is hydrophilic.

17. The gastroretentive oral dosage form of claim 15, wherein said antibiotic is a beta-lactam antibiotic.

18. The gastroretentive oral dosage form of any of claims 1 to 17, being characterized by a gastric retention time of at least 3 days.

19. The gastroretentive oral dosage form of any of claims 1 to 18, wherein said therapeutically effective amount provides said animal with a serum concentration of said therapeutically active agent which is at least a minimum effective concentration of said therapeutically active agent.

20. The gastroretentive oral dosage form of claim 19, wherein said serum concentration of said therapeutically active agent is at least said minimum effective concentration over a period of at least 40 hours.

21. The gastroretentive oral dosage form of claim 15, wherein said therapeutically effective amount provides said animal with a serum concentration of said antibiotic which is at least a minimum inhibitory concentration of said antibiotic towards a pathogen which infects said animal, over a period time which is at least a treatment time of said antibiotic against said pathogen.

22. The gastroretentive oral dosage form of any of claims 1 to 21, wherein said animal is a carnivore.

23. The gastroretentive oral dosage form of any of claims 1 to 22, being packaged in a packaging material and identified in print, in or on said packaging material, for use in a treatment of a medical condition in the animal.

24. The gastroretentive oral dosage form of claim 23, wherein said medical condition is treatable by exposure to said therapeutically active agent for at least 2 days.

25. A method of treating a medical condition in an animal subject, the method comprising orally administering the gastroretentive oral dosage form of any of claims 1 to 22 to said animal subject, wherein said medical condition is treatable by exposure to said therapeutically active agent for at least 2 days.

26. The method of claim 25, comprising a single administration of said dosage form or a plurality of administrations of said dosage form, wherein said plurality of administrations are at intervals of at least 2 days.

27. The method of claim 25, being for treating a non-human animal.

28. The method of any of claims 25 to 27, wherein said medical condition is associated with a pathogen.

29. A formulation comprising a therapeutically active agent and a pharmaceutically acceptable solid carrier which comprises a first polymer which swells upon contact with an aqueous solution by at least 100 %, and a second polymer which swells upon contact with an aqueous solution by up to 100%.

30. The formulation of claim 29, identified for use in the manufacture of a gastroretentive oral dosage form for an animal which swells when in a stomach of the animal from a first size and shape to a second size and shape, wherein a short axis of said second size and shape is at least 50 % longer than a short axis of said first size and shape, wherein said first size and shape are selected suitable for said oral dosage form to be swallowed as a whole by said animal, and said second size and shape are selected so as to prevent passage of said dosage form while in a stomach of the animal through the

pylorus of said animal, said dosage form being capable of continuously releasing a therapeutically effective amount of said therapeutically active agent over a period of at least 2 days.

31. Use of the formulation of claim 29 in the manufacture of a gastroretentive oral dosage form for an animal which swells when in a stomach of the animal from a first size and shape to a second size and shape, wherein a short axis of said second size and shape is at least 50 % longer than a short axis of said first size and shape, wherein said first size and shape are selected suitable for said oral dosage form to be swallowed as a whole by said animal, and said second size and shape are selected so as to prevent passage of said dosage form while in a stomach of the animal through the pylorus of said animal, said dosage form being capable of continuously releasing a therapeutically effective amount of said therapeutically active agent over a period of at least 2 days.

32. The formulation of claim 30 or use of claim 31, wherein the dosage form is capable of continuously releasing a therapeutically effective amount of said therapeutically active agent over a period of at least 5 days.

33. The formulation of claim 30 or use of claim 31, wherein the dosage form is capable of continuously releasing a therapeutically effective amount of said therapeutically active agent over a period of 7 days.

34. The formulation of claim 30 or use of claim 31, wherein a length of said short axis of said first size and shape is no more than 75 % of a length of an axis perpendicular to said short axis.

35. The formulation or use of any of claims 30 to 34, wherein a short axis of said second size and shape is at least 100 % longer than a short axis of said first size and shape.

36. The formulation or use of any of claims 30 to 35, wherein each axis of said second size and shape is at least 20 % longer than a corresponding axis in said first size and shape.

37. The formulation or use of any of claims 30 to 36, wherein at least one of two surfaces of said dosage form which are perpendicular to said short axis is a convex surface.

38. The use of any of claims 31 to 37, wherein forming said dosage form from said formulation comprises a punch and die.

39. The formulation or use of any of claims 30 to 38, wherein said dosage form is characterized by a gastric retention time of at least 3 days.

40. The formulation or use of any of claims 30 to 39, wherein said therapeutically effective amount provides said animal with a serum concentration of said therapeutically active agent which is at least a minimum effective concentration of said therapeutically active agent.

41. The formulation or use of claim 40, wherein said serum concentration of said therapeutically active agent is at least said minimum effective concentration over a period of at least 40 hours.

42. The formulation or use of any of claims 30 to 41, wherein said animal is a carnivore.

43. The formulation or use of any of claims 29 to 42, wherein said first polymer is polycarbophil.

44. The formulation or use of any of claims 29 to 43, wherein said second polymer is selected from the group consisting of hydroxypropyl methyl cellulose, methyl cellulose and ethyl cellulose.

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45. The formulation or use of any of claims 29 to 44, wherein said therapeutically active agent is an antibiotic.

46. The formulation or use of any of claims 29 to 45, wherein said therapeutically active agent is hydrophilic.

47. The formulation or use of claim 45, wherein said antibiotic is a beta-lactam antibiotic.

48. A process of preparing the gastroretentive oral dosage form of any of claims 1 to 24, the process comprising:

a) providing a formulation comprising said therapeutically active agent and said pharmaceutically acceptable solid carrier; and

b) using a punch and die to shape said formulation into said dosage form having said first size and shape.

49. The process of claim 48, wherein said punch is applied in a direction of said short axis of said first size and shape of said dosage form.

50. The process of claim 49, wherein at least one of said punch and said die is characterized by a concave surface, such that at least one of two surfaces of said dosage form which are perpendicular to said short axis of said dosage form is a convex surface.

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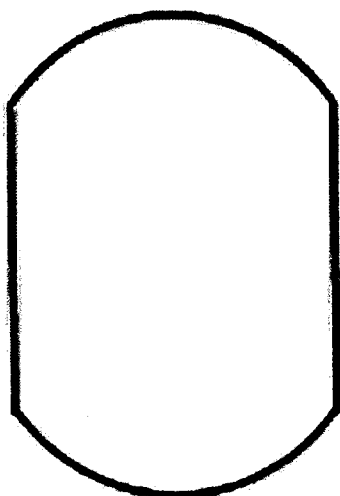


FIG. 1A

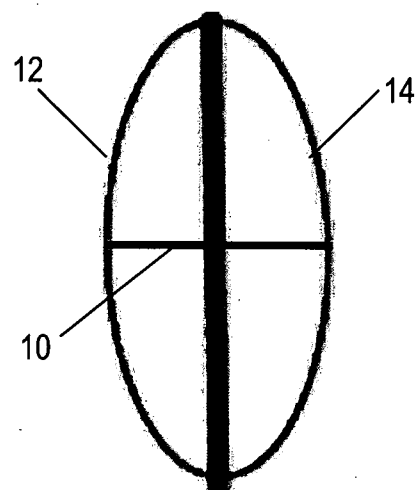


FIG. 1B

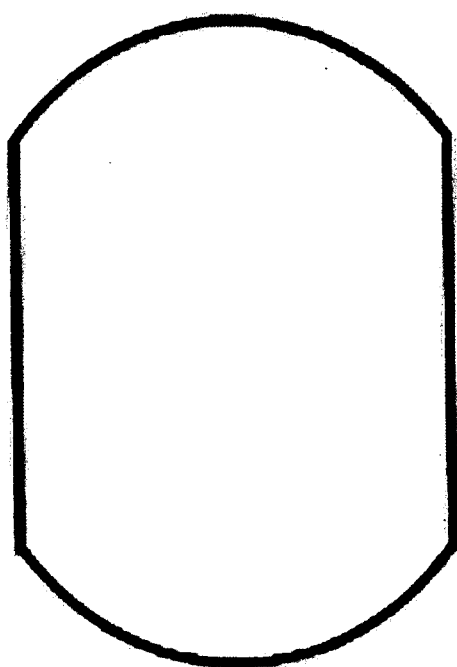


FIG. 2A

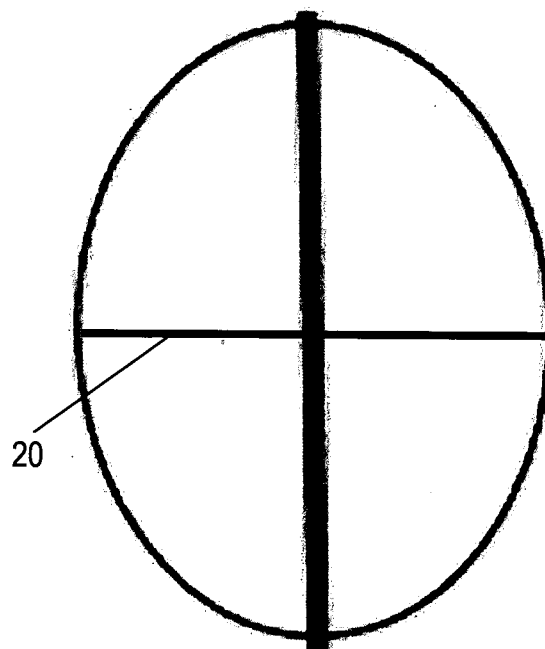


FIG. 2B

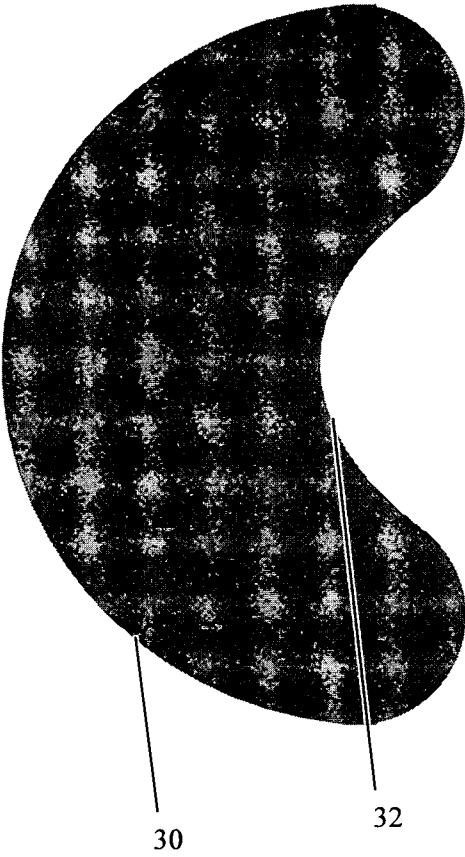


FIG. 3A

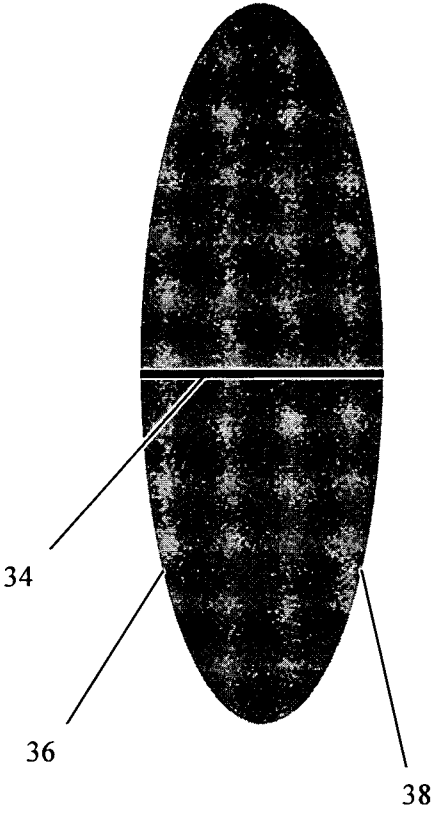


FIG. 3B

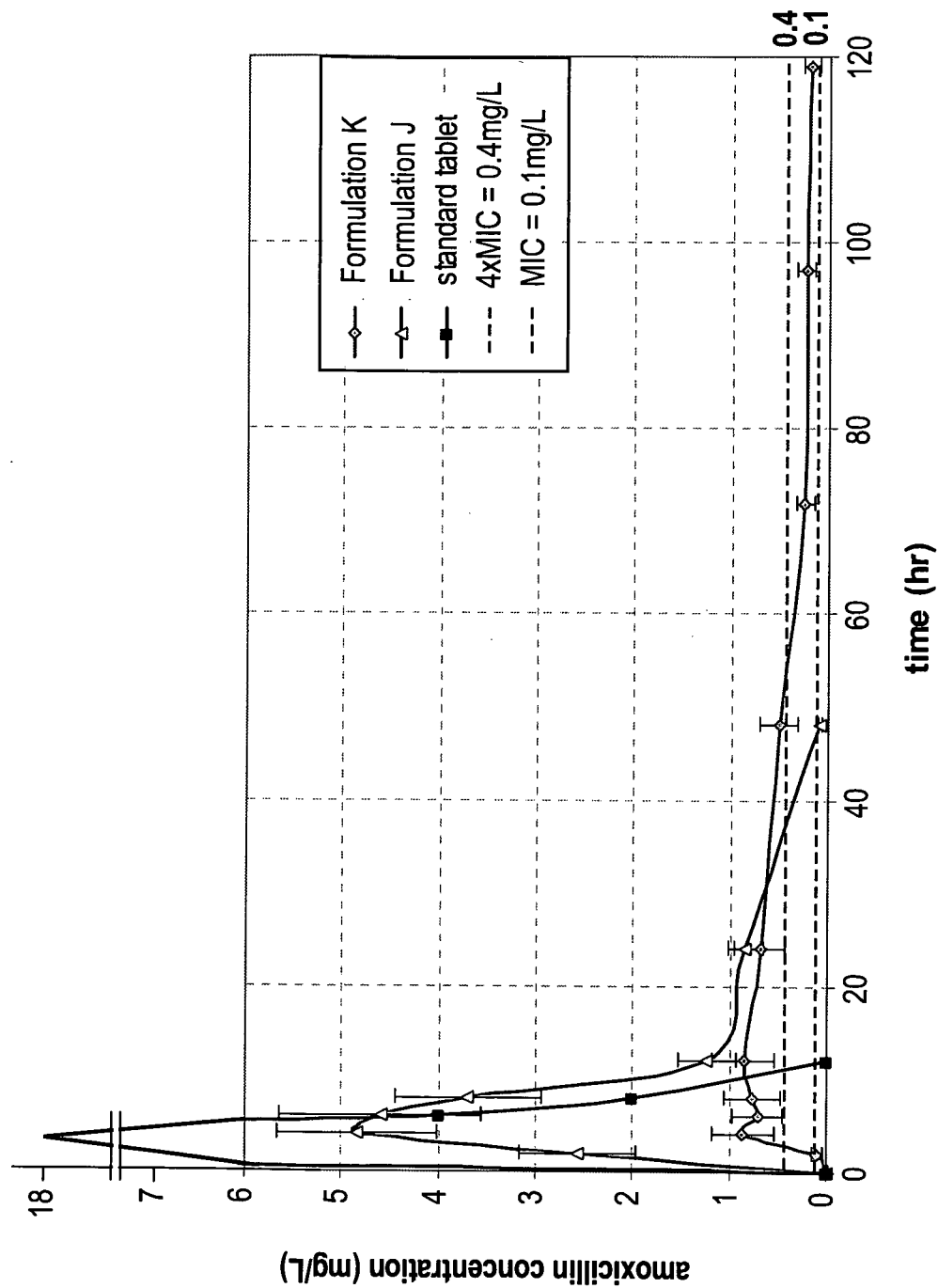


FIG. 4

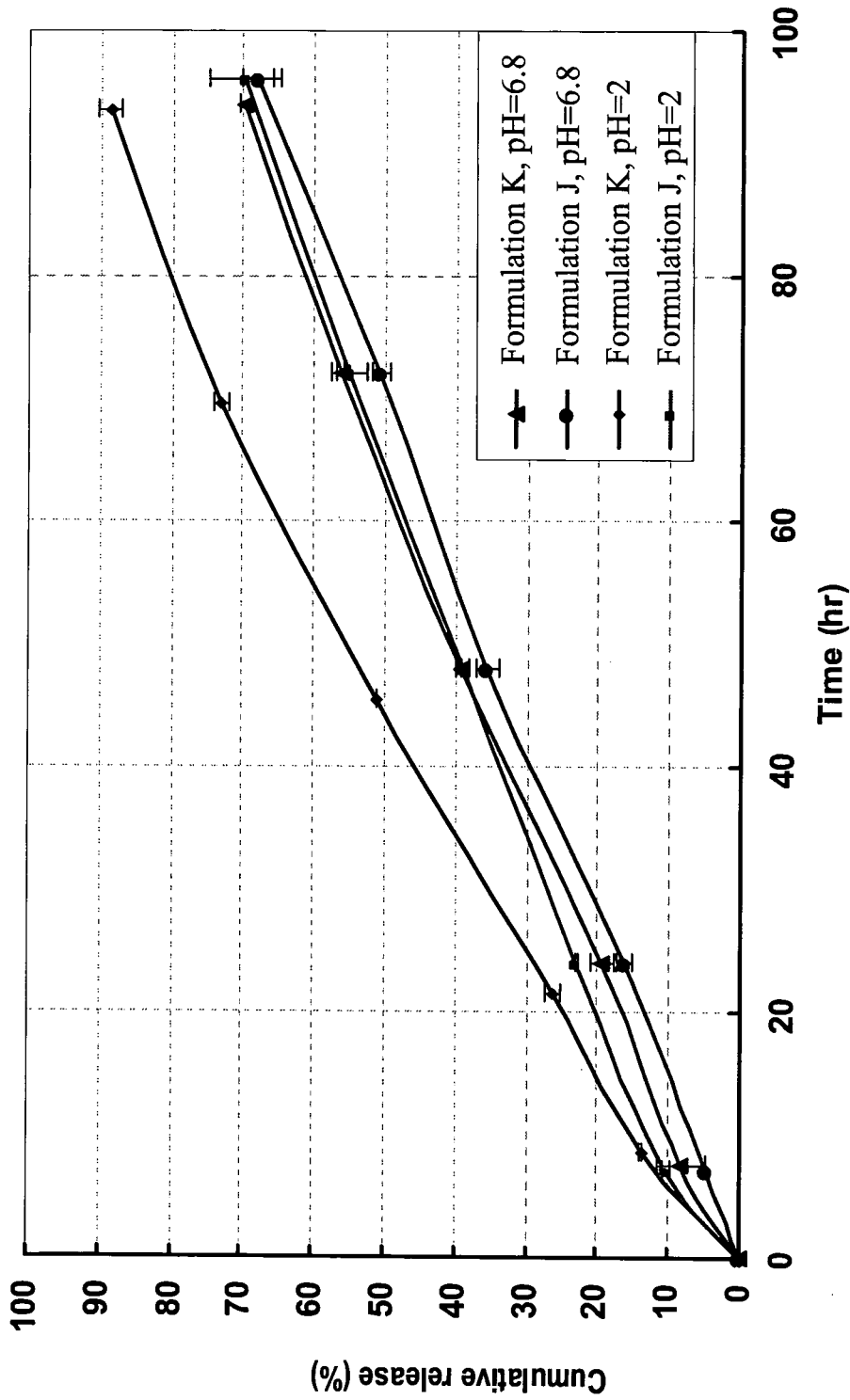


FIG. 5

INTERNATIONAL SEARCH REPORT

International application No
PCT/IL2010/000724

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 A61K9/00
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 practical, search terms used)

EPO-Internal, CHEM ABS Data, EMBASE, WPI Data, BIOSIS, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BARDONNET P L ET AL: "Gastroretentive dosage forms: Overview and special case of Helicobacter pylori", JOURNAL OF CONTROLLED RELEASE, ELSEVIER, AMSTERDAM, NL, vol. 111, no. 1-2, 10 March 2006 (2006-03-10), pages 1-18, XP024957424, ISSN: 0168-3659, DOI: DOI:10.1016/J.JCONREL.2005.10.031 [retrieved on 2006-03-10] figures 11a, b, 12 page 7, column 1, last paragraph - page 7, column 2 Superporous hydrogels; page 8, paragraph 2.5 ----- -/--	1,2, 4-10,13, 14, 18-26,28

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

☒ See patent family annex.

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Date of the actual completion of the international search

3 January 2011

Date of mailing of the international search report

11/01/2011

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

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INTERNATIONAL SEARCH REPORT

International application No

PCT/IL2010/000724

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	WO 2008/073282 A2 (SCHERING CORP [US]; WAN JIANSHENG [US]; CHEN XIAOMING [US]; GUPTA PRAN) 19 June 2008 (2008-06-19) examples claims 1-18 -----	1,2, 4-14,16, 18-26, 28-41, 43,46, 48-50
X	US 2004/219186 A1 (AYRES JAMES W [US]) 4 November 2004 (2004-11-04) examples -----	1-50

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Information on patent family members

International application No

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			JP 2010512317 T	22-04-2010
			US 2010081672 A1	01-04-2010
US 2004219186	A1	04-11-2004	NONE	